

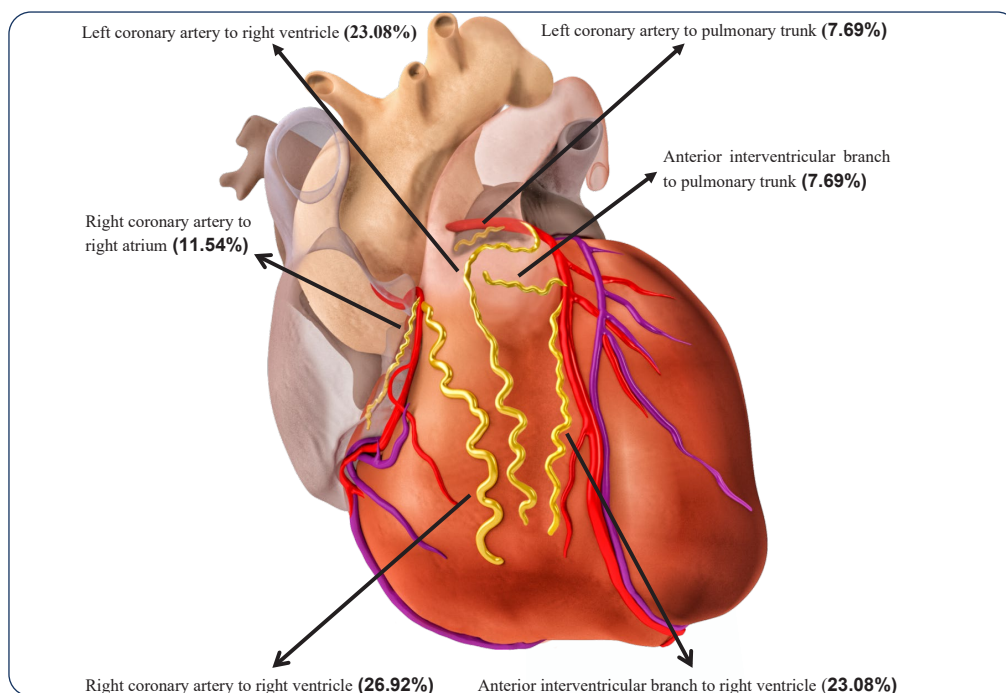


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Fúlvio Pileggi: An Icon of Brazilian Cardiology

Education and STEMI outcomes

ST-Segment Performance in the Pharmaco-Invasive Approach

Aortic biological versus mechanical valve prostheses

Cardiometabolic risk in adults and elderly

Mortality Due to IHD in Northeastern Brazil

Circulatory malformations: diagnosis and treatment

Resting heart rate of adolescents

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Fúlvio Pileggi: An Icon of Brazilian Cardiology

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Carlos Eduardo Rochitte

In this special editorial, we would like to pay tribute to an icon of Brazilian Cardiology who was directly responsible for developing one of the greatest cardiology institutions in the world, The Heart Institute (InCor), at the *Hospital das Clínicas* of the Faculty of Medicine of the University of São Paulo (USP). In the words of 3 people who were very close to him (Professors Kalil, Mady, and Protásio da Luz), we shall remember the career and the personality traits that characterized him as an undisputed leader for a generation of cardiologists. As a resident of InCor, I had the honor of meeting and interacting with Professor Pileggi, and he played a fundamental role in my academic career. First, there was apparently an obstacle to getting into a postgraduate program, "To enroll in a postgraduate program, you must have completed an internship abroad." This, in association with the fact that nearly all scholarships to study abroad required, as a pre-requisite, that the applicant be enrolled in a postgraduate program, seemed to be an insurmountable barrier, which only served to stimulate me to look even harder for alternative ways to surmount it. And, in fact, he was the one who opened all the doors to make it possible for me to complete an internship at Johns Hopkins University. After that, the rest was history. I am eternally indebted to him for his teachings.

On behalf of the *Arquivos Brasileiros de Cardiologia* (ABC Cardiol) and the scientific community as a whole, we would like to thank Professor Pileggi for all the contributions that he made, directly and indirectly, to the science of Cardiology. To give a brief overview, Professor Pileggi published, as author or co-author, 341 articles in ABC Cardiol, and InCor is currently the institution responsible for the highest number of publications in this journal.

But let us hear from those who knew him best, in all of his diverse nuances.

Protásio L. da Luz

Born in the city of São Carlos, São Paulo, Fúlvio José Carlos Pileggi¹ graduated from the USP Faculty of Medicine in 1947. He completed an internship at the Ignacio Chávez Institute of Cardiology in Mexico, as a postgraduate student of

Cardiology. Upon his return to Brazil, he dedicated his entire academic career to the USP, constantly alongside Professor Luiz V. Décourt, whom he would eventually replace as Full Professor of Cardiology. He became the Director of InCor in 1982, a position which he would hold until 1997. Diverse facets of his character are worthy of mention. He had a strong, memorable personality; he was a critical thinker, with broad interests including sports and classical music; he became a notable wine connoisseur. He was constantly faithful to his countless friends, and he enjoyed exchanging points of view on any subject imaginable. His friendships included an array of politicians, businesspeople, lawyers, magistrates, and university colleagues, and he made no distinctions of race or gender. In all personal dealings, he was affable and respectful.

As a doctor, he excelled in knowledge, good sense, and humanism. With his solid clinical background, he knew how to surround himself with specialists from new areas of Cardiology, in a manner that successfully combined the human aspects of the profession with technological advances in diagnosis and treatment. Guided by integrity, he always placed his patients' interests above everything else. He treated important Brazilian figures, including presidents, the same way he treated everyday citizens. As a tireless scholar, he was always up-to-date. Thanks to these qualities, he founded an important private clinic, gaining his patients' unconditional trust.

As a university professor, he had an exceptionally distinguished academic career, giving absolute priority to competence, integrity, and dedication. He was one of the professors who fought hardest against the politicization of the universities, defending the idea that academic positions, for example, university deans, should be nominated by academic peers, rather than by individuals from the outside who did not participate in the university's fundamental principles. He sought professional excellence in all branches of medicine, and he guided countless disciples whom he consistently stimulated, even after they graduated from USP. Singularly, he taught by example, more than by rhetoric.

As a manager, he made InCor and USP his life goal. By creating full-time, well-paid careers in research, he brought scientists to the institute, in both basic areas and in physiology, genetics, molecular biology, immunology, and vascular biology, in addition to clinical research. This took InCor to a new level. It went from a primary care hospital to a research institute that produced knowledge. He was a demanding administrator, but he was understanding, informal, upright, and fair. He had a clear vision of the academic institution's formative, groundbreaking role. Thus, he understood and implemented the concept wherein InCor was based on three pillars: teaching, care, and research. With respect to teaching, InCor has, for many years, prepared specialists on the highest levels of Cardiology, Pneumology, and Cardiac and Thoracic Surgery, with its master's,

Keywords

Cardiology; History; Teaching; Research; Humanism.

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doctorate, and specialization courses. Its undergraduate course is high-ranking, and it provides the basis that every doctor should have in Cardiology and Pneumology. With respect to care, he always sought to guarantee that InCor would provide the highest quality of diagnostic, therapeutic, psychological, social, nutritional, and other forms of care to all patients, both those covered by Brazil's public Unified Health System (SUS) and those with private healthcare plans, regardless of race, gender, ideology, or religion. Through the Zerbini Foundation, he implemented several programs in technical and human areas. He was able to guarantee support from diverse leaders of civil society in order to build InCor as an entity of excellence. The institute's public/private model has been a source of inspiration to many other institutions throughout Brazil. At the time of his leadership, InCor was able to allocate 10% of beds to patients with private healthcare plans or private patients who paid for the excellent services provided by the institute's cardiologists. The other 90% of beds were reserved for patients from the SUS, who received InCor's state-of-the-art services, made possible by funds obtained from private healthcare plans and private individuals. This flexible management model has, today, become a reference for foundations and hospital managers all around Brazil.

He received countless awards and distinctions, including Full Member of the Brazilian National Academy of Medicine, the Conrado Wessel Foundation Award, and diverse academic distinctions from other universities. InCor's Research Center was named after him.

He was author or co-author of approximately 480 articles in Brazilian scientific journals and 233 articles in international journals. He was a visionary who managed to inspire his disciples and collaborators in the mission of creating a high-quality, world-class institution: InCor. As he himself stated in his final speech at InCor, "The key to happiness is dreaming. The key to success is making dreams come true."

While Brazilian medicine says goodbye to one of its greatest icons, his example of a life full of achievements on behalf of humanity remains. We can say of Fúlvio Pileggi that he fought throughout his entire life, and he, therefore, deserves to be described in the words of Bertolt Brecht:

"There are men who fight for a day, and they are good. There are others who fight for a year, and they are better. There are those who fight many years, and they are very good, but there are those who fight their whole lives, and they are indispensable."

Charles Mady

At InCor, the Faculty of Medicine of USP, the *Hospital das Clínicas*, and medical and civil societies, we have lost Fúlvio José Carlos Pileggi, a remarkable, historical figure. He had a unique, transparent and sincere personality, whether other people liked it or not. It is easy to professionally describe an academic, with his publications and teaching experience. It is more difficult to comment on the human being, his visions and thoughts, which are certainly his greatest legacy and which led him to develop our institution after the Zerbini and Décourt administrations. It cannot have been easy to succeed two giants, but Pileggi managed to elevate InCor

even higher. We all have virtues and defects, but, on this scale, virtues predominated overwhelmingly. I was, together with many, privileged to live with him on an almost daily basis, closely watching his performance as he led InCor, and, before that, at the Second Medical Clinic, as Assistant Professor to Professor Décourt.

It was on that occasion, as a fourth year student, in 1968, that I met him and, he said, jokingly, that I went everywhere with a book or magazine under my arm. We started to discuss medicine frequently, and this contact brought us very close, even during my internship, residency, and teaching. It was the period that I learned the most, and it built the foundation of my training as a general practitioner and cardiologist. Postgraduate studies started at the master's level, and Pileggi encouraged me to enroll in the first class. Soon after, he invited me to be hired as an assistant doctor, and placed me, along with others, in the doctorate course; after that, he followed us around the clock, wanting to be informed regarding the progress of all activities at the institution. He instructed me to defend free teaching, without waiting for an answer. He simply told me to do it, and so I did. How can I not be grateful to someone who participated actively, constructively, in my training? There was an academy, a team that, under his guidance, led InCor to its peak, forming leaders internally and externally, demanding quality.

He was also passionate about another team, the Brazilian football club Palmeiras.

He knew everyone and everything, and he was a great leader. He demanded results in his own way, aided by an enviable team, with Macruz, Tranchesi, Serro-Azul, Bellotti, Ebaid, Del Nero, and many others standing by his side. He aggregated those who produced, receiving the respect of all, valuing merit. He was wild, like a good descendant of Calabrians, kicking and screaming, but he was not a man of sorrows. As a heartfelt man, he overcame any aggressiveness. We naturally had our conceptual differences, but they were soon resolved. The door to his office was always open, and he welcomed everyone without an appointment. He came to tears, listening to his Italian tenors and baritones. Once, at home, he cried when he heard Giglio after a few glasses of wine, another of his passions. He built an enviable wine cellar, and he was generous in sharing it. Another time, at dinner at his home, in the company of an Italian researcher, he offered us a Romanée-Conti and gave him a bottle of Château Lafite as a present. For our Wednesday lunches, at the Massimo restaurant, I brought the best. He was also an admirer of fine cuisine, and the host made a point of pleasing him. Once, he told us with emotion, his told his father that he had placed third in the USP entrance exam, to which his father replied, "Why weren't you first?" Demands and demanding since childhood.

InCor's reins were always in his hands, even on weekends and holidays. He was driven by passion. Influential people were always urged to make donations to the institute. Once, after a banker had undergone surgery in his office, he requested a certain amount for the purchase of equipment. The patient hesitated, and Pileggi told him that, as his doctor, he demanded the sum, because the hospital had saved his life. That very moment, he called the bank to authorize the transfer.

Editorial

He put InCor above all else, saying that he stayed here more than at his home, because it was also his home. This legacy, this academic spirit was, for me, the most important thing he worshipped. He consistently used his considerable influence for the sake of this house. He was rarely discouraged as a result of any political events, and, when he was, he would soon get up and start producing again. He was averse to the media, never seeking their attention. On the contrary, the media attempted to reach him, without success.

In his competitive exam for Full Professor, the chosen theme was "Pericardites", on which he had taught a master's class. He retired at the age of seventy, disgusted with certain facts. With great difficulty, we managed to bring him back, reuniting old friends and bringing joy to everyone.

For all that you have accomplished, you will always hold a prominent place in Medicine. Wherever you are, know that your InCor has enormous respect for you, and that you will always be lovingly remembered for the unforgettable legacy you have left. You made a difference, with courage and determination. Rest in peace.

Roberto Kalil Filho

Professor Fúlvio Pileggi completed his specialization in Cardiology in Mexico. When he returned to Brazil, he became a major reference in Cardiology for decades. Together with Professor Zerbini and Professor Décourt, he was one of the founders of InCor at the *Hospital das Clínicas* of the USP Faculty of Medicine. Professor Pileggi guided and led the development of InCor, building the institute that is part of the public network of university hospitals dedicated to

patient care, teaching, and research, based on humanism. InCor branched out into the areas in which it now acts, and it disseminated teaching and skilled training throughout society. I had the privilege of witnessing Professor Pileggi's contributions, as he united his peers, professors, and society as well. He later reached out to Professor Jatene, with his well-known contribution.

This institute was his life.

As a daily and constant presence, even on weekends and holidays, he was attentive to every detail of the institute. One of Professor Pileggi's concerns was the timely implementation of the most modern and advanced pieces of technology. He would frequently appoint people to go abroad to discover new technological developments. Professor Fúlvio Pileggi's leadership of colleagues, professors, and other professionals, made it possible for InCor to achieve excellence in patient care, teaching, and research. He was an excellent physician who was very dedicated to his patients, and he was always attentive to their needs. As Professor Pileggi's assistant for a long time, I was able to follow his concerns in continually providing care for patients. He studied hard, on a daily basis, until late at night, assiduously staying up-to-date on medical literature. He was an outstanding human being, doctor, and scientist, and he is still alive in the legacy that he built and left us.

In this manner, Professor Pileggi is still with all of us in his teachings. We can feel his presence in every corner of the hospital.

Our great reverence and gratitude to the distinguished human being and Professor of Medicine likewise endure.



Figure 1 – Professor Fúlvio Pileggi made InCor - HC FMUSP his life's objective.

References

1. Roberts WC. Brazil and Brazilian cardiology. Am J Cardiol. 1988;62(13):991-3. doi: 10.1016/0002-9149(88)90914-9.



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The Impact of Education on All-cause Mortality Following ST-Segment Elevation Myocardial Infarction (STEMI): Results from the Brazilian Heart Study

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Abstract

Background: Low schooling has been considered an important modifiable risk factor for the development of cardiovascular disease for a long time. Despite that, whether this factor impacts the outcomes following ST-segment elevation myocardial infarction (STEMI) is poorly understood.

Objective: To investigate whether schooling stands as an independent risk factor for mortality in STEMI patients.

Methods: STEMI-diagnosed patients were consecutively enrolled from a prospective cohort (Brasilia Heart Study) and categorized according to years of study quartiles (0-3, 4-5, 6-10 and >10 years). Groups were compared by student's t test for continuous variables and chi-square for categorical. Incidence of all-cause mortality was compared with Kaplan-Meier with Cox regression adjusted by age, gender, and GRACE score. Values of $p < 0.05$ were considered significant. SPSS21.0 was used for all analysis.

Results: The mean schooling duration was 6.63 ± 4.94 years. During the follow-up period (mean: 21 months; up to 6.8 years), 83 patients died (cumulative mortality of 15%). Mortality rate was higher among the lowest quartile compared to those in the highest quartile [18.5 vs 6.8%; HR 2.725 (95% CI: 1.27-5.83; $p=0.01$)]. In multivariate analysis, low schooling has lost statistical significance for all-cause mortality after adjustment for age and gender, with HR of 1.305 (95% CI: 0.538-3.16; $p=0.556$), and after adjustment by GRACE score with an HR of 1.767 (95% CI: .797-3.91; $p=0.161$).

Conclusion: Low schooling was not an independent risk factor for mortality in STEMI patients.

Keywords: Cardiovascular Diseases; Risk Factors; Mortality; Cohort Studies; Acute Coronary Syndrome; Atherosclerosis; Scholasticity.

Introduction

Over the past decades, a great effort has been spared towards the prevention of modifiable risk factors for cardiovascular disease. Among others, low socioeconomic status, assessed by years of study, stands as a multifaceted factor that impacts both incidence and mortality rates of myocardial infarction (MI).¹ One plausible reason is the link between education and health literacy, which comprises the capacity to acknowledge health information and efficiently perform self-care practices.² According to this hypothesis, those with higher level of instruction are more likely adherent to therapeutical instructions following the index event, which may ultimately favor prognosis.³ On the other

hand, those least instructed may present a higher prevalence of comorbidities³ and frequently show delayed access to healthcare facilities,² leading to limited access to reperfusion strategies and increased rates of death.

In cardiovascular care, the aforementioned hypothesis is supported by a growing body of evidence, suggesting that long-term mortality among the least educated patients is greatly increased. Though such link is now well-supported, most data were collected from high-income nations, such as Norway,^{4,5} the United States,⁶ and Germany.⁷ In these countries, as a result of an overall excellent educational service, schooling may play a wider role on health literacy than it does in developing countries, in which education remains challenged by lack of resources and relentless drop-out rates in the earlier stages of instruction.^{8,9} Therefore, whether schooling stands as a significant modifiable risk factor for cardiovascular disease in low-to-middle income countries remains unanswered.

To date, previous results suggest that those least educated have a higher incidence of MI in Brazil. Nonetheless, whether overall survival is also determined by this factors remains unknown.¹⁰ As coronary artery diseases remain the main cause of death in this country, elucidating the role of

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schooling as a plausible surrogate marker of mortality risk is mandatory.¹¹ In this scenario, the present study investigated if lower schooling stands as an independent risk factor for mortality and estimated its impact on cardiovascular health in a Brazilian cohort of MI patients.

Methods

Study population

We prospectively enrolled patients from the Brasília Heart Study (ClinicalTrials.gov Identifier: NCT02062554), an ongoing cohort study of which details are published elsewhere.¹² Out of 662 consecutive patients included between June/2006 and November/2016, 542 were included in this analysis and 120 were excluded due to missing data. Briefly, this study enrolled patients of any age admitted for ST-segment elevation MI (STEMI) at a public high-complexity (tertiary) hospital (Hospital de Base do Distrito Federal, Brasília City, Federal District, Brazil). The admission criteria included: (i) less than 24 hours from the onset of symptoms of MI; (ii) ST-segment elevation of at least 1 mm (frontal plane) or 2 mm (horizontal) in contiguous leads; and (iii) myocardial necrosis, as evidenced by an increase to at least one value above the 99th percentile above the reference limit of CK-MB (25 U/L) and troponin I (0.04 ng/mL), followed by a decline of both.

Within 24h of hospital admission, blood samples were collected after 12h fasting and biochemical analysis was performed for the following measurements: creatine kinase-MB, total cholesterol and fractions, C-reactive protein, fasting glucose, glycated haemoglobin, creatinine, and triglycerides. Cockcroft-Gault and Friedewald formulas were used to estimate clearance and LDL-c, respectively. All biochemical analyses were performed in the same clinical laboratory certified by the Accreditation Program of Clinical Laboratories of the Brazilian Society of Clinical Pathology.

Groups Definition

At hospital admission, patients were asked about their schooling. The informed number of schooling years was then registered when feasible or presumed according to the highest level of education achieved by the patient. In this matter, schooling years according to the Brazilian educational system, as follows, were considered: illiterate (<4th year), primary education (8th year), high school (11th year), and college education (>15th year). Finally, subjects were divided in years of study quartiles, as follows: 0-3, 4-5, 6-10, and >10 years of study (Figure 1).

Follow up and endpoints

Patients were followed with monthly outpatient clinic visit or telephone contact. The median follow-up time was of 611 (IQR:724) days, ranging from 1 to 2,504 days. The primary endpoint of the study was all-cause mortality. The secondary composite outcome was major adverse cardiac events (MACE), defined as fatal or non-fatal MI, in-hospital cardiovascular death and sudden cardiac death. Other outcomes registered comprised: non-fatal stroke, intra-stent thrombosis, and angina. For all endpoints, information was obtained from medical records and death certificates.

Statistical analysis

Data are mean $\pm$ standard deviation for normally distributed data, and categorical variable are presented as percentages (%). The normality of the quantitative variables was assessed with the Kolmogorov-Smirnov test. Comparisons between 0-3 and >10 schooling groups were performed using the chi-square test for categorical variables, and paired student's t-test, for continuous variables. Survival curves were analyzed with the Kaplan-Meier method and compared with the Log Rank Mantel-Cox test. Cox proportional hazards model was used to examine the association between schooling

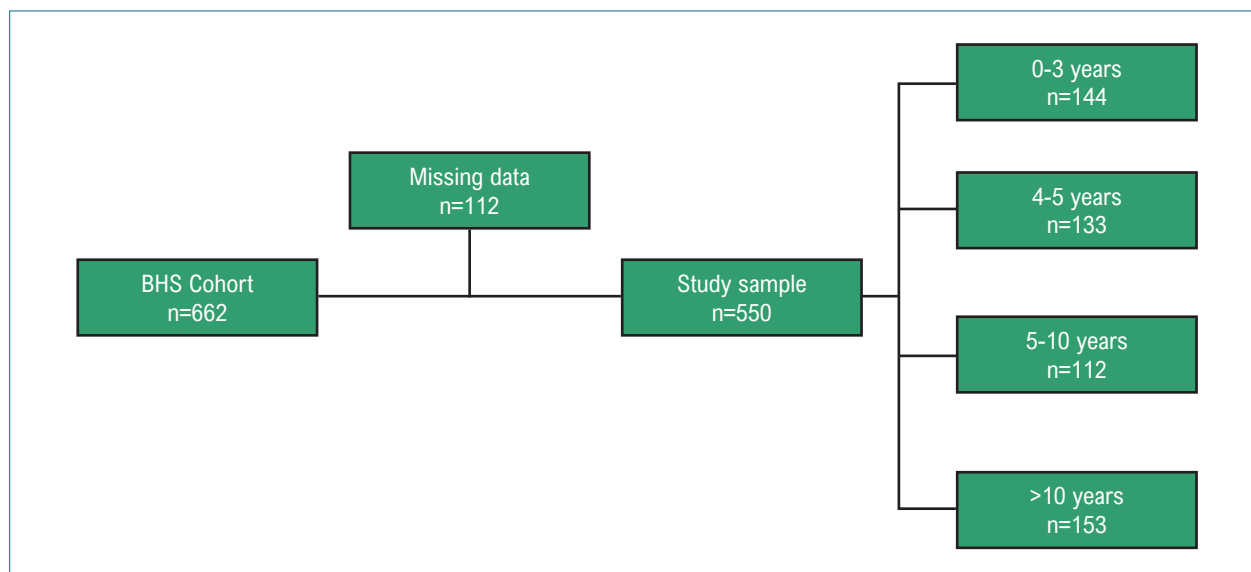


Figure 1 – Flowchart for participants in the present study.

and time to MACE, in which three pre-defined models were used [model 1: unadjusted; model 2: adjusted for sex, age; model 3: adjusted for GRACE score]. A two-sided p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Mac, version 20.0.

Results

The mean schooling duration was 6.63 ± 4.94 years. Baseline characteristics according to years of study quartile are detailed in Table 1. Most importantly, those least educated were older and showed slightly lower rates of statin treatment following STEMI, lower body mass index (BMI) as well as higher rates of hypertension. However, comorbidities [smoking, diabetes, dyslipidaemia], reperfusion strategy, and delay from symptoms onset to hospital admission were all comparable across schooling groups. Comparison between intermediate quartiles showed that those with 6-10 years of schooling were significantly younger and were mostly male, prior MI, and family history of coronary artery disease (CAD) when compared to those with 4-5 years of schooling (Table 1).

During the follow-up period (mean: 21 months; range: 0-6.8 years), 83 patients died (cumulative mortality of 15%). In linear model, schooling significantly reduced the chance of dying, according to our follow up period, with HR of 0.927 (95% CI: 0.877-0.981; $p=0.008$). Mortality rate was higher among the lowest quartile compared to those with >10 years of study (18.5 vs 6.8%, $p=0.016$) (Figure 2). In univariate analysis, the following variables were related to higher mortality rates: age ($p=0.001$), smoking ($p=0.046$), Killip class ($p=0.013$), and schooling ($p=0.021$). Compared to individuals with >10 years of schooling, having <3 years of study was related to all-cause mortality with an HR of 2.725 (95% CI: 1.27-5.83; $p=0.01$). In multivariate analysis, only age and Killip $> I$ remained significantly associated to mortality. In group comparison, having less than three years of study has lost statistical significance after adjustment by age and gender, with HR of 1.305 (95% CI: 0.538-3.16; $p=0.556$), and after adjustment by GRACE score with HR of 1.767 (95% CI: .797-3.91; $p=161$) (Table 2). Similarly, neither of intermediate quartiles were significantly related to outcomes in multivariate analysis.

Discussion

In the present study, low schooling was not independently related to mortality after STEMI. Despite that, a 2.7-fold increased mortality rate was found for those least educated in comparison to the highest quartile in crude models, result which was neutralized after adjustment by age or GRACE score. Many are the possible reasons for this finding.

It may not be unconsidered that least educated patients were also significantly older. Such discrepancy is recurrent in other studies, as an overall increase in expected schooling years has occurred globally over the past decades. In fact, United Nations Development Programme (UNDP) reports estimate that the expected schooling years rose from 13 to 16 years in high-income countries, and from five to nine

years in low and middle-income countries over the past 30 years.¹³ In Brazil, in the same period, the mean schooling years rose from 2.6 to 7.8 years, decreasing illiteracy rates from past 25% to current 9.6%.^{13,14} As age stands as a well-established risk factor for mortality from any cause, its link to schooling undermines the attempts to answer whether schooling is an independent surrogate marker of mortality in infarcted patients. Therefore, conflicting results are found in the literature (Table 3).

Accordingly, Kirchberger et al.⁷ analyzed data from 3,400 MI patients, which were grouped as low or high educational backgrounds using a cut-off of 13 schooling years. In accordance to our findings, though low schooling was related to a 1.46-fold increased mortality rate in crude analysis, adjustment by age has rendered it statistically not significant.⁷ Furthermore, in agreement with the previously exposed reasons, schooling regained statistical significance when patients were re-stratified in age groups.⁷

Contrastingly, Mehta et al.¹⁵ reported a five-fold increased mortality among least educated STEMI patients, which remained significant after adjustment by age.¹⁵ Of note, whereas least educated group comprised 2,249 subjects, those with >16 years of study were only 469 patients.¹⁵ Such difference may have undermined the effect size of age disparities on outcomes.¹⁵ Besides that, the study analyzed data collected from nine high-income countries.¹⁵ Therefore, the high standards of education delivered in these countries may have powered its contribution to health outcomes to a sufficient level for it not to be exceeded by the effect of age discrepancies. In this matter, Mehta et al.¹⁵ included data from Norway, currently the 1st in educational ranking, whereas Brazil stands as the 87th country in terms of education, hence providing reasonable explanations for the discrepancies reported.^{13,14} Moreover, Mehta et al.¹⁵ compared its groups to a higher schooling (>16 years) than our study did (>10 years), which may have significantly fuelled the verified effect size.

Finally, highlighting that income is by far the most narrowly related to clinical outcomes following STEMI among socioeconomic factors is important.^{16,17} In this sense, one may argue that the impact of education on clinical outcomes would in part result from its relation to income, which is plausibly higher among high-income countries, where wealthiness is more fairly distributed. In fact, the median annual income of Brazilian citizens with no instruction level is US\$3,070,¹⁸ nearly 85% lower than the income for those with the same instruction level in the United States (US\$20,000).¹⁹ Correspondingly, schooling was only weakly related to income ($R=0.3$) in the present study, which plausibly translates into a slighter impact of schooling on access to health care services and overall improvement of clinical outcomes, providing a plausible mechanism for the reported discrepancies.

Study limitations and strengths

The present study has several limitations. Firstly, the number of patients was lower than in previous studies. Secondly, our groups had divergent prevalence of known risk factors, chiefly age. The cohort did not include patients

Table 1 – Sample characteristics

	Schooling, years				p-value [†]
	0 - 3	4 - 5	6 - 10	>10	
N	144	133	112	153	
Demographics					
Age, years	67.31 ± 12	62.4 ± 12 [¶]	59.4 ± 11	58.12 ± 10	.001
Schooling, years	2.4 ± 0.8	4.3 ± 0.5 [¶]	7.5 ± 0.9	12.8 ± 3.1	.001
Male, %	69.4	74.4 [¶]	84.8	77.1	.037
BMI, kg/m ²	26 ± 4.9	26.4 ± 4.3	27.2 ± 4	27.9 ± 4.3	.003
Medical History					
Prior MI, %	11.1	9 [¶]	16.1	8.5	.213
Smoking, %	37.1	31.6	39.3	37.3	.613
Diabetes mellitus, %	34	29.3	29.5	32.7	.794
Hypertension, %	66.7	64.7	61.6	51.6	.039
Dyslipidemia, %	45	47	48	46	.886
Family history for CAD, %	33.3	43.6 [¶]	57.1	52.3	.001
Hemodynamics					
SBP, mmHg	132.3 ± 30	133.5 ± 29	138.3 ± 27	139.9 ± 32	0.091
DBP, mmHg	81.9 ± 17	83.8 ± 19	88.5 ± 18	87 ± 21	.02
Heart Rate, bpm	77.3 ± 18	76.2 ± 17	77.3 ± 16	78.6 ± 16	0.70
GRACE, units	150 ± 28	138.5 ± 27	131.9 ± 21	128.7 ± 26	.001
LV Ejection fraction, %	51.5 ± 11	56.8 ± 11	50 ± 10	56 ± 11	.007
Killip class I, %	83	90	92	92	.267
Biochemical Analyses					
Fasting glucose, mg/dL	143.6 ± 65	152 ± 67	150 ± 57	155 ± 77	.51
Glycosylated hemoglobin, %	6.5 ± 1.7	6.6 ± 1.9	6.3 ± 1.5	6.5 ± 2.1	.644
CrCl, ml/min/1.73m ²	65.6 ± 24	72.1 ± 23	71.6 ± 20	71.9 ± 24	.052
HDL-C, mg/dL	40.2 ± 11.1	37 ± 9.9 [¶]	37.3 ± 10.5	37.2 ± 11	.045
LDL-C, mg/dL	125 ± 151	124.6 ± 66	119.1 ± 40	128.3 ± 44	.894
TG, mg/dL	137.3 ± 88	154.4 ± 113	183.7 ± 148	208.8 ± 258	.002
CRP, mg/L	1.6 ± 2.9	1.1 ± 1.5	1.4 ± 2.6	1.4 ± 2.5	.390
CK-MB peak, mg/dL	264 ± 213	290.9 ± 206	281 ± 193	240 ± 169	.147
Infarction mass (CMR), g	17.5 ± 9	15.9 ± 9	19.5 ± 13	14 ± 10	.192
Treatment					
Tenecteplase, %	60.4	63.2	65.2	62.7	.89
Primary PCI, %	50	42.9	50	55.6	.204
Time to reperfusion, min	160.9 ± 149.3	199.8 ± 194	167.5 ± 167	156.7 ± 164	.139
Time to hospital, min	128 ± 111	134 ± 144	130 ± 129	119 ± 127	.344
Simvastatin, %	60.1	65.4	76.9	70.7	.032
Outcomes					
All-cause death, n (%)	20 (18.5)	22 (17.3) [¶]	16 (9.5)	10 (6.8)	.016
MACE, n (%)	18 (16.7)	20 (15.7)	22 (13.1)	15 (10.2)	.515

*US\$ 1 = R\$ 3.91. [†]P-value for comparison between lowest and highest quartile of schooling for categorical and continuous variables by chi square and paired student's t-test, respectively. [¶]P<0.05 for second (4-5) vs. third (6-10 years) quartiles.

BMI: body mass index; MI: myocardial infarction; CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; CrCl: creatinine clearance; CRP: C-reactive protein; CK-MB: creatine kinase M class B; CMR: cardiac magnetic resonance; LV: left ventricular; PCI: percutaneous coronary intervention; MACE: major adverse cardiovascular events.

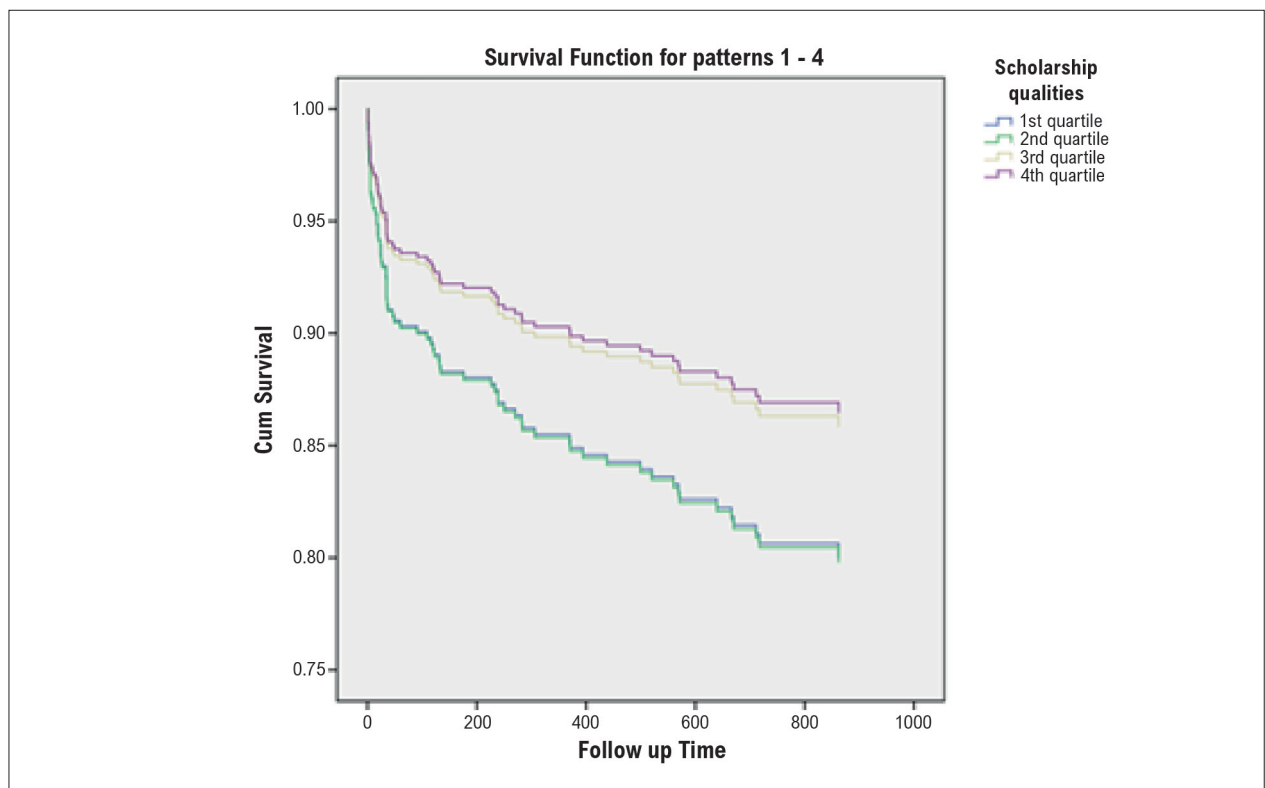


Figure 2 – Kaplan-Meier of all-cause mortality stratified by years of study quartiles

Table 2 – Cox regression of all-cause mortality

Variable	Model 1 (Crude)			Model 2 ^a			Model 3 ^b		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Age	1.081	1.06-1.11	.001	1.071	1.05-1.10	.001	1.079	1.05-1.11	.001
Male	1.063	0.65-1.75	.810	1.054	0.61-1.85	.854	1.012	.575-1.78	.967
Dyslipidemia	1.218	0.75-1.99	.428	1.314	.756-2.28	.333	1.356	.779-2.36	.282
Diabetes mellitus	1.146	0.67-1.96	.620	.957	.531-1.72	.957	1.055	.581-1.91	.860
Hypertension	0.683	0.42-1.10	.117	.723	.412-1.27	.258	.825	.485-1.40	.479
Smoking	1.685	1.01-2.81	.046	1.102	.611-1.99	.747	1.068	.607-1.87	.686
Killip class > I	1.912	1.15-3.18	.013	1.932	1.13-3.31	.017	1.985	1.12-3.50	.018
Schooling Quartiles			.021			.844			.223
1 st vs. 4 th	2.725	1.27-5.83	.010	1.305	.538-3.16	.556	1.767	.797-3.91	.161
2 nd vs. 4 th	2.469	1.17-5.22	.018	1.470	.634-3.41	.369	2.206	1.01-4.83	.048
3 rd vs. 4 th	1.386	0.63-3.05	.419	1.324	.579-3.024	.506	1.018	1.01-1.03	.497

with presumably new left branch block as a STEMI at hospital admission. Finally, though it is validated and widely used, the division in groups according to schooling years underestimate the role of content over quantity of years studied, which may add an undesired bias to our analysis, as previously discussed.

On the other hand, many are the strengths of this study. Most importantly, it stands as one of the few studies to prospectively evaluate the impact of schooling on

STEMI outcomes in a developing country. Furthermore, it reinforced that results obtained from high-development countries may not be extrapolated to the Brazilian scenario.

Conclusion

Low schooling was not an independent predictor of death nor MACE following STEMI in the present study.

Table 3 – Comparison with other studies

Study	Data	Groups	Outcomes	Results
Present study	n=542, prospective cohort of STEMI patients, Brazil	<3, 4-6, 7-10, >10 years of study	All-cause mortality	Not independently related
Mehta et al., 2011	11,326 STEMI, retrospective, 9 developed countries	< 8 vs. > 16 years of study	One-year mortality rate	five-fold higher in those least educated patients; significant after adjustment for baseline characteristics and country of enrollment
Strand, Tverdal, 2004 ⁴	n=44,684, prospective, Norway	High education (secondary level/ university/ college) vs. low (primary or no schooling)	IHD mortality	Adjustment for risk factors reduced excess IHD mortality in the low educational groups by 91% for men and 67% for women.
J. Igland et al., 2014 ⁵	N=111,993; AMI; Norway	Basic vs. tertiary education	28-day and one-year mortality	1.18-fold increase in one year, and 1.04-fold increase in 30-day mortality rate, for fully adjusted model for patients aged 70-94 years old. Included income in adjustment model.
L. Consuegra-Sanchez et al., 2011 ²⁰	N=5797; AMI; eight years prospective follow-up; Spain;	No schooling or basic education vs. Secondary school or higher education	All-cause mortality	15% higher risk in the least educated group
Coady et al., 2014 ⁶	N=15972; United States	Lower than high school education vs. college degree	Long-term mortality (1-5 years)	1.6- and 1.37-fold increased long-term mortality for the least educated men and women, respectively.
Kirchberger et al., 2014 ⁷	N=3419; AMI; Germany	Low education (without completed formal vocational training) vs. High education	Long-term mortality	No effect of education on mortality was found for the total sample. In 65+ years old patients, those least educated had 1.4-fold increased mortality rate.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Oliveira JB, Sposito AC, Carvalho LS; Acquisition of data and Critical revision of the manuscript for intellectual content: Oliveira JB, Quinaglia JC, Sposito AC, Carvalho LS; Statistical analysis and Writing of the manuscript: Oliveira JB, Carvalho LS; Obtaining financing: Sposito AC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

- Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(9):873-98. doi: 10.1161/CIR.0000000000000228.
- Rymer JA, Kaltenbach LA, Anstrom KJ, Fonarow GC, Erskine N, Peterson ED, et al. Hospital evaluation of health literacy and associated outcomes in patients after acute myocardial infarction. *Am Heart J*. 2018;198:97-107. doi: 10.1016/j.ahj.2017.08.024.
- Aaby A, Friis K, Christensen B, Rowlands G, Maundal HT. Health literacy is associated with health behaviour and self-reported health: a large population-based study in individuals with cardiovascular disease. *Eur J Prev Cardiol*. 2017;24(17):1880-8. doi: 10.1177/2047487317729538.
- Strand BH, Tverdal A. Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 year follow up of 50,000 Norwegian men and women. *J Epidemiol Community Health*. 2004;58(8):705-9. doi: 10.1136/jech.2003.014563.
- Igland J, Vollset SE, Nygard OK, Sulo G, Sulo E, Ebbing M, et al. Educational inequalities in 28 day and 1-year mortality after hospitalisation for incident acute myocardial infarction - a nationwide cohort study. *Int J Cardiol*. 2014;177(3):874-80. doi: 10.1016/j.ijcard.2014.10.04.

6. Coady SA, Johnson NJ, Hakes JK, Sorlie PD. Individual education, area income, and mortality and recurrence of myocardial infarction in a Medicare cohort: the National Longitudinal Mortality Study. *BMC Public Health*. 2014;14:705. doi: 10.1186/1471-2458-14-705.
7. Kirchberger I, Meisinger C, Golüke H, Heier M, Kuch B, Peters A, et al. Long-term survival among older patients with myocardial infarction differs by educational level: results from the MONICA/KORA myocardial infarction registry. *Int J Equity Health*. 2014;13:19. doi: 10.1186/1475-9276-13-19.
8. Frisvold D, Golberstein E. School quality and the education-health relationship: evidence from blacks in segregated schools. *J Health Econ*. 2011;30(6):1232-45. doi: 10.1016/j.jhealeco.2011.08.003.
9. Cardoso AR, Dorte V. School drop-out and push-out factors in Brazil: the role of early parenthood, child labor, and poverty. *IZA Discus Pap*. 2006;1-21.
10. Piegas LS, Avezum A, Pereira JC, Rossi Neto J, Hoepfner C, Farran JA, et al. Risk factors for myocardial infarction in Brazil. *Am Heart J*. 2003;146(2):331-8. doi: 10.1016/S0002-8703(03)00181-9.
11. Ribeiro ALP, Duncan BB, Brant LCC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular health in Brazil: trends and perspectives. *Circulation*. 2016;133(4):422-33. doi: 10.1161/CIRCULATIONAHA.114.008727.
12. Sposito AC, Carvalho LS, Cintra RM, Araújo AL, Ono AH, Andrade JM, et al. Rebound inflammatory response during the acute phase of myocardial infarction after simvastatin withdrawal. *Atherosclerosis*. 2009;207(1):191-4. doi: 10.1016/j.atherosclerosis.2009.04.008
13. The United Nations. Human Development Report 2016. New York: The United Nations; 2016.
14. Instituto Brasileiro de Geografia e Estatística. Censo 2010. Brasília (DF): IBGE; 2021.
15. Mehta RH, O'Shea JC, Stebbins AL, Granger CB, Armstrong PW, White HD, et al. Association of mortality with years of education in patients with ST-segment elevation myocardial infarction treated with fibrinolysis. *J Am Coll Cardiol*. 2011;57(2):138-46. doi: 10.1016/j.jacc.2010.09.021.
16. Ohm J, Skoglund PH, Discacciati A, Sundström J, Hambræus K, Jernberg T, et al. Socioeconomic status predicts second cardiovascular event in 29,226 survivors of a first myocardial infarction. *Eur J Prev Cardiol*. 2018;25(9):985-93. doi: 10.1177/2047487318766646.
17. Manderbacka K, Arffman M, Lumme S, Keskimäki I. Are there socioeconomic differences in outcomes of coronary revascularizations--a register-based cohort study. *Eur J Public Health*. 2015;25(6):984-9. doi: 10.1093/eurpub/ckv086.
18. Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional por Amostra de Domicílios Contínua - PNAD Contínua. Brasília (DF): IBGE; 2017.
19. Boshara R, Emmons WR, Noeth BJ. The Demographics of wealth: how age, education and race separate thrivers from strugglers in today's economy. *Federal Reserve Bank*. 2015(2):1-28.
20. Consuegra-Sanchez L, Melgarejo-Moreno A, Gálcerá-Tomás J, Alonso-Fernández N, Díaz-Pastor Á, Escudero-García G, et al. Educational level and long-term mortality in patients with acute myocardial infarction. *Rev Esp Cardiol*. 2015;68(11):935-42. doi: 10.1016/j.rec.2014.11.025.



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Education as a Social Determinant Associated with Cardiovascular Risk

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Short Editorial related to the article: *The Impact of Education on All-cause Mortality Following ST-Segment Elevation Myocardial Infarction (STEMI): Results from the Brazilian Heart Study*

The SARS-Cov2 pandemic has caused the world to reflect on the importance of the relationship between countries regarding the discussion of public health problems. Chronic-degenerative diseases are universal, and countries need to act together to better face the problems. This health promotion was highlighted at the first international conference held in 1986 in Ottawa, aimed at improving the population's health. The so-called social determinants (SD)¹ included education, housing, food, income, a stable ecosystem, sustainable resources, social justice, equity and peace. In 2005, the World Health Organization (WHO) created a Commission to outline the social determinants of health (SDH), to influence government and society, and draw attention to coping with social factors that culminate in inequality for vulnerable individuals.² It also defined SDH quite broadly as "the circumstances in which people are born, grow, live, work and age, and the systems implemented to deal with the disease". In a more recent document, the WHO emphasizes education as a fundamental factor associated with population health.³

In 2015, the American Heart Association published a document establishing the concept of SD for cardiovascular diseases. This position was based on socioeconomic factors (including wealth and income), education, employment, race, ethnicity, social support (including social networks), culture, access to medical care and residential environments. These factors are very interrelated, with socioeconomic factors being the main determinants (around three-quarters) and the others, such as genetic, biological and behavioral factors, contributing with the smallest part.⁴⁻⁶

Concerned with the topic of SD related to cardiovascular diseases (CVD) in our country, which has several social contrasts and continental dimensions, the Brazilian Society of Cardiology updated the Cardiovascular Prevention Guideline published in 2019 and included a specific topic to address this subject. Aimed at health managers and the scientific community, it brings up Education and the aspects associated with other SDs as a way to reduce CVD.⁷

Keywords

Educação; Mortalidade; Determinantes Sociais da Saúde; Doenças Cardiovasculares.

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Although apparently obvious, the topic of isolated education as an SD and the association with CVD is little explored, and the study by Barreto et al.⁸ was one of the first to address education in relation to acute myocardial infarction in a developing country. In this article, 542 patients hospitalized with ST-Segment Elevation Myocardial Infarction (STEMI) were included, during an approximate period of 10 years. The highest level of schooling attained by the patients was considered and divided into quartiles, with the lowest being between 0-3 years of schooling and the highest being >10 years of schooling. The mean time of follow-up was 21 months, and the mean level of schooling was 6.63 ± 4.94 years. In the linear analysis, mortality was higher in the group with fewer years of schooling. In the univariate analysis, the factors that influenced mortality were age, smoking, Killip classification and schooling. When assessed by the multivariate analysis, the level of schooling and others were not significant, prevailing only the Killip classification.⁸

Although this study demonstrates that schooling had no independent relationship with the mortality rate after acute myocardial infarction (AMI), several studies mention the importance of education for coronary heart disease evolution.^{9,10} Associated with several risk factors, the level of schooling, which is associated with family income influences adherence to treatment, access to medications with greater efficacy and safety, greater access to appropriate complementary exams, in addition to other elements that impact patient survival.^{7,9,10}

From the point of view of education, the United Nations have declared that it constitutes a human right. Article 26 of the Universal Declaration of Human Rights states that everyone has the right to education, and that it should be free at least at the level of Elementary School and that the education shall be directed towards the development of the human personality and to strengthen the respect for human rights and fundamental freedoms.¹¹

In Brazil, some studies indicate a higher number of CVD mortality associated with socioeconomic status, such as that by Piegas et al.,¹² when analyzing the risk factors for AMI in the AFIRMAR study, carried out in 104 hospitals and in 51 cities in Brazil, which found a relationship with education and family income as factors for the increase in myocardial infarction.¹² Bassanesi et al.,¹³ in a study carried out in 73 districts of Porto Alegre, found that more than half of CVD mortality cases under the age of 65 years could be attributed to poverty.¹³ Soares et al.¹⁴ studied the socioeconomic and cardiovascular mortality indicators in the states of Rio de Janeiro, São Paulo and Rio Grande do Sul, and found a strong correlation between CVD reduction and the increase in gross domestic product (GDP) and level of schooling.¹⁴

International studies have addressed education in the context of SD, such as Janßen et al.,¹⁵ who carried out a

systematic review of 20 studies on social inequalities and health prevention in Germany. They demonstrated a significant association between morbidity and mortality and the so-called "horizontal" (age, gender, marital status and nationality) and "vertical" inequalities (occupation, education and income).¹⁵ In India, Jeemon et al.¹⁶ confirmed the association of low socioeconomic level with the presence of greater morbidity and mortality due to cardiovascular diseases and diabetes and observed the occurrence of 52% of deaths from CVD at the age < 70 years. The most vulnerable groups were those with low level of schooling in more urbanized communities.¹⁶

References

1. World Health Organization. [Internet]. Health promotion. Geneva: World Health Organization; 2021. [cited 2021 May 10]. Available from: <http://www.who.int/healthpromotion/conferences/previous/ottawa/en>.
2. World Health Organization. [Internet]. Social determinants. Geneva: World Health Organization; 2021. [cited 2021 May 10]. Available from: http://www.who.int/social_determinants/thecommission/en/index.html.
3. World Health Organization. [Internet]. Health in 2015: from MDGs, millennium development goals to SDGs, sustainable development goals. Geneva: World Health Organization; 2021. [cited 2021 May 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/200009/9789241565110_eng.pdf;jsessionid=1983E3779FBA344FE50AA29A1D7FFEAC?sequence=1
4. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(9):873-98. doi: 10.1161/CIR.0000000000000228.
5. Carrapato C, Correia P, Garcia B. Determinantes da saúde no Brasil: a procura da equidade em saúde. *Saude Soc São Paulo*, 2017;26(3):676-89. doi: 10.1590/S0104-12902017170304.
6. Brennan LK, Baker EA, Metzler M. Promoting health equity: a resource to help communities address social determinants of health. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
7. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated cardiovascular prevention guideline of the Brazilian Society of Cardiology - 2019. *Arq Bras Cardiol*. 2019;113(4):787-891. doi: 10.5935/abc.20190204.
8. Barreto J, Silva JCQ, Sposito AC, Carvalho LS. Impacto da educação na mortalidade por todas as causas após infarto do miocárdio com supradesnívelamento do segmento ST (IAMCSST): resultados do Brasília Heart Study. *Arq Bras Cardiol*. 2021; 117(1):5-12.
9. Manderbacka K, Arffman M, Lumme S, Keskinäki I. Are there socioeconomic differences in outcomes of coronary revascularizations - a register-based cohort study. *Eur J Public Health*. 2015;25(6):984-9. doi: 10.1093/eurpub/ckv086.
10. Safford MM, Reshetnyak E, Sterling MR, Richman JS, Muntner PM, Durant RW, et al. Number of social determinants of health and fatal and nonfatal incident coronary heart disease in the REGARDS study. *Circulation*. 2021;143(3):244-53. doi: 10.1161/CIRCULATIONAHA.120.048026.
11. United Nations [Internet]. History. New York: United Nations; 2021. [cited 2021 May 10]. Available from: <https://www.un.org/en/documents/udhr/history.shtml>
12. Piegas LS, Avezum A, Pereira JC, Rossi Neto JM, Hoepfner C, Farran JA, et al. Risk factors for myocardial infarction in Brazil. *Am Heart J*. 200;146(2):331-8. doi: 10.1016/S0002-8703(03)00181-9.
13. Bassanesi SL, Azambuja MI, Achutti A. Premature mortality due to cardiovascular disease and social inequalities in Porto Alegre: from evidence to action. *Arq Bras Cardiol*. 2008;90(6):370-9. doi: 10.1590/s0066-782x2008000600004.
14. Soares GP, Brum JD, Oliveira GM, Klein CH, Silva NAS. Evolution of socioeconomic indicators and cardiovascular mortality in three Brazilian states. *Arq Bras Cardiol*. 2013;100(2):147-56. doi: 10.5935/abc.20130028.
15. Janßen C, Sauter S, Kowalski C. The influence of social determinants on the use of prevention and health promotion services: results of a systematic literature review. *Psychosoc Med*. 2012;9:1-12. doi: 10.3205/psm000085.
16. Jeemon P, Reddy KS. Social determinants of cardiovascular disease outcomes in Indians. *Indian J Med Res*. 2010;132(5):617-22. doi: 10.4103/0971-5916.73415.

Final considerations

Currently, the importance of SDH and cardiovascular disease is well established. Despite the modern diagnostic and treatment resources, the implementation of preventive measures can be greatly affected by the non-observance of the multiple factors that comprise the social determinants.

It is essential that the other SDH are taken into account and more broadly studied, aiming to establish the real dimension of the problem and then, solutions can be proposed. Countries must provide the broadest discussion and collaborate in joint decision-making.



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Accuracy of Post-thrombolysis ST-segment Reduction as an Adequate Reperfusion Predictor in the Pharmacoinvasive Approach

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Abstract

Background: Primary percutaneous coronary intervention is considered the “gold standard” for coronary reperfusion. However, when not available, the drug-invasive strategy is an alternative method and the electrocardiogram (ECG) has been used to identify reperfusion success.

Objectives: Our study aimed to assess ST-Segment changes in post-thrombolysis and their power to predict recanalization and using the angiographic scores TIMI-flow and Myocardial Blush Grade (MBG) as an ideal reperfusion criterion.

Methods: 2,215 patients with ST-Segment Elevation Myocardial Infarction (STEMI) undergoing fibrinolysis [(Tenecteplase)-TNK] and referred to coronary angiography within 24 h post-fibrinolysis or immediately referred to rescue therapy were studied. The ECG was performed pre- and 60 min-post-TNK. The patients were categorized into 2 groups: those with ideal reperfusion (TIMI-3 and MBG-3) and those with inadequate reperfusion (TIMI and MBG <3). The ECG reperfusion criterion was defined by the reduction of the ST-Segment >50%. A p-value <0.05 was considered for the analyses, with bicaudal tests.

Results: The ECG reperfusion criterion showed a positive predictive value of 56%; negative predictive value of 66%; sensitivity of 79%; and specificity of 40%. There was a weak positive correlation between ST-Segment reduction and ideal reperfusion angiographic data ($r = 0.21$; $p < 0.001$) and low diagnostic accuracy, with an AUC of 0.60 (95%CI: 0.57-0.62).

Conclusion: The ST-Segment reduction was not able to accurately identify patients with adequate angiographic reperfusion. Therefore, even patients with apparently successful reperfusion should be referred to angiography soon, to ensure adequate macro and microvascular coronary flow.

Keywords: Percutaneous Coronary Intervention; Myocardial Infarction; Coronary Angiography; Thrombolytic Therapy; Electrocardiography/methods; Chest Pain; Myocardial Reperfusion.

Introduction

Although primary percutaneous coronary intervention (PCI) is considered the “gold standard” treatment for ST-Segment elevation myocardial infarction (STEMI), it is not always available, especially in developing countries.¹ Considering this scenario, the drug-invasive strategy, with fibrinolysis and referral for coronary angiography, has proved to be a viable

option, according to the guidelines and observed in several studies, including STREAM, with unquestionable benefits when applied within the first hours of the event.²⁻⁵ Therefore, a project was started in 2010, by the Municipal Health Department, Universidade Federal de São Paulo and the Itinerant Health Care Service, which organized a planned system of thrombolysis in suburban health centers, including transfer to the university center for angiography and treatment of the related artery. Hence, the use of bedside biomarkers is essential for the discrimination of patients who have obtained adequate results and those who should be referred for rescue angioplasty.

The electrocardiogram (ECG) is an accessible method to evaluate patients with chest pain, not only for diagnostic purposes, but also in the stratification assessment. Thus, observing the behavior of the ST-Segment as a predictor of post-thrombolysis therapeutic success in reperfusion has been proposed.⁶ Therefore, our study aimed to assess the

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modifications of the post-fibrinolysis ST-Segment and its predictive power, with the angiographic scores “Thrombolysis in Myocardial Infarction” (TIMI-flow) as the outcome variable and the “Myocardial Blush Grade” (MBG) as the appropriate macro and microvascular reperfusion criteria.

Methods

This was a cross-sectional study, with retrospective analysis of the variables of interest, carried out from March-2010 to January-2018. A total of 2,215 patients were consecutively enrolled and submitted to thrombolytic therapy with tenecteplase (TNK) in primary health centers, with electrocardiographic confirmation of STEMI and referred for angiography within 24 hours post-fibrinolysis, or immediately if rescue therapy was necessary. A centralized database was used for the present study. It contained demographic, and clinical information, ECG results, treatments, time intervals and hospital events. This study is in accordance with the Declaration of Helsinki, was approved by the local Ethics Committee, and the free and informed consent was obtained from patients or their legal representatives. The study is registered in the *ClinicalTrials.gov* database, under number NCT02090712. The study flowchart is shown in Figure 1.

Drug-invasive strategy

The drug-invasive strategy was defined as the use of thrombolysis with TNK, using a weight-adjusted dose ,

followed by cardiac catheterization within 24 hours.⁷ After the STREAM³ study results in 2013, patients aged >75 years received half a dose (1/2-TNK). Only patients with an unquestionable contraindication to fibrinolysis were excluded from this analysis. The patients were premedicated with a loading dose of acetylsalicylic acid and clopidogrel. Rescue angiography was indicated by the local medical staff due to the suspected ineffective thrombolysis for the treatment of the infarct-related artery (IRA).

Assessed electrocardiographic variable

The electrocardiographic criterion for successful reperfusion was defined by the reduction >50% of ST-Segment elevation in the lead with the highest elevation. The ECGs were performed pre-and 60-minutes post-fibrinolysis and obtained in 12 leads (velocity 25 mm/s; 10 mm/mV). The ST-Elevation was defined as the elevation of the J-point in 2 or more contiguous leads, with a limit of ≥ 0.2 mV in the V1-V3 and ≥ 0.1 mV in the other leads. The analysis of the ST-Segment was performed retrospectively and by independent observers who were unaware of the patients' clinical and angiographic characteristics.

Assessed angiographic variables

Experienced interventionist cardiologists performed the angiographic analyses according to the TIMI-flow and MBG scores described below:

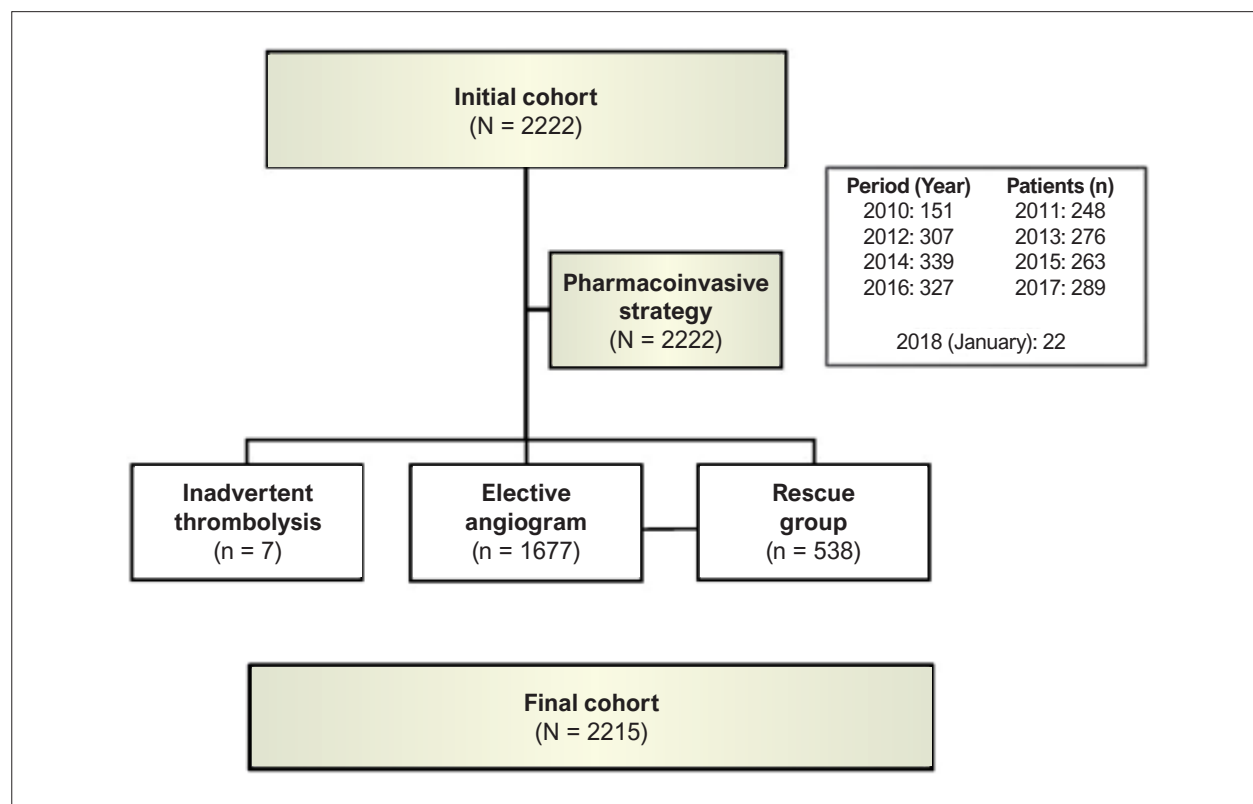


Figure 1 – Flowchart of the studied cohort.

A) Thrombolysis in Myocardial Infarction (TIMI-flow): **grade 0:** complete obstruction of IRA; **grade 1:** contrast penetrates beyond the point of obstruction, not completely opacifying the vessel; **grade 2:** opacification throughout the vessel, but with delayed flow; **grade 3:** full perfusion in the IRA, with normal flow.

B) Myocardial Blush Grade (MBG): **grade 0:** no myocardial blush or contrast density; **grade 1:** minimal myocardial blush or contrast density; **grade 2:** moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and **grade 3:** normal myocardial blush or contrast density, comparable with that obtained during the angiography of a contralateral or ipsilateral non-infarct-related coronary artery.

The patients were categorized according to the TIMI-flow and MBG into two groups: those with adequate perfusion (TIMI-3 and MBG-3 flow) and those without optimal reperfusion (TIMI flow <3). Intrinsic aspects to the procedure, such as access route, administration of glycoprotein IIb/IIIa inhibitors and thrombus-aspiration, were a medical team choice. The analyses of the angiography were performed retrospectively by independent researchers, who were unaware of the clinical and epidemiological characteristics of the patients included in the study.

Statistical analysis

Continuous variables were described as mean $\pm$ standard deviation (m $\pm$ sd) or median and interquartile range, md (IQR), when the data did not show a normal distribution. The Kolmogorov-Smirnov test and analyses of the coefficients of kurtosis and asymmetry were performed to assess the normal distribution. The categorical variables were described as absolute and relative frequency distributions. For comparisons between the groups, independent Student's t Test or Mann-Whitney non-parametric U-test was used for continuous variables and Pearson chi-square test (χ^2) was used for categorical variables, with Yates correction. Kendall's tau coefficient, a nonparametric hypothesis test, was used to verify the correlation between ST-Segment reduction and the angiographic patterns in dichotomous categorical variables. ROC (Receiver Operating Characteristic) curves were developed for the analysis of sensitivity/specificity of the ST-Segment regression based on the TIMI-flow and MBG scores. The positive likelihood ratio (LR) was calculated: LR (+): $V = \text{sensitivity} / (1 - \text{specificity})$. Good diagnostic tests have a LR (+) >10 and its positive result has a significant contribution. The likelihood ratio for a negative LR (-) is a good indicator to rule out the diagnosis. Good diagnostic tests have LR (-) <0.1; calculated: LR (-) = $(1 - \text{sensitivity}) / \text{specificity}$. The diagnostic odds ratio (DOR), is also a measure of accuracy, used to estimate the discrimination power and comparison of accuracy between the tests. The DOR was the ratio of the chance of positivity in the group with ST-Segment reduction >50% with the chances of positivity in the group without ST-segment reduction. A priori, a p-value <0.05 was considered statistically significant for all analyses, with bicaudal tests. The analyses were performed using the SPSS software, version-20 (IBM-SPSS Statistics, New York, USA)[®]

Results

Patients of both genders, 70.2% of which were men were included; the median age was 58 years, IQR (50-66). The time from symptom onset to the primary care center was 220 minutes, IQR (140-345). The prevalence of risk factors and the patients' characteristics in the basal period is reported in Table 1. Briefly, 60.7% were hypertensive; 29.8% had diabetes; 63.1% were smokers. In addition, 11% had a previous myocardial infarction and 4.3% had a previous stroke. The risk predictors used were recorded at the baseline period. Most patients were in low functional class by the Killip-Kimball classification:⁸ **I** (73%), **II** (16.3%), **III** (2.2%), **IV** (8.6%); and had a low risk profile according to the prediction scores, TIMI-Risk:⁹ 3, IQR(2-5); GRACE¹⁰: 136, IQR (117-161), meaning a low risk profile.

Distribution of coronary flow according to TIMI / MBG

In the subjective evaluation of TIMI flow and MBG, the inter-observer agreement was 94%. The ARI distribution according to the TIMI-flow score (0-3) was: 21%; 3.6%; 14.4%; and 61% respectively. MBG grade was (0-3): 42%; 3.5%; 2.5%; and 52%, respectively, evaluated only in patients with TIMI-3 flow.

Distribution of the infarct-related arteries

We observed the following distribution of the IRA: left anterior descending artery (40.3%); right coronary artery (35.3%); left circumflex coronary artery (6.8%); and branches of the main arteries (17.6%). The description of the IRA and the analysis of the regions involved in the ECG and their distribution, according to gender, can be seen in Table 2.

Distribution of measurements by ECG criterion according to TIMI flow / MBG

The prediction of adequate coronary reperfusion using the ECG criterion (ST-Segment reduction >50%) showed a positive predictive value of 56% [95% CI (0.54-0.59)]; a negative predictive value of 66% [95% CI (0.62-0.70)]; sensitivity of 79% [95% CI (0.76-0.81)]; and specificity of 40% [95% CI (0.38-0.44)], a Positive likelihood ratio (LR +) of 1.32; and a negative likelihood ratio (LR -) of 0.52. The diagnostic odds ratio (DOR) was 2.55 (odds ratio of positivity in the group with ST-Segment reduction in relation to the chances of positivity in the group without ST-segment reduction). Thus, a weak positive correlation was observed between the ST-Segment reduction and the angiographic pattern of reperfusion, considering TIMI-3 and MBG-3, ($r = 0.21$; $p < 0.001$) as shown in Figure 2. We also highlight the behavior of the ECG criterion for arterial recanalization and its association with angiographic scores, stratified by gender, which were not significantly different (Table-3). Figure 3 shows the area under the curve (AUC) of 0.60 [95% CI (0.57-0.62)] in those with ST-Segment reduction and the angiographic pattern (TIMI-3 / MBG-3):[(**A**-overall; **B**-female; **D**-male)].

Clinical characteristics of patients referred for rescue therapy

Patients were referred for rescue therapy after consensus of the local medical team, with a rate of 24.28%. The clinical-

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Table 1 – Characteristics of the cohort studied in the basal period

Variables	All Patients (N = 2215)	Patients With ST- Reduction (n = 1511)	Patients Without ST- Reduction (n = 704)	P-value
Demographics				
Age, years; MD (IQR)	58 (50-66)	58 (50-66)	58 (49-66)	0.62
Male; (%)	70.2%	70.5%	69.6%	0.41
Body Mass Index, Kg/m ² ; MD (IQR)	26 (24-29)	26 (24-29)	26 (24-30)	0.004
Hemodynamic Characteristics				
Systolic Blood Pressure, mmHg; MD (IQR)	130 (115-150)	130 (116-150)	130 (110-150)	0.098
Diastolic Blood Pressure, mmHg; MD (IQR)	80 (70-93)	80 (70-94)	80 (70-93)	0.23
Heart rate, bpm; MD (IQR)	76 (66-90)	75 (66-88)	80 (68-95)	<0.001
Risk Factors				
Hypertension; (%)	60.7%	59.2%	64.5%	0.01
Diabetes mellitus; (%)	29.8%	28.1%	33.5%	0.01
Current smokers; (%)	63.1%	66.1%	57.5%	<0.001
Previous myocardial infarction; (%)	11%	9.9%	4.9%	0.02
Previous Stroke; (%)	4.3%	4.2%	4.1%	0.98
eGFR [†] , mL/min/1.73 m ² ; MD (IQR)	86 (67-108)	88 (70-110)	84 (63-106)	0.015
Risk Scores				
TIMI-Risk score; MD (IQR)	3 (2-5)	3 (2-5)	4 (2-6)	<0.001
GRACE-score; MD (IQR)	136 (117-161)	134 (118-157)	140 (115-171)	0.004
Pivotal Times				
Pain-Needle Time; MD (IQR) min.	220 (140-345)	220 (145-345)	220 (140-356)	0.34
Door-Needle Time; MD (IQR) min.	75 (45-135)	74 (45-130)	75 (44-150)	0.057
Time TNK [‡] -Cath-lab; MD (IQR) min.	740 (335-1380)	960 (405-1440)	410 (270-841)	<0.001

Data on medical history, comorbidities and presentation time were largely derived from medical interviews. Demographic information and risk factors were reported by patients and trained staff reviewed the data during hospital admission. For comparisons between groups, the Mann-Whitney nonparametric test for continuous variables and χ^2 test for discrete variables were used. The data are expressed as median (MD) and interquartile range (IQR), or number and percentage. eGFR[†]: glomerular filtration rate estimated by MDRD (Modification of Diet in Renal Disease); TNK[‡]: Tenecteplase; Cath-lab: catheterization laboratory.

epidemiological characteristics between the rescue group and the elective angiography group is shown in Table 4. In the rescue group, the sensitivity and specificity was 59% and 53%, respectively, for the ST-segment reduction in the prediction of TIMI-3 / MBG-3. The AUC was 0.56 [95% CI (0.51-0.62)] as shown in Figure-3, (C-rescue group).

Discussion

A critical aspect of damage reduction associated with myocardial infarction is the guarantee of access to the emergency care, in which the identification of symptoms and the performance of the initial ECG are fundamental. With primary PCI unavailable in basic health units and in many hospitals, the drug-invasive strategy is recommended in STEMI.² The best method to obtain reperfusion has been widely debated, essentially skewed by the competitive perception regarding the possibilities of revascularization. It is well established that the best strategy is the one available within well-established deadlines, being indifferent within

the first hours of the onset of ischemic symptoms. The trialist group demonstrated that in patients with pain within 6 hours, 30 deaths were prevented/1,000; between 7 and 12 hours, approximately 20 deaths/1,000 would be prevented.¹¹ Thus, the importance of the fast identification of ischemic symptoms and prompt care are highlighted. Consequently, even the primary PCI, as well as fibrinolysis, are well-established treatments and the benefits are maximized when treatment occurs as soon as possible.¹² A meta-analysis reported an increased risk of recent-onset heart failure, with a relative increase in the incidence per one hour-delay in reperfusion strategies.¹³

Our study was an attempt to provide a risk stratification through the interpretation of changes in bedside post-fibrinolysis ECG, determining which patients should be referred for urgent angiographic study and the ones that could be electively referred. In fact, the ECG plays a fundamental role in diagnostic accuracy and should be obtained as soon as possible. In the scenario of acute syndromes, reperfusion biomarkers, obtained at the bedside, are crucial for the

Table 2 – Description of the infarct-related artery and analysis of electrocardiographic regions with ST-segment elevation and its distribution according to gender

Infarct-related artery	All Patients N (%)	Men (%)	Women (%)
Anterior Descending Artery	893 (40.3)	41.9	36.4
Right Coronary Artery	782 (35.3)	33.5	39.6
Circumflex Coronary Artery	151 (6.8)	6.5	7.6
Left Coronary Artery (Trunk)	11 (0.5)	0.6	0.3
Posterior Descending Coronary Artery	8 (0.36)	0.3	0.5
Posterior Ventricular Coronary Artery	14 (0.63)	0.6	0.6
Left Marginal Coronary Artery	27 (1.21)	1.2	1.4
Diagonal Artery	15 (0.67)	0.6	0.9
Unidentified artery or other	335 (15.2)	15.4	13.1
ST-Segment- elevation (ECG)	All Patients N (%)	Men (%)	Women (%)
Anteroseptal wall	892 (40.3)	41.9	36.4
Anterior Wall	782 (35.3)	33.5	39.6
Extensive Anterior wall	151 (6.8)	6.5	7.6
Posterior wall	12 (0.5)	0.6	0.3
Inferolateral wall	49 (2.2)	2.1	2.4
Lateral wall	15 (0.7)	0.6	0.9
Unidentified or other	314 (14.2)	14.8	4.7

The data are expressed as frequency and percentage (%). A team of independent experts reviewed the electrocardiographic findings. The agreement between observation pairs and the Kappa index was used as a measure of variability. The ECG reviewers were unaware of the patients' baseline characteristics. ST-Segment elevation was measured 20 ms after point J. Infarction was considered as: anteroseptal (V1-V4); anterior: (V1-V6); extensive anterior: (V1-V6 + DI, aVL); inferior (DII, DIII, aVF); inferolateral: (DII, DIII, aVF + V5-V6); lateral (V5-V6). The infarct-related artery was identified according to the presence of thrombus, total occlusion or delayed antegrade flow.

stratification. Thus, the usefulness of the ST-Segment reduction criterion in predicting reperfusion has been used as a substitute outcome in some clinical trials. In a subgroup analysis from the DANAMI-2 cohort (DANish trial in Acute Myocardial Infarction-2), ST resolution after 4 hours was associated with higher reinfarction rates among patients receiving fibrinolytics, while it was not observed in patients receiving percutaneous treatment.¹⁴ The time to obtain the ECG after fibrinolysis is variable. In the REACT study, an ST-reduction of 50% was defined at 90 minutes post-fibrinolysis, while the MERLIN study defined coronary reperfusion using the same criterion at 60 minutes. The mean time from symptom onset to PCI rescue was 414-minutes in the MERLIN study and 327 minutes in the REACT trial.^{15,16} Successful reperfusion was considered when the distal flow was restored to the infarct-related artery using the previously described TIMI-flow angiographic score.

In this context, the “open artery” hypothesis was postulated, indicating the prognostic impact if the artery was recanalized.¹⁷ Within this broad spectrum, Gibson et al.¹⁸ introduced a refined method for the myocardial perfusion value: TIMI-flow and reperfusion therapy were considered angiographically successful when TIMI-3 was reached.^{19,20} However, even when this score is reached, some patients have inadequate tissue perfusion and several mechanisms have been suggested, among others, distal embolization and the no-reflow phenomenon.²¹⁻²³ Subsequently, Hoffmann et al.²⁴ disclosed the MBG concept

with the angiographic index of the microvascular flow, since patients with TIMI-3 and normal MBG flow had lower mortality rates. The restoration of the coronary patency is not a guarantee of tissue perfusion; therefore, we understand that the presence of adequate MBG is a relevant prognostic characteristic and should be added to the TIMI- flow classification, commonly used to define successful angiographic reperfusion.²⁵⁻²⁷ The abnormalities evaluated by MBG correlate with unfavorable ventricular remodeling, even after adjustment for the presence of TIMI-3 flow.²⁸⁻³¹

Used as a reperfusion criterion, trials associated the persistence of ST-Segment elevation with the prognoses. In an interesting study, it was observed that in patients undergoing primary PCI, the ST-segment reduction did not predict long-term mortality.³² Another study found no changes in the prognostic value of post-PCI ST-segment reduction in long-term follow-up for the main outcomes.³³ In turn, the ST-Segment behavior within 60 minutes after successful primary PCI was also evaluated according to its association with lower short-and long-term mortality rates, with gradation of the ST-segment reduction (>70%; 30-70%; <30%). In this study, in the absence of ST-Segment reduction, patients with a lower chance of benefiting from early flow restoration of IRA were identified, probably due to microvascular damage and subsequent lower myocardial preservation.³⁴ However, most of these studies enrolled patients submitted to primary

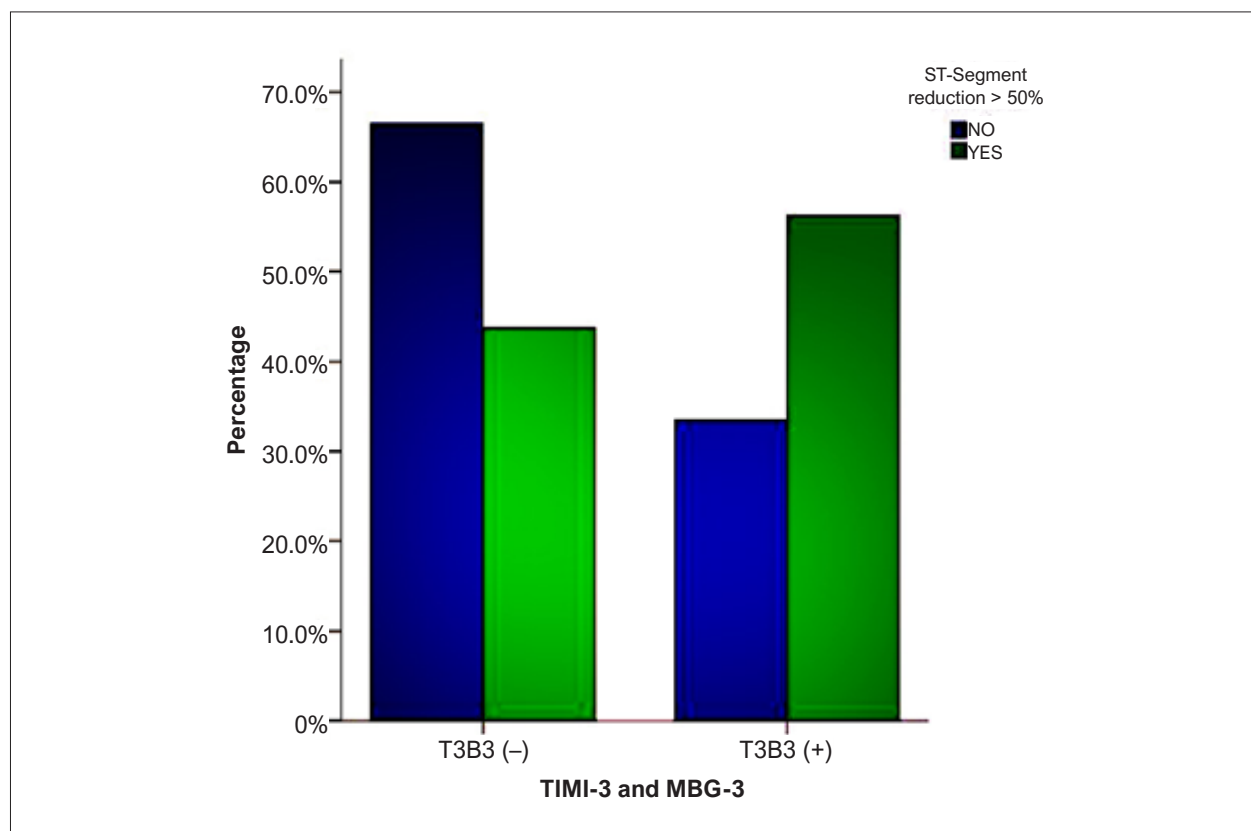


Figure 2 – Correlation between angiographic patterns (TIMI-3 and MBG-3) and the electrocardiographic criteria for reperfusion.

Table 3 – Correlation between ST-Segment reduction and TIMI-3 / Blush-3 scores, stratified by gender

Correlation Coefficient (Kendall index)				
Sex		ST Segment Reduction		TIMI-3 / Blush-3
Men	Kendall coefficient	ST-Reduction	Correlation Coefficient	1.0
			N	1537
		TIMI-3 / Blush-3	Correlation Coefficient	0.203*
			N	1506
Women	Kendall coefficient	ST-Reduction	Correlation Coefficient	1.0
			N	652
		TIMI-3 / Blush-3	Correlation Coefficient	0.231*
			N	637

*The correlation was significant at the level of 0.05 (bicaudal test).

PCI, not post-thrombolysis, and did not consider the MBG pattern as a defining variable of a better angiographic pattern of reperfusion. The presence of angiographically verified early resolution of the ST-Segment elevation post-primary PCI successfully identifies patients that are more likely to benefit from early restoration of flow in the IRA. It is also noteworthy that the TIMI-flow measures greatly overestimate the success in the primary PCI. In the post-fibrinolysis studies, the definition of angiographic success was characterized by the

presence of TIMI 2 and 3. However, patients with TIMI-flow <3 show a worse clinical evolution, especially in the medium and long-term, when compared to the group of patients with TIMI-flow 3.

The accurate measurement of ST-Segment elevation is complex and could impair the simplicity of the model, especially in the emergency room. However, in most cases, accurate measurements are not necessary, as they can be easily obtained through the visual comparison of ECGs.³⁵

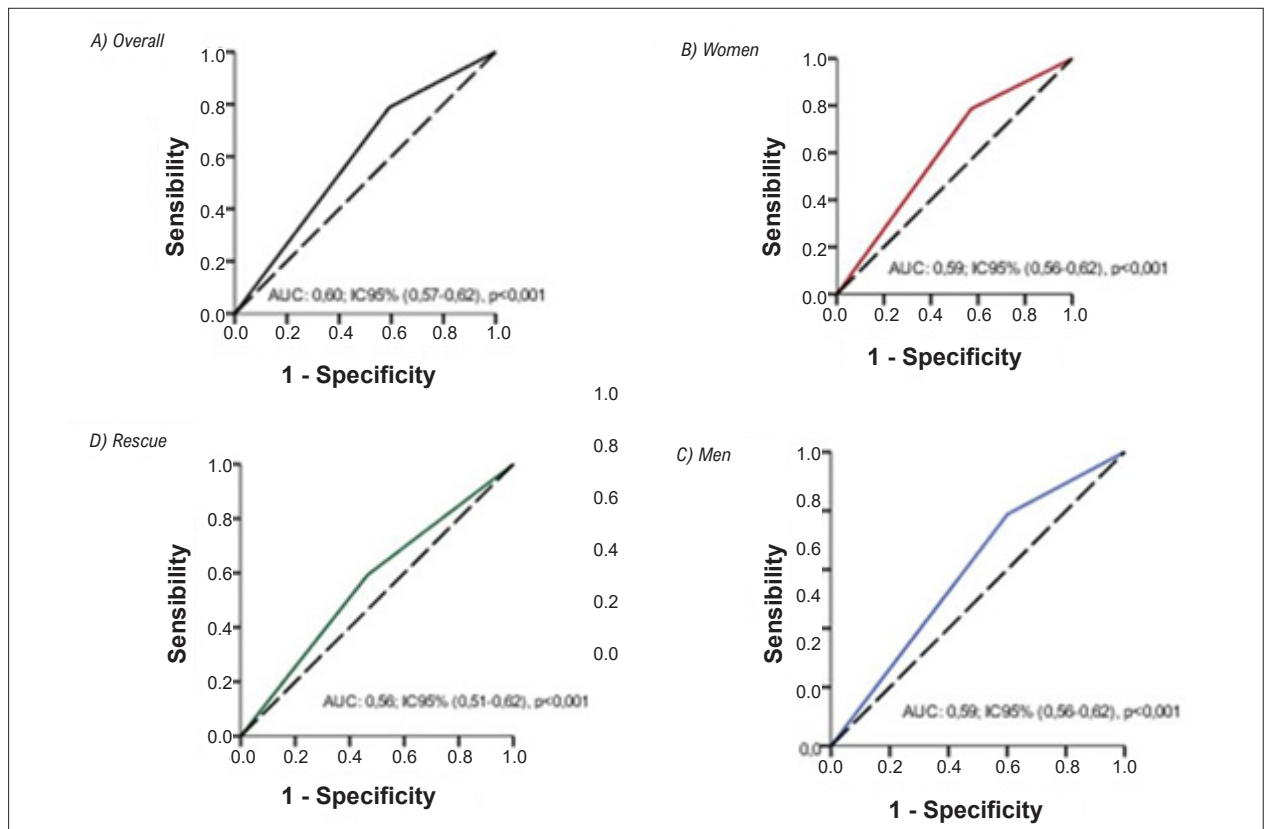


Figure 3 – Area under the curve of patients with TIMI-flow 3 / Myocardial Blush Grade 3 and ST-Segment reduction for all patients and stratified by gender. A) Overall; B) Women; C) Rescue group; D) Men.

Table 4 – Clinical and epidemiological characteristics of patients in the elective angiography group and those referred for rescue angioplasty

Variables	Elective Angiography (n = 1677)	Rescue Angioplasty (n = 538)	P-value
Demographic			
Age, (years), m ± sd	58.26 ± 11.61	58.67 ± 11.53	0.47
Male, n (%)	1178 (71. 7%)	358 (66.5%)	0.03
Risk Factors			
Previous Myocardial Infarction, n (%)	218 (11.2%)	57 (10.6%)	0.75
Previous stroke, n (%)	108 (0.5%)	14 (2.6%)	0.05
Current smokers, n (%)	589 (35. 9%)	211 (39. 2%)	0.18
Hypertension, n (%)	678 (41. 3%)	186 (34. 7%)	0.01
Diabetes mellitus, n (%)	490 (27. 8%)	186 (34. 5%)	0.006
Hemodynamic Variables			
Systolic BP†, (mmHg), m ± sd	134.3 ± 27.56	130.91 ± 29.65	0.06
Diastolic BP†, (mmHg), m ± sd	82.78 ± 18.36	81.16 ± 19.50	0.11
Heart rate, (bpm). m ± sd	78 ± 17.55	81 ± 19.70	0.002

Data are expressed as mean (m) ± standard deviation (sd) or percentage (%). Clinical demographic and risk factors were reviewed during hospital admission. BP†: Blood Pressure.

Several methods for evaluating ST-segment resolution are described, most of which include percentage of resolution; some use a single lead, while others measure the sum of deviations in multiple channels. In our notes, the detection of reperfusion using more rigorous criteria, such as complete resolution of the ST-Segment or reduction $>70\%$, showed better specificity, but with low sensitivity and low predictive capacity. The prognostic accuracy of different methods in the evaluation of the ST-Segment after PCI was analyzed in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study, demonstrating that the ST-segment analysis as absolute values in a single lead on the post-intervention ECG was at least equivalent, from the prognostic point of view, to more complex algorithms.³⁶ The evaluation of angiographic reperfusion as predicted by the ST-Segment changes was reported in our cohort. When we applied the correlation index between the TIMI-3 and MBG-3 criterion and the reperfusion, according to the ECG criterion, we obtained a value similar to that observed when only the angiographic classification of TIMI-3 flow was considered. Even after grouping and comparing patients with ischemic alterations in anterior wall vs. "non-anterior" infarction, the ST-Segment reduction $>50\%$ did not accurately predict the best angiographic patterns.

Even with effective therapies, there is still a lack of qualitative information available for stratification, specifically in the drug-invasive strategy model, where preliminary evaluation in centers and basic health units can be used to develop a better prognosis. The use of multivariate models as scores represents an interesting approach in prediction, superior to the obtained subjectively only by clinical impression. Tools that assist medical capacity by quickly and accurately assessing risk are therefore of great interest. Despite the existence of well-characterized predictors, risk estimation is challenging, due to complex profiles that require integration of variables and with calibration for local populations.³⁷

In this cohort, we recorded 116 deaths (5.3%) and as expected, with a higher incidence in the rescue group (11.5% vs. 2.4%). Complications such as cardiogenic shock and severe electrical instabilities were the main causes of mortality, with patients with the highest lethality rates belonging to functional classification IV (Killip-Kimball). In the multivariate regression model, the Killip-Kimball class was the most powerful predictor, with an increasing risk of mortality with each degree of worsening of the category. Another important information to note is that the group that received earlier thrombolysis showed lower mortality rates, reinforcing the concept that early reperfusion attenuates the risk of complications, at least in the short term.

Ideally, a reperfusion indicator should be readily obtained and applicable mainly at the bedside. In our cohort, referral to the early angiographic study was possibly due to changes in the ST-Segment, because patients who did not have post-thrombolysis reduction were more rapidly referred to rescue therapy. In the group with ST-segment reduction $>50\%$, the mean time between thrombolysis and the catheterization laboratory was 960 minutes vs. 410 minutes in the group without ST-segment reduction. However, this may have been

a mistaken option, because 24.5% had TIMI-3 / MBG-3, characterizing a diagnosis of false-positive severity. In addition, 38.5% of the group with a reduction $>50\%$ showed an angiographic pattern of TIMI-flow <3 , underestimating the real risk. In a recent study by our group, which assessed 104 patients, the analysis of the measurement of the QT interval and its dispersion in the 12 leads, and also only in the region with ST-segment elevation (named regional dispersion of the QT interval) pre and 60-minutes post-lysis, showed an increase in the regional dispersion of the QT interval (dQT-Reg) post-lysis in anterior wall infarctions in the cases with TIMI-3 / MBG-3 flow, with sensitivity and specificity of 93% and 71%, respectively. Although the study evaluated a small number of patients, these data suggest dQT-Reg as a promising instrument in the noninvasive identification of reperfusion.³⁸

The ability to predict relief of ischemic symptoms during reperfusion is clinically recognized.³⁹ However, this report is linked to idiosyncratic influences, as well as possible masking of symptoms by drugs (nitrates, analgesia, sedation). A serious problem identified in some centers is the inadvertent fibrinolysis by incorrect reading of ECGs, with reports that 5.7% to 11.0% of patients treated for STEMI did not have a myocardial infarction.⁴⁰ In our cohort, we identified 7 cases that inadvertently received thrombolytics for the following causes: acute pericarditis, non-ischemic abnormalities of ventricular repolarization, and aortic dissection.

The implementation of early thrombolytic therapy remains a cornerstone to improve post-STEMI survival. However, as evidenced in our notes, the delay between symptom onset and admission to health units was prolonged, but there were no differences in the behavior of the ST-Segment after thrombolysis. In the multinomial regression, our data indicate the best angiographic results in patients referred early to hemodynamic study, regardless of the behavior of the ST-Segment. Therefore, we believe that the best post-thrombolysis strategy is the rapid referral to the angiography unit.⁴¹ Unfortunately the time available for these patients remains inadequate, possibly due to the serious logistical problems faced in large cities. For this reason, reducing these times remains a challenge in public health projects.⁴²

Limitations of the study

The limitations of the present study should be stated. This was an exploratory and single-center analysis. In addition, ECGs and angiographies were retrospectively analyzed. In clinical networks, risk stratification is only one of the parameters that determine the delay to the angiography. In the STREAM study,³ the mean time until the angiography was 2.2 hours for patients who required urgent intervention and 17 hours for the remaining 64%. However, our findings indicate higher times, especially for the rescue group, maybe due to difficulties in transporting patients to the hemodynamic center (ambulance not immediately available). However, this is a common situation of public services in a large city. As a last point to be mentioned, our study did not specifically test ECG performance for reperfusion but analyzed the recommended ECG guidelines criteria.

Conclusion

Our results suggest that the ST-Segment reduction, analyzed as recommended, could not accurately identify patients with adequate angiographic reperfusion, based on TIMI-flow and MBG scores. We believe that an early angiographic study offers the opportunity to identify fibrinolysis failures. Thus, in the absence of better biomarkers, even patients with apparently successful reperfusion should be referred to the hemodynamics laboratory as soon as possible, aiming to ensure adequate coronary flow, considering the macro and microvascular aspects.

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Author Contributions

Conception and design of the research: Bianco HT, Fonseca FAH; Acquisition of data: Bianco HT, Stefanini E, Barbosa AHP, Alves CMR, Gonçalves Jr I, Moraes PIM, Paola AAV, Almeida D,

Fonseca FAH; Analysis and interpretation of the data: Bianco HT, Póvoa R, Luna Filho B, Fonseca HA, Barbosa AHP, Caixeta AM, Gonçalves Jr I, Lopes RD, Paola AAV, Almeida D, Moises VA, Fonseca FAH; Statistical analysis: Bianco HT, Póvoa R, Izar MC, Luna Filho B, Fonseca HA, Caixeta AM, Lopes RD, Moises VA; Writing of the manuscript: Bianco HT, Izar MC, Moreira FT, Fonseca HA, Caixeta AM, Lopes RD, Moises VA, Fonseca FAH; Critical revision of the manuscript for intellectual content: Bianco HT, Póvoa R, Izar MC, Luna Filho B, Moreira FT, Stefanini E, Fonseca HA, Alves CMR, Moraes PIM, Lopes RD, Paola AAV, Almeida D, Fonseca FAH.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

- Piegas LS, Haddad N. Percutaneous coronary intervention in Brazil: results from the Brazilian Public Health System. *Arq Bras Cardiol.* 2011;96(4):317-23.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, et al. Document Reviewers; 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2017;39(2):119-77.
- Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med.* 2013 Apr 11; 368(15):1379-87.
- Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol.* 1997;30(5):1181-6.
- Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, et al. The FAST-MI Investigators. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmacologic-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. *Eur Heart J.* 2020;41(7):858-66.
- Schweitzer P. The electrocardiographic diagnosis of acute myocardial infarction in the thrombolytic era. *Am Heart J.* 1990;119(3Pt1):642-54.
- Larson DM, McKavanagh P, Henry TD, Cantor WJ. Reperfusion options for ST Elevation myocardial infarction patients with expected delays to percutaneous coronary intervention. *Interv Cardiol Clin.* 2016 Oct;5(4):439-50.
- Killip 3rd T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* 1967;20(4):457-64.
- Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation An intravenous nPA for Treatment of Infarcting Myocardium Early II Trial substudy. *Circulation.* 2000;102(17):2031-7.
- Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* 2004;291(22):2727-33.
- Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet.* 1994;343(8893):311-22.
- Widimský P, Groch L, Zelízko M, Aschermann M, Bednár F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J.* 2000 May;21(10):823-31.
- Goel K, Pinto DS, Gibson CM. Association of time to reperfusion with left ventricular function and heart failure in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: A systematic review. *Am Heart J.* 2013;165(4):451-67.
- Sejsten M, Valeur N, Grande P, Nielsen TT, Clemmensen P, DANAMI-2 Investigators. Long-term prognostic value of st-segment resolution in patients treated with fibrinolysis or primary percutaneous coronary intervention: results from the DANAMI-2 (DANish trial in acute myocardial infarction-2). *J Am Coll Cardiol.* 2009;54(19):1763-9.
- Shiomi H, Morimoto T, Kitaguchi S, Nakagawa Y, Ishii K, Haruna Y, et al. The ReACT Trial: Randomized Evaluation of Routine Follow-up Coronary Angiography after Percutaneous Coronary Intervention Trial (ReACT), JACC Cardiovasc Interv. 2017 Jan 23;10(2):109-17

16. Sutton AG, Campbell PG, Graham R, Price DJ, Gray JC, Grech ED, et al. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial. *J Am Coll Cardiol*. 2004;44(2):287-96.
17. Roe MT, Ohman EM, Maas AC, Christenson RH, Mahaffey KW, Granger CB, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. *J Am Coll Cardiol*. 2001 Jan;37(1):9-18.
18. Gibson CM, Cannon CP, Daley WL, Dodge Jr JT, Alexander Jr B, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996 Mar 1;93(5):879-88.
19. Hof AWJ. Successful reperfusion therapy: from epicardial to myocardial salvage. *Rev Esp Cardiol*. 2010;63(7):757-9.
20. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for acute myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 study. *Circulation*. 1993;87(6):1829-39.
21. Fernandes MR, Fish RD, Canales J, Aliota J, Silva GV, Perin EC, et al. Restoration of microcirculatory patency after myocardial infarction. results of current coronary interventional strategies and techniques. *Tex Heart Inst J*. 2012;39(3):342-50.
22. Stambuk K, Krcmar T, Zeljkovic I. Impact of intracoronary contrast injection pressure on reperfusion during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: A prospective randomized pilot study. *Int J Cardiol Heart Vasc*. 2019 Aug 20;24:100412.
23. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, et al. Clinical implications of the "no reflow" phenomenon: a predictor of complications and left ventricular remodelling in reperfused anterior wall myocardial infarction. *Circulation*. 1996;93(2):223-8.
24. Hoffmann R, Haager P, Lepper W, Franke A, Hanrath P. Relation of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction. *Heart*. 2003;89(10):1147-51.
25. Henriques JPS, Zijlstra F, Hof AWJ, Boer MJ, Dambrink JHE, Gosselink M, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. *Circulation*. 2003;107(16):2115-9.
26. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol*. 2002;39(4):591-7.
27. Kampinga MA, Nijsten MW, Gu YL, Dijk WA, de Smet BJ, Heuvel AF, et al. Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in patients with ST-elevation myocardial infarction in routine clinical practice? *Circ Cardiovasc Interv*. 2010 Jun 1;3(3):216-23.
28. Prado AP, Fernández-Vázquez F, Cuellas-Ramón JC, Gibson CM. Coronary angiography: beyond coronary anatomy. *Rev Esp Cardiol*. 2006;59(6):596-608.
29. Dibra A, Mehilli J, Dirschinger J, Pache J, Nerverve J, Schwaiger M, et al. Thrombolysis in myocardial infarction myocardial perfusion grade in angiography correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis. *J Am Coll Cardiol*. 2003;41(6):925-9.
30. Angeja BG, Gunda M, Murphy SA, Sobel BE, Rundle AC, Syed M, et al. TIMI myocardial perfusion grade and ST segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. *Circulation*. 2002;105(3):282-5.
31. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheter Cardiovasc Interv*. 2008;72(7):950-7.



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ST-Segment Elevation Regression as a Predictor of Reperfusion in Acute Myocardial Infarction: A Persistent Unknown

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Short Editorial related to the article: Accuracy of Post-thrombolysis ST-segment Reduction as an Adequate Reperfusion Predictor in the Pharmacologic-Invasive Approach

Ischemic heart disease is the leading cause of death worldwide, as well as in Brazil.¹ Its most severe presentation is the ST-segment elevation myocardial infarction (STEMI),² for which early reperfusion constitutes the main therapy to decrease mortality.³ Although primary percutaneous coronary intervention (PCI) is considered the “gold standard” treatment for STEMI, it is not sufficiently available, and access to PCI is still unequal.^{3,4} The electrocardiogram (ECG) is the main tool for the early diagnosis of AMI and for the decision about the ideal therapy to be implemented.⁵ Considering the ease to obtain the ECG, as well as its availability and feasibility in the emergency department, the ST-segment elevation reduction (STR) is proposed as the best tool to predict therapeutic success after thrombolysis.⁶ However, the method has recognized limitations, which have motivated further investigations.

In this context, the article “Accuracy of Post-thrombolysis ST-segment Reduction as an Adequate Reperfusion Predictor in the Pharmacologic-Invasive Approach”⁷ aimed to assess changes in the post-fibrinolysis ST-segment and its power to predict adequate reperfusion using the angiographic scores TIMI-flow and myocardial blush grade (MBG) as criteria for ideal reperfusion. In this study, 2,215 patients diagnosed with STEMI were submitted to fibrinolysis and referred for angiography within 24 hours, or immediately referred to rescue PCI in case of failure. The ECG was performed pre-Tenecteplase (TNK) and 60 min after, and the patients were categorized into: those with ideal reperfusion (TIMI-3 and MBG-3) and those with inadequate reperfusion (TIMI flow <3). The reperfusion criteria was defined as an STR >50%. The reperfusion criterion at the ECG showed a positive predictive value (PPV) of 56%; negative predictive value (NPV) of 66%; 79% of sensitivity; and 40% of specificity. There was a weak positive correlation between the STR and the ideal reperfusion angiographic data ($r = 0.21$; $p < 0.001$) and low diagnostic precision, with an area under the ROC curve of 0.60 (95% CI; 0.57-0.62). The results showed that the STR was unable to

accurately identify patients with appropriate angiographic reperfusion. Therefore, it is proposed that even patients with apparently successful reperfusion in the ECG should be referred to angiography, to ensure an adequate macro/microvascular flow.

In a review with preliminary data, Lemos and Braunwald⁸ evaluated the STR as a tool to measure the effectiveness of reperfusion therapy. It was observed that, despite differences between the studies regarding the medications and cutoffs considered for the STR, this would be a highly accurate predictor of the patency of the infarcted artery (PPV = 90%), but at the expense of a NPV of only approximately 50%. Lemos and Braunwald⁸ pointed out that the STR, associated with pain and the serum levels of myocardial necrosis markers could be used to predict reperfusion failure, and three criteria were proposed: STR <50% in 90 min, persistent chest pain in 90 min and a ratio of serum myoglobin at 60 minutes/baseline <4. Although the use of these criteria together improved accuracy, there were considerable false-positive rates in predicting reperfusion success.⁸

Another study evaluated the STR after thrombolysis in patients aged 65 years or older with STEMI, with serial ECGs being performed during follow-up. On days 1 and 2 following treatment, the percentage of STR was higher in younger patients. Moreover, the left ventricular ejection fraction was significantly lower in the elderly. Therefore, these data demonstrated a worse response to thrombolytic therapy in older patients, suggesting that impaired systolic function in this group could be associated with delayed STR. Moreover, it was proposed that early angiography and PCI could be more adequate for this population.⁹ Furthermore, studies that analyzed clinical factors related to STR after primary PCI also found a better response in younger individuals. This makes us think about the possibility that elderly people presented microvascular dysfunctions prior to the AMI, contributing to incomplete STR.¹⁰

However, additional electrocardiographic parameters are still being investigated, to improve the accuracy of post-thrombolysis therapeutic success prediction. Dotta et al.¹¹ analyzed the performance of QT-interval dispersion as an early reperfusion marker, in addition to the classic criteria. The angiography was performed in all patients, with flow assessment using the TIMI and MBG criteria of the culprit artery. Data suggest that the regional dispersion of the QT interval, corrected by heart rate, may be a useful parameter for non-invasive identification of reperfusion.¹¹

That being said, the literature review reinforces the conclusions of the present study.⁷ Post-thrombolysis STR alone does not accurately stratify patients with adequate reperfusion

Keywords

Regression; ST-segment elevation; Predictor; reperfusion

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(Table 1). There are some clinical factors related to lower rates of STR – such as older age and longer duration of AMI evolution – which may indicate early angiography, and new ECG

parameters may add to the predictive power of STR. Therefore, further investigations are necessary to identify the ideal markers of adequate angiographic reperfusion.

Table 1 – Summary of studies that evaluated ST-segment resolution as a success criterion for reperfusion in acute myocardial infarction

Articles	Main findings
Acurácia da Redução do Segmento-ST Pós-trombólise como Preditor de Reperusão Adequada em Estratégia Fármaco-Invasiva ⁷	ECG reperfusion criteria: ST-segment reduction >50%; 56% PPV; 66% NPV; 79% sensitivity; 40% specificity; Conclusion: there was a weak positive correlation between ST-segment reduction and ideal reperfusion by angiographic data, in addition to a low diagnostic accuracy (AUC = 0.60).
ST segment resolution as a tool for assessing the efficacy of reperfusion therapy ⁸	ST segment resolution is a highly accurate predictor of infarct artery patency (90% of PPV); However, it is inaccurate to predict persistent occlusion of the infarct-related artery (50% of PPV). The association of this variable with pain and the serum levels of myoglobin can be used together to predict reperfusion failure. However, there is still a limitation of false-positive diagnoses of reperfusion.
Resolution of ST-segment Elevation After Thrombolytic Therapy in Elderly Patients With Acute Myocardial Infarction ⁹	Elderly people seem to have a worse response to thrombolytic therapy in terms of ST-segment resolution, which may be associated with worse left ventricular function in this group; Early percutaneous coronary intervention may be a more recommended method for this population.
A Dispersão do Intervalo QT Regional como Preditor Precoce de Reperusão em Pacientes com Infarto Agudo do Miocárdio Pós-terapia Fibrinolítica ¹¹	Dispersion of the regional QT-interval, corrected by heart rate, may be an additional useful ECG parameter for non-invasive identification of reperfusion in the culprit coronary artery, 60 min post-thrombolysis.

NPV: negative predictive value; PPV: positive predictive value.

References

- Nascimento BR, Brant LCC, Oliveira GMM, Malachias MVB, Reis GMA, Teixeira RA, et al. Cardiovascular disease epidemiology in portuguese-speaking countries: data from the global burden of disease, 1990 to 2016. *Arq Bras Cardiol.* 2018;110(6):500-11. doi: 10.5935/abc.20180098.
- Soeiro AM, Silva PGM, Roque EAC, Bossa AS, Biselli B, Leal TCAT, et al. Prognostic differences between men and women with acute coronary syndrome. Data from a brazilian registry. *Arq Bras Cardiol.* 2018;111(5):648-53. doi: 10.5935/abc.20180166.
- Fraga CL, Macedo FVB, Rocha RTL, Ferreira Filho DSG, Nascimento BR. Gender equity in access to reperfusion in acute myocardial infarction: still a long way to go. *Arq Bras Cardiol.* 2021;116(4):704-5. doi: 10.36660/abc.20210082.
- Piegas LS, Haddad N. Percutaneous coronary intervention in Brazil: results from the brazilian public health system. *Arq Bras Cardiol.* 2011;96(4):317-24. doi: 10.1590/s0066-782x2011005000035.
- Resende LO, Destro Filho JB, Andreão RV, Resende ES, Rocha LSS, Freitas GRR. Myocardial infarction analysis based on ST-segment elevation and scores. *Journal of Cardiovascular Sciences.* 2015;28(6):504-10. doi: 10.5935/2359-4802.20150074.
- McLaughlin MG, Stone GW, Aymong E, Gardner G, Mehran R, Lansky AJ, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *J Am Coll Cardiol.* 2004;44(6):1215-23. doi: 10.1016/j.jacc.2004.06.053.
- Bianco HT, Povoas R, Izar MC, Luna Filho B, Moreira FT, Stefanini E, Fonseca HA, et al. Accuracy of Post-thrombolysis ST-segment Reduction as an Adequate Reperfusion Predictor in the Pharmacologic-Invasive Approach. *Arq Bras Cardiol.* 2021; 117(1):15-25.
- Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. *J Am Coll Cardiol.* 2001;38(5):1283-94. doi: 10.1016/s0735-1097(01)01550-9.
- Mehta NJ, Mehta RN, Khan IA. Resolution of ST-segment elevation after thrombolytic therapy in elderly patients with acute myocardial infarction. *Am J Ther.* 2003;10(2):83-7. doi: 10.1097/00045391-200303000-00002.
- Unikas R, Budrys P. Association between clinical parameters and ST-segment resolution after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. *Medicina (Kaunas).* 2016;52(3):156-62. doi: 10.1016/j.medic.2016.03.004.
- Dotta G, Fonseca FAH, Izar MCO, Souza MT, Moreira FT, Pinheiro LFM, et al. Regional QT interval dispersion as an early predictor of reperfusion in patients with acute myocardial infarction after fibrinolytic therapy. *Arq Bras Cardiol.* 2019;112(1):20-9. doi: 10.5935/abc.20180239.



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Late Outcomes of Aortic Valve Replacement with Bioprosthesis and Mechanical Prosthesis

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Abstract

Background: Despite constant improvement and refinement of the prostheses, the decision between mechanical and biological valves for aortic valve replacement is still controversial.

Objective: To compare outcomes of aortic valve replacement with bioprosthesis and mechanical prosthesis.

Methods: This was an observational, historical cohort study with review of medical records. A total of 202 patients who underwent heart valve replacement surgery between 2004 and 2008 were selected, with a mean follow-up of 10 years. The level of significance set at 5%.

Results: Mean age of patients was approximately 50 years; most patients were male (70%). Overall mortality- and reoperation-free survival was significantly higher in patients with mechanical prosthesis (HR=0.33; 95%CI=0.13-0.79; p=0.013). No difference was found in late mortality between the two groups. On the other hand, the risk of reoperation was significantly higher in patients with bioprosthesis than mechanical prosthesis (HR=0.062; 95%CI=0.008-0.457; p=0.006). The risk of composite adverse events – stroke, bleeding, endocarditis, thrombosis and paravalvular leak – was similar between the groups (HR=1.20; 95%CI= 0.74-1.93; p=0.44). The risk of bleeding was significantly higher in patients with mechanical prosthesis (HR=3.65; 95%CI= 1.43-9.29; p = 0.0064), although no case of fatal bleeding was reported.

Conclusion: No difference in 10-year mortality was found between the groups. The risk of reoperation significantly increases with the use of bioprosthesis, especially for patients younger than 30 years. Patients with mechanical prosthesis are at increased risk of nonfatal bleeding.

Keywords: Aortic Valve; Bioprosthesis/trends; Heart Valve Prosthesis Implantation/complications; Heart Valve Prosthesis; Rheumatic Fever.

Introduction

Surgical aortic-valve replacement has been performed since the 1950s.¹ Since then, technical advances in prosthetic manufacturing and optimization in surgical procedure have reduced the risk of complications related to the procedure, and significantly improved long-term prognosis.¹

Despite constant improvement and refinement of the prostheses, the decision between mechanical and biological valves for aortic valve replacement is still controversial. The main disadvantage of biological prostheses is deterioration of the leaflets; in contrast, compared with mechanical prostheses, bioprostheses are less thrombogenic, requiring lower time of anticoagulation, and do not produce any sounds. On the other hand, mechanical prostheses require long anticoagulation

therapy, significant lifestyle changes and impose a higher risk of thromboembolic and hemorrhagic events in long term.²

There are few studies in Brazil comparing the performance of biological and mechanical prostheses and describing the influence of epidemiological parameters on 10-year outcomes.

In Brazil, rheumatic fever is the main cause of valvular heart disease and, compared with developed countries, patients undergo surgical intervention at a younger age.³ In addition, many patients with valvular heart disease come from low-income backgrounds and hence likely to have a poor anticoagulation control.

The aim of the present study was to assess mortality, reoperation, and adverse events in patients undergoing aortic valve replacement surgery with mechanical or biologic valve prosthesis in a São Paulo State public tertiary hospital.

Methods

This was an observational, historical cohort study with review of medical records.

Study sample

The study sample was composed of patients aged between 18 and 65 years, who underwent an aortic valve replacement

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surgery with mechanical or biologic valve prosthesis between January 01, 2004 and December 31, 2008, with a mean follow-up of 10 years. All mechanical prostheses were two-leaflet prosthetic heart valves, and all bioprostheses were national prostheses available in the Brazilian national unified health system.

The combined primary outcome was reoperation-free survival and late all-cause mortality (30 days after surgery). Secondary outcome: event-free survival time, composed of stroke, bleeding, endocarditis, thrombosis and paravalvular leak.

In addition, age, sex, aortic valve dysfunction, heart rhythm, use of anticoagulation, and echocardiographic data (degree of pulmonary hypertension, left ventricular ejection fraction, and ventricular diameters) were also evaluated. The choice of prosthesis was left to the discretion of the treating cardiologist, considering patient's age, clinical features, socioeconomic status, and possible anticoagulation.

Ethical aspects

Clinical and surgical aspects during the study period were collected from patients' medical records. Regarding privacy and confidentiality, participants' anonymity was ensured, and information gathered during the study was used only for the study purposes. The study was approved by ethics committee of Dante Pazzanese Institute of Cardiology (registration number 4864/2018).

Definitions

Definitions used in this study followed the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Society of Cardiology (ESC), and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines, and the 2017 Update of the Brazilian Guidelines on Valvular Heart Disease.

Statistical analysis

Quantitative variables were described as mean and standard deviation, and qualitative variables as absolute and relative frequencies.

For group comparisons, the Student's t-test for independent samples was used for quantitative variables, and the Fisher's exact test for qualitative variables (rates and proportions). The Kaplan-Meier curve was used for analysis of survival time, reoperation-free survival time, and event-free survival time (stroke, bleeding, endocarditis, thrombosis and paravalvular leak), and the Log-rank test used for comparisons of the curves between the groups.

Analysis of the outcomes was made using the cox proportional hazards model. A multiple regression analysis of variables was not performed, since the stepwise selection model resulted in a simple Cox proportional hazards regression model itself. For measurement of effect, the instantaneous incidence rate (hazard ratio) and respective 95% confidence interval (95%CI) was calculated. Significance level was set at 5%. Data were analyzed with the support of the statistical programming environment R (R Core Team, 2019).

Differences in early mortality between the groups were compared using Fisher's exact test, considering the number of eligible patients and six patients were excluded for death within 30 days of surgical procedure. These six patients were not considered in the analysis. The analysis was robust to this censoring assumption, since the p-value remained non-significant, even when all patients excluded for loss to follow-up (absent for more than 30 days), were considered as 'early death' or 'no early death'.

For analysis of reoperation rate across age subgroups (18-29 years / 30-49 years / ≥ 50 years), the Bonferroni test was used, with an adjusted p-value of $0.05/3 = 0.016666$.

Results

Study sample

A total of 221 patients who underwent aortic valve replacement alone were studied. Thirty-day postoperative mortality was 2.7% (n=6). Thirteen patients (5.8%) were lost to follow-up. Then, 202 patients were considered eligible; 132 (65.3%) with bioprosthesis – 126 of them (95.5%) with a porcine bioprosthesis and six (4.5%) with a bovine pericardium bioprosthesis – and 70 (34.7%) with a mechanical prosthesis as described in Figure 1.

Mean follow-up was 9.3 ± 3.8 years, median of 10.45 years; 74% of patients were followed for more than eight years. The maximum duration of follow-up was 14.25 years for bioprostheses and 14.34 years for mechanical prostheses.

Baseline characteristics were similar between patients with bioprosthesis and mechanical valve prosthesis (Table 1). As expected, the use of anticoagulation was more prevalent in the group of patients who underwent aortic valve replacement with a mechanical prosthesis ($p < 0.001$). No difference between the groups was found in any other variables - age, sex, cause of valve dysfunction, heart rhythm or echocardiographic parameters (PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; LFEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVEDD: LV end-diastolic diameter).

No difference in early mortality rate was seen between the two types of valve prostheses (1.3% mechanical prosthesis versus 3.5% biological prosthesis; $p = 0.666$). Six of 221 (2.7%) patients died less than 30 days after surgery and were excluded from the analysis since the aim of this study was to compare the performance of the prostheses in long term.

Survival and reoperation data

All-cause survival rate was significantly higher in patients with bioprosthesis compared with those with mechanical prosthesis (HR = 0.33; 95%CI 0.13-0.79; $p = 0.013$) (Figure 2).

In a ten-year period, eight patients with bioprosthesis and five patients with mechanical prosthesis died, corresponding to an adjusted percentage of 6.1% and 7.9%, respectively, respectively ($p = 0.68$).

On the other hand, the analysis of reoperation alone revealed a significant difference in favor of mechanical

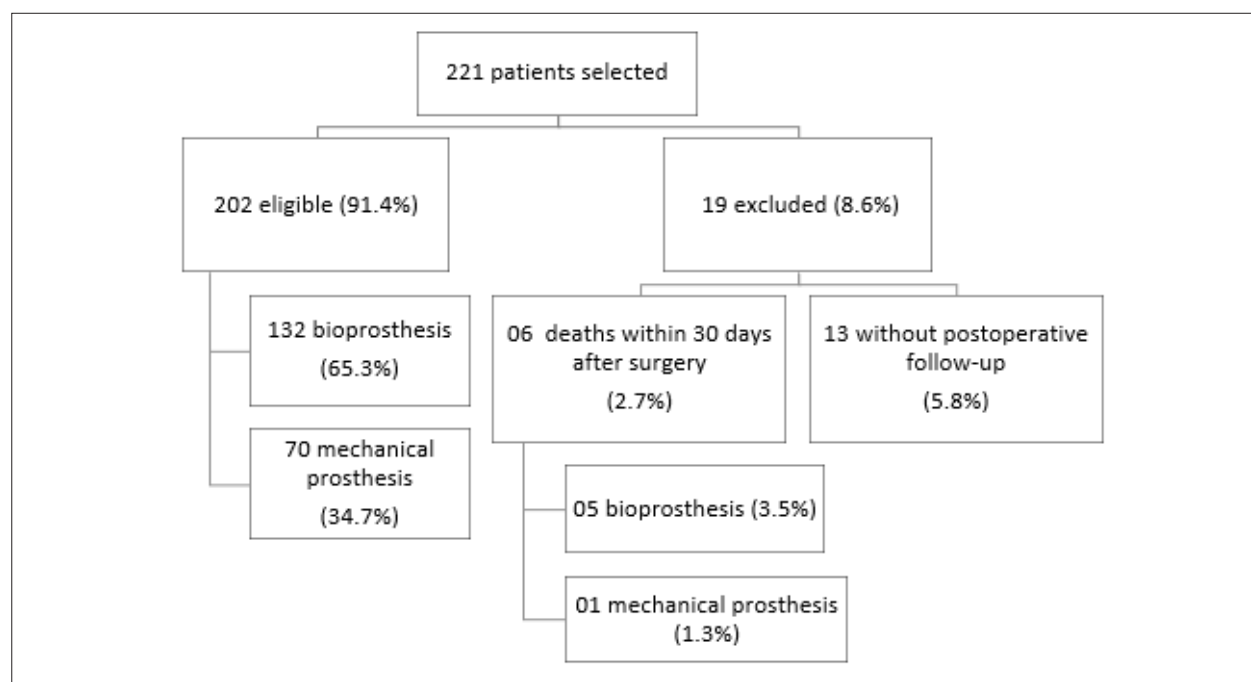


Figure 1 – Flowchart of patient selection

prosthesis (HR=0.062; 95%CI = 0.008-0.457; $p=0.006$). In ten years, 19 (21.24%) patients with bioprosthesis were reoperated, whereas no event was recorded in the mechanical prosthesis group.

Reoperation was analyzed according to subgroups of age – <30 years, between 30 and 49 years and ≥ 50 years. Probability of reoperation was higher in patients younger than 30 years compared with those aged 30-49 years (HR= 6.69; 95%CI=1.88-23.8; $p=0.003$) and patients aged ≥ 50 years (HR= 3.51; CI95% = 1.37-9.03; $p=0.008$). No difference was observed between patients ≥ 50 years and those aged 30-49 years (HR= 0.50; 95%CI= 0.16-1.50; $p=0.219$) (Figure 3).

Adverse events

Secondary outcome composed of stroke, bleeding, endocarditis, thrombosis and paravalvular leak was similar between the two groups (HR=1.20; 95%CI= 0.74-1.93; $p=0.44$), as illustrated in Figure 4.

Results of the analysis of secondary outcome by the hazard ratio was represented by a forest plot (Figure 5).

The risk of bleeding was significantly higher in patients with mechanical prosthesis than patients with bioprosthesis (HR=3.65; 95%CI = 1.43-9.29; $p=0.0064$). After adjustment for censored data, the 10-year risk of bleeding was 5.38% in patients with bioprosthesis, and 20.97% in patients with mechanical prosthesis.

The rate of stroke in 10 years was 14.10% for the group of biological prosthesis and 11.56% for the group of mechanical prosthesis ($p=0.47$). The risk of paravalvular leak was similar between patients with biological and mechanical heart valve prostheses (HR=0.71; 95%CI= 0.22-2.24; $p=0.56$). The 10-

year rate of paravalvular leak, adjusted for censored data, was 6.53% for patients with bioprosthesis and 3.38% for patients with mechanical valve.

The risk of endocarditis was similar between the groups (HR=1.30; 95%CI= 0.46-3.66; $p=0.61$). The 10-year rate of endocarditis, adjusted for censored data, was 6.12% for patients with bioprosthesis and 1.57% for patients with mechanical valve prosthesis.

The risk of thrombosis was similar between the groups ($=0.1$). The 10-year rate of thrombosis, adjusted for censored data, was 5.06% for patients with bioprosthesis and no event was recorded in the group with mechanical valve prosthesis.

The observed rate of paravalvular leak identified in the first echocardiography was 3.78% ($n=5$) for patients with biological valve and no event was recorded in the group with mechanical valve. A more detailed statistical analysis was not possible since no event was recorded in the group of mechanical valve prosthesis.

Discussion

More than 30 years have passed since the introduction of modern heart valve prostheses, and the choice between mechanical and biological valves remains controversial. There are few randomized, controlled studies, involving a large number of patients, to guide the selection of the best prosthesis. The level of evidence in most guidelines is low (level C), and the selection of prosthesis has depended on limited data, clinical experience, and common sense. We hope that this study will add knowledge about the performance of mechanical and biological heart valve prostheses in this specific group of patients.

Table 1 – Characteristics of the study groups

Variable	Study groups		p-value*
	Bioprosthesis (N= 132)	Mechanical prosthesis (N= 70)	
Age ± SD	50.78±11.67	47.67±14.09	0.116
Sex - n (%)			0.504
Male	75.8%	71.4%	
Female	24.2%	28.6%	
Etiology - n (%)			0.357
Degenerative	62.1%	57.1%	
Rheumatic	21.9%	22.9%	
Aortic dilatation	12.1%	10%	
Bicuspid	3.9%	10%	
ECG rhythm- n (%)			0.568
Sinus	80.3%	84.3%	
AF/Atrial flutter	19.7%	15.7%	
Anticoagulant therapy – (Marevan) n (%)			< 0.001
Yes	12.1%	97.1%	
No	87.9%	2.9%	
Preoperative ECHO			
PASP ± SD			0.551
Without PH	78%	82.6%	
Mild PH	16.7%	11.6%	
Moderate PH	3.8%	5.8%	
Severe PH	1.5%	0%	
LVEF ± SD	58.51±12.71	61.68±10.9	0.067
LVESD ± SD	41.01±11.79	40.06±11.28	0.547
LVEDD ± SD	60.92±11.68	60.74±12.7	0.923

* $p < 0.05$

SD: standard deviation; ECG: electrocardiogram; AF: atrial fibrillation; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter; ECHO: echocardiogram.

In the present study, we aimed to assess the outcomes of aortic valve replacement with a biological or a mechanical prosthesis in a group of patients who use public healthcare services in Brazil. Degenerative disease was the main cause of valvulopathy, followed by rheumatic disease, which accounted for nearly 22% of the cases. This predominance of degenerative disease is similar to that in developed countries; however, the relatively modest percentage of rheumatic disease may be explained by the fact that we included patients aged at least 18 years and that this is a study on isolated aortic valve disease.⁴

It is of note that approximately 80% of total patients were in sinus rhythm; although 19.7% of patients with bioprosthesis had atrial fibrillation, only 12.1% were receiving anticoagulation treatment. Despite recommendations and the risk of thrombosis, two patients with mechanical valve prosthesis were using anticoagulants; one had stroke and the other died. These findings reflect the difficulty of

performing anticoagulation in less privileged groups. No statistically significant difference was found in the preoperative echocardiographic parameters between patients with biological and mechanical valve prostheses. Most patients had preserved left ventricular function and did not have severe pulmonary hypertension.

Mean age of patients was 50 years. The risk of reoperation was significantly higher in patients with bioprosthesis, mainly in those younger than 30 years. The distance between the curves becomes larger in the fourth year of valve prosthesis implantation, more evidently after eight years of surgery, when 50% of patients younger than 30 years already had indication for reoperation. In a mean of 10 years, only one patient with mechanical prosthesis required reoperation. In accordance with these findings, Hammermeister et al.⁵ reported a greater number of interventions in patients with a bioprosthesis compared with a mechanical prosthesis for aortic valve replacement (29% versus 10%; $p = 0.004$).⁵ It

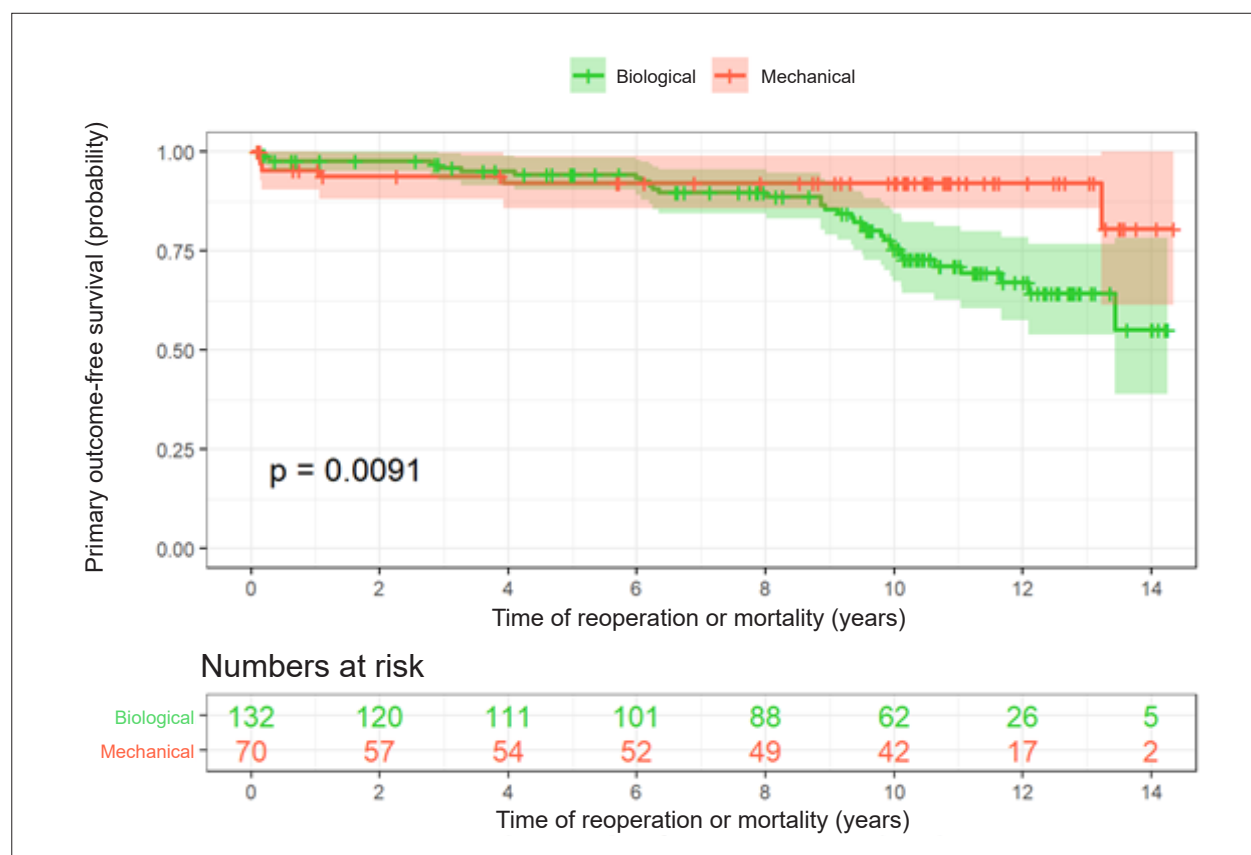


Figure 2 – Kaplan-Meier curve for primary outcome-free survival (death or reoperation).

is worth mentioning that reoperation rates do not accurately reflect the likelihood of structural valve degeneration, since some patients with significant structural deterioration are not candidates for reoperation due to high surgical risk.

Late mortality was similar between the two groups, with similar adjusted rates – 6.11% in patients with bioprosthesis and 7.93% in patients with mechanical prosthesis ($p=0.68$). However, more recent studies have reported mixed results, with a trend of lower mortality rates in patients with mechanical prosthesis, younger than 55 years.⁶

Bleeding occurred in patients of both groups; however, although the use of anticoagulation therapy was more frequent in patients with mechanical prosthesis than bioprosthesis (97.1% vs. 12.1%), bleeding was more frequent in the former group ($p=0.0064$). No case of fatal bleeding or hemorrhagic stroke was reported. Likewise, in the Veterans Affairs Cooperative Study, 575 patients were randomly assigned to receive either a mechanical valve or a biological one. The risk of bleeding in 11 years was significantly higher in patients with mechanical valves (42% versus 26%).⁷

In our cohort, there was no significant difference in the risk of endocarditis between biological and mechanical valve prostheses. The frequency of infections is usually similar between patients with the two types of valve prosthesis during the first postoperative year. In long-term follow-up, the incidence rates of endocarditis in patients with bioprosthesis

is comparable to or slightly higher than mechanical prosthesis, although available data are scarce.⁸

The literature has shown a higher incidence of valve prosthesis thrombosis among patients with mechanical than biological prosthesis and highlighted the need for continuous anticoagulation in these patients.⁹ This is in accordance with our results, as no statistically significant difference was found in the rate of thrombosis, with an adjusted rate of 5.06% for biological prosthesis and no case recorded for mechanical prosthesis. This may be explained by the fact that our patients were treated in a center specialized in anticoagulation. Chiquette et al.¹⁰ compared treatment with usual medical care and treatment at an anticoagulation center, and reported lower rates of thromboembolic events (minor, major and fatal events).¹⁰

There was no difference in the risk of ischemic stroke between the two groups (adjusted rate of 14.1% for the biological prosthesis versus 11.5% for mechanical prosthesis at 10 years; $p = 0.47$). Data in the literature suggested that the risk of thromboembolic complications is usually similar or lower in patients with biological prosthesis compared with patients with mechanical prosthesis and anticoagulation therapy. In an observational study, the cumulative risk of stroke in patients aged between 45 and 54 years undergoing aortic valve replacement was significantly lower (approximately 10% versus 16% at 15 years; HR = 0.64; 95%CI 0.46-0.86; $p <$

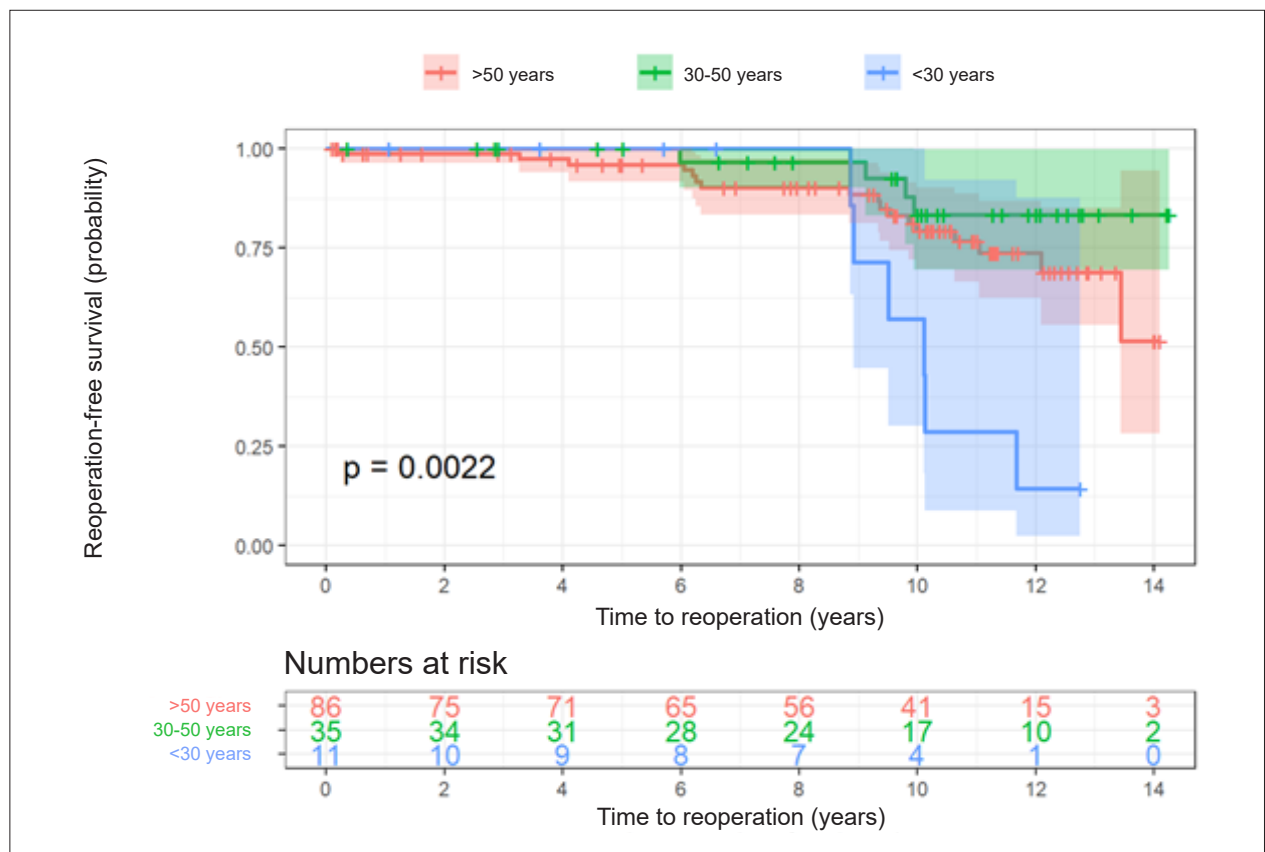


Figure 3 – Kaplan-Meier curve for reoperation-free survival by age groups (18-29 years, 30 - 49 years and ≥ 50 years).

0.05).⁶ The increased risk of stroke in our population may be explained by the high prevalence of comorbidities associated, absence of anticoagulation therapy among patients with atrial fibrillation, and lack of prothrombin time control of patients.

In addition, no difference was found in the risk of paravalvular leak between the aortic valves (biological and mechanical). The 10-year rate of paravalvular leak, adjusted for the censored data was 3.38% for the patients with mechanical prosthesis, which is corroborated by the literature, which reports an incidence of 2-10% in patients with aortic valve prostheses. As an example, studies using transesophageal echocardiography after heart valve replacement surgery, the incidence of paravalvular leak varied from 3% to 6%, with a statistical trend for a higher prevalence in patients with mechanical valve prostheses.¹¹

In our study, prosthesis-patient mismatch (PPM) was present in 3.76% of patients with bioprosthesis and in no patient with mechanical prosthesis and, for this reason, a simple descriptive analysis was performed. Data in the literature have reported higher incidence of PPM, ranging from 20% to 70%.¹² According to the meta-analysis by the European Heart Journal of 34 studies and a total of 27,186 patients, the presence of PPM was associated with a reduced long term survival (HR = 1.34, 95% CI = 1.18-1.51).¹³ IN the comparison between biological and mechanical prostheses, it is probable that

bioprosthesis is more prone to PPM, since the effective orifice area of mechanical prostheses is relatively larger due to the area occupied by the suture ring. In patients with a small aortic annulus, the effective orifice area is crucial to improve the hemodynamic performance of the prosthesis, and thereby prevent the occurrence of PPM. In some cases, patients with a small aortic annulus may benefit from a mechanical prosthesis.¹

In the present study, the mean waiting time for surgery was 202 days, with a wide range of distribution, which may be explained by the different indications for surgery and different characteristics of patients.

Study limitations

One limitation of the present study was its nonrandomized design, which limits the external validity of the results. However, the findings may serve as a basis for further analytical and prospective studies to obtain more consistent conclusions. Other caveats include the fact that this was a single center study, the insufficient sample size for rare events, and loss to follow-up.

In addition, we did not assess reoperation-related mortality, which may have underestimated mortality rates in the bioprosthesis group. Also, prothrombin time data were not evaluated, which makes it difficult to understand the high incidence of ischemic stroke in both groups.

Original Article

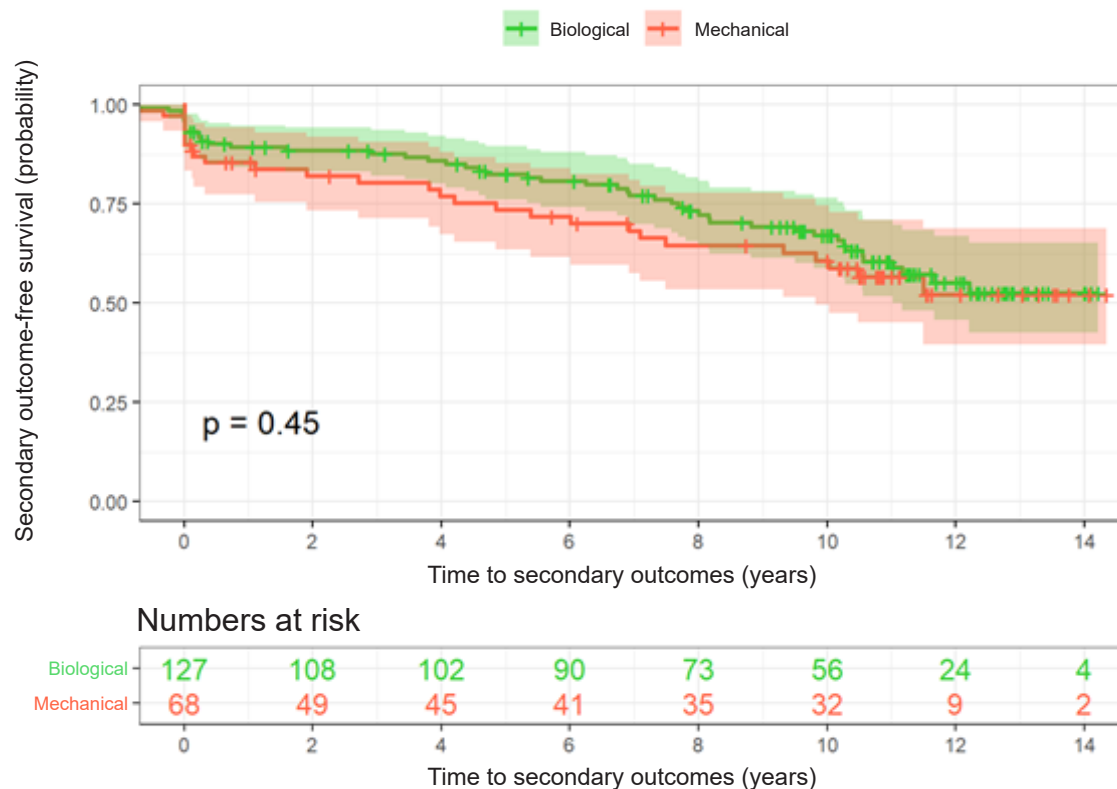


Figura 4 – Kaplan-Meier curve for secondary outcome-free survival (stroke, bleeding, endocarditis, thrombosis and paravalvular leak).

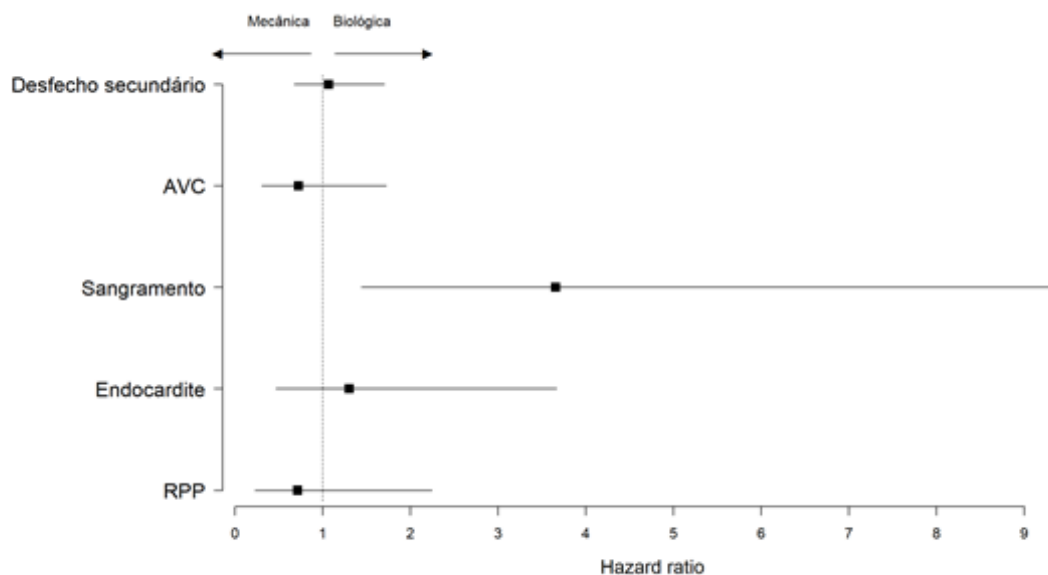


Figure 5 – Forest Plot of adverse effects by type of heart valve prosthesis (mechanical or biological).

Conclusion

The probability of overall mortality- and reoperation-free survival in patients with a mean age of 50 years undergoing heart valve replacement surgery in a public tertiary hospital in Sao Paulo State was significantly higher in patients with mechanical valve prosthesis at the expense of a greater durability of this type of prosthesis. No difference was seen in 10-year mortality or in combined adverse events between the groups. A greater need for reoperation was found in patients with bioprosthesis younger than 30 years old. Although no case of fatal bleeding was reported, bleeding was more frequent in patients with mechanical prosthesis than bioprosthesis.

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Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bruscky LVR, Gun C, Ramos AIO; Acquisition of data: Bruscky LVR; Analysis and interpretation of the data: Bruscky LVR, Gun C, Ramos AIO, Morais AL; Statistical analysis: Morais AL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

- Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. *Eur Heart J*. 2017;38(28):2183-91. doi:10.1093/eurheartj/ehx141
- Schnittman SR, Adams DH, Itagaki S, Toyoda N, Egorova NN, Chikwe J. Bioprosthetic aortic valve replacement: Revisiting prosthesis choice in patients younger than 50 years old. *J Thorac Cardiovasc Surg*. 2018;155(2):539-47.e9. doi:10.1016/j.jtcvs.2017.08.121
- Maria M, Passos B, Carneiro EM, Martins A, Alves M. Perfil Epidemiológico De Pacientes Submetidos À Cirurgia Cardíaca Em Hospital Universitário Do Piauí. 2017;8:173-7.
- Fernandes AMS, Bitencourt LS, Lessa IN. Impact of socio-economic profile on the prosthesis type choice used on heart surgery. *Rev Bras Cir Cardiovasc*. 2012;27(2):211-6. doi:10.5935/1678-9741.20120056
- Hammermeister KE, Henderson WG, Burchfiel CM. Comparison of Outcome After Valve Replacement With a Bioprosthesis Versus a Mechanical Prosthesis : Initial 5 Year Results of a Randomized Trial. 1987;10(4):919-32. doi:10.1016/S0735-1097(87)80263-2
- Goldstone AB, Chiu P, Baiocchi M. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. *N Engl J Med*. 2017;377(19):1847-57. doi:10.1056/NEJMoa1613792
- Lund O, Bland M. Risk-corrected impact of mechanical versus bioprosthetic valves on long-term mortality after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2006;132(1):20-6. doi:10.1016/j.jtcvs.2006.01.043
- Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S; for the Veterans Affairs Cooperative Study on Valvular Heart Disease. A comparison of outcomes in men 11 years after heart-valve-replacement with a mechanical valve or bioprosthesis. *N Engl J Med*. 1993;328(18):1289-96.
- Amsterdam EA, Wenger NK, Brindis RC, Casey Jr DE, Ganiats TG, Holmes Jr DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST- elevation acute coronary syndrome. *Circulation*. 2014;130(25):2354-94.
- Chiquette E, Amato MG, Bussey HI. Comparison of an Anticoagulation Clinic With Usual Medical Care. *Arch Intern Med*. 1998;158(15):1641-7. 2015;158:1641-7.
- Pinheiro CP, Rezek D, Costa EP, et al. Paravalvular regurgitation: Clinical outcomes in surgical and percutaneous treatments. *Arq Bras Cardiol*. 2016;107(1):55-62. doi:10.5935/abc.20160086
- Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: Definition, clinical impact, and prevention. *Heart*. 2006;92(8):1022-9. doi:10.1136/hrt.2005.067363
- Head SJ, Mokhles MM, Osnabrugge RLJ, et al. The impact of prosthesis/patient mismatch on long-term survival after aortic valve replacement: A systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J*. 2012;33(12):1518-29. doi:10.1093/eurheartj/ehs003



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Mechanical Prosthesis X Biological Prosthesis: an Individualized and Shared Decision

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Short Editorial related to the article: Late Outcomes of Aortic Valve Replacement with Bioprosthesis and Mechanical Prosthesis

Surgical valve interventions are performed primarily in patients with severe valve heart disease, with associated symptoms and/or anatomical/hemodynamic consequences, and no contraindication to the procedure. The choice of prosthetic valve should be based on a shared decision-making process that must account for the trade-offs between durability (and the need for reintervention), bleeding, and thromboembolism.

The manuscript: “Late Outcomes of Aortic Valve Replacement with Bioprosthesis and Mechanical Prosthesis”¹ is an observational retrospective study intended to evaluate the long-term follow-up of patients (n=202) who underwent aortic valve replacement, comparing biological (65.3%) and mechanical prostheses (34.7%). The patients were relatively young (mean age: 49 years), with predominantly degenerative aortic valve disease. On the other hand, 22% of the study population had rheumatic disease, the most prevalent etiology of valve disease in Brazil.²

The authors found no difference in mortality rates after 10 years of follow-up; however, the implantation of a mechanical prosthesis was associated with a lower rate of reoperation (with no reoperation in the mechanical prosthesis group). When analyzing specifically the bioprosthesis reoperations, patients under 30 years old had the highest rates, compared to those older than 50 years, and even to patients between 30 and 49 years of age. A recent meta-analysis found that younger age was a significant risk factor for aortic structural valve degeneration, besides body surface area, smoking and patient-prosthesis mismatch.³ In the present study, 50% of the subgroup of patients under 30 years old was reoperated in 10 years.

In the same direction, studies based on transthoracic echocardiogram follow-up estimate that approximately 30% of patients with a surgical aortic valve bioprosthesis develop evidence of valve dysfunction over 10 years after implantation, with young age (<60 years) being one of the risk factors associated with accelerated (<5 years) valve deterioration.⁴ The American College of Cardiology / American Heart Association Guideline for the management of valvular

heart disease recommends a transthoracic echocardiogram evaluation 5 and 10 years after the implantation of a bioprosthetic surgical valve, and an earlier evaluation if there are clinical symptoms or signs that suggest prosthetic valve dysfunction.⁵ However, patients typically remain asymptomatic until valve dysfunction is severe enough to result in adverse hemodynamic consequences or atrial fibrillation. However, in the present study, it was not clear whether this was the approach used, which could have delayed the diagnosis of a prosthesis dysfunction.

Bleeding risk was higher in the mechanical prosthesis group (20.97% x 5.38%), while there was no difference in the rates of stroke, paravalvular leak, thrombosis or endocarditis between the two groups. Interestingly, there was no thrombosis in the mechanical prosthesis group, even though two patients were not on oral anticoagulation therapy. Although it is an uncommon complication, valve thrombosis is more frequently observed in patients with mechanical prosthesis.⁶

There was no difference regarding the risk of ischemic stroke between the groups. However, the rates were relatively high (14.1% for bioprosthesis and 11.5% for mechanical prosthesis). It would be interesting and relevant to know whether those patients had documented atrial fibrillation before the occurrence of stroke and also if they were on oral anticoagulation therapy, an information not available in the study.

In general, this topic is very challenging and relevant. Despite the significantly higher rate of bioprosthetic structural valve deterioration observed in younger *versus* older patients, many younger patients choose to avoid receiving a mechanical prosthesis, either because they are unwilling to consider long-term warfarin therapy or due to the inconvenience of monitoring, pregnancy, dietary restrictions, medication interactions, and the need to restrict participation in some types of athletic activities. As mentioned before, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences. More recently, the availability of transcatheter procedures, with the growing experience with aortic valve-in-valve procedure, adds another issue to be taken into account when deciding the type of valve prosthesis. Transcatheter valve-in-valve aortic valve replacement has emerged as a less invasive alternative to redoing surgical replacement for inoperable or high-risk patients with degenerative bioprosthesis. A recent study showed that about 3 out of 4 patients survived after a median follow-up of 3 years, with valve hemodynamics remaining stable over time, and there was a low rate of clinically relevant structural valve disease, supporting the transcatheter aortic valve-in-valve procedure as an alternative to redoing surgical replacement for treating bioprosthetic aortic valve failure.⁷

Ultimately, one important limitation of the present study is the lack of information about time in therapeutic range for

Keywords

Bioprosthesis; Heart Valve Prosthesis Implantation/ complications; Heart Valve Prosthesis; Epidemiology; Aortic Valve; Rheumatic Fever.

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Short Editorial

patients receiving anticoagulation. The socioeconomic status has a great influence on treatment adherence. A Brazilian study showed that only approximately one-third of the patients showed an adequate anticoagulation level in more than half of the consultations.⁸

Because of its retrospective, nonrandomized, unicentric and observational design, the present study is insufficient to allow drawing robust conclusions. Even though, it addresses an important step of decision-making in valvular heart disease management.

References

1. Bruscky LVR, Gun C, Ramos AIO, AMorais AL. Late Outcomes of Aortic Valve Replacement with Bioprosthesis and Mechanical Prosthesis. *Arq Bras Cardiol.* 2021; 117(1):28-36.
2. Figueiredo ET, Azevedo L, Rezende ML, Alves CG. Rheumatic Fever: A Disease without Color. *Arq Bras Cardiol.* 2019 Jul 29;113(3):345-54.
3. Ochi a, Cheng K, Zhao B, Hardikar AA, Negishi K. Patient Risk Factors for Bioprosthetic Aortic Valve Degeneration: A Systematic Review and Meta-Analysis. *Heart, Lung and Circulation* 2020;29(5):668-78.
4. Chiang YP, Chikwe J, Moskowitz AJ. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA.* 2014;312(13):1323-9.
5. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021 Feb 2;77(4):e25-e197.
6. Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa VEE, Accorsi TAD, et al. Atualização das Diretrizes Brasileiras de Valvopatias – 2020. *Arq Bras Cardiol.* 2020; 115(4):720-75.
7. Guimaraes LFC, Uerena M, Wijeyesundera HC, Munoz-Garcia A, Serra V, Benitez L, et al. Long-Term Outcomes After Transcatheter Aortic Valve-in-Valve Replacement. *Circ Cardiovasc Interv* 2018 Sep;11(9):e007038.
8. Campos NL, Andrade RR, Silva MA. Oral anticoagulation in carriers of mechanical heart valve prostheses: experience of ten years. *Rev Bras Cir Cardiovasc.* Oct-Dec 2010;25(4):457-65.



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Clusters of Cardiometabolic Risk Factors and Their Association with Atherosclerosis and Chronic Inflammation among Adults and Elderly in Florianópolis, Southern Brazil

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Abstract

Background: The significant increase in cardiovascular diseases in developing countries alerts about their impact on underprivileged populations.

Objective: To identify the relationship of clusters of metabolic syndrome (MS) components with atherosclerosis and chronic inflammation among adults and elderly.

Methods: Cross-sectional analysis using data from two population-based cohort studies in Florianópolis, Southern Brazil (EpiFloripa Adult Cohort Study, n = 862, 39.9±11.5 years; EpiFloripa Aging Cohort Study, n = 1197, 69.7±7.1 years). Blood pressure (BP), waist circumference (WC), and lipid and glucose levels were analyzed as individual factors or as clusters (either as the number of components present in an individual or as combinations of components). Outcomes included carotid intima-media thickness (IMT), atherosclerotic plaques, and C-reactive protein (CRP) levels. Multiple linear and logistic regression analyses adjusted for confounding factors were used. The statistical significance adopted was 5%.

Results: Individuals with high BP, elevated WC, dyslipidemia and hyperglycemia (6.1% of the sample) showed higher IMT and CRP than those negatives for all MetS components. Elevated WC was a common determinant of systemic inflammation, while the coexistence of high BP and elevated WC (clusters of two or three factors) was associated with higher IMT (β between +3.2 and +6.1 $\times 10^{-2}$ mm; p value < 0.05) and CRP (β between 2.18 and 2.77; p value < 0.05).

Conclusion: The coexistence of high BP and elevated WC was associated with increased IMT and CRP levels, but central obesity affected systemic inflammation either alone or in combination with other risk factors.

Keywords: Cardiovascular Diseases; Adult; Aged; Epidemiology; Metabolic Syndrome; Lipid Metabolism Disorders; C-Reactive Protein; Risk Factors.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for an estimated 17.8 million deaths in 2017, corresponding to 330 million years of life lost and another 35.6 million years lived with disability.^{1,2} The World Health Organization estimates the number of cardiovascular deaths will reach 23.6 million by 2030, mainly because of heart disease and stroke.³ Approximately 75% of CVD are preventable, and an appropriate control of cardiometabolic risk factors (high blood pressure, body fat excess, high blood glucose, dyslipidemia) is crucial to reduce morbidity and mortality.³

The pathophysiological mechanism of the relationship between CVD and cardiometabolic risk factors involve chronic inflammation – high levels of C-reactive protein (CRP), interleukin-6, tumor necrosis factor- α – as well as micro and macrovascular changes.^{4,5} Biomarkers of chronic inflammation are directly related to the genesis of atherosclerosis, development of unstable plaques,⁶ and most CVD.⁷

According to the literature, some cardiometabolic risk factors are more atherogenic, and although clusters of these factors may coexist within the same individual, their combined effect on atherosclerosis and chronic inflammation has been barely investigated.⁸⁻¹⁰ The available evidence suggests that the atherogenic effect of cardiometabolic risk factors depends on which combination is affecting an individual and may be exacerbated by the coexistence of unhealthy lifestyle (e.g., smoking, sedentary lifestyle, inadequate eating habits).⁸⁻¹⁰ Therefore, identifying clusters of cardiometabolic risk factors with a strong atherogenic effect may contribute to the development of better-targeted preventive strategies. Investigations in this field are particularly relevant for low- and middle-income countries as, in absolute terms, early deaths related to CVD are concentrated in these countries.^{3,11}

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However, most studies investigating this topic have been performed in high-income settings.^{9,10}

Therefore, this study aims to identify the relationship of clusters of cardiometabolic risk factors with atherosclerosis and indicators of chronic inflammation, *i.e.*, carotid intima-media thickness (IMT), presence of atherosclerotic plaque, and C-reactive protein levels (CRP) at a population level, by using a community-based sample of adults and elderly individuals in Florianópolis, Southern Brazil.

Methods

This study has a cross-sectional design based on data from two population-based cohort studies (EpiFloripa Adult Cohort Study and EpiFloripa Aging Cohort Study). Both studies were conducted with individuals living in Florianópolis, a state capital in Southern Brazil. The city is predominantly urban (421,240 habitants, 59% adults), with a Municipal Human Development Index of 0.847 (third largest in Brazil) and life expectancy of 77.3 years.¹²

Details of both cohort studies can be found in previous publications.¹³⁻¹⁵ In summary, the baseline of the EpiFloripa Adult Cohort Study occurred in 2009, when 1,720 individuals aged 20-59 years were interviewed at home. Sampling was performed in two stages: initially 10 census tracts were systematically selected in each decile of family income (63/420 sectors in the city), and subsequently, 1,134/16,755 households in these sectors were also systematically selected. Considering an average of 1.78 adults per household, the sampling process would allow identifying 2,016 adults. Individuals who were amputated or bedridden, hospitalized,

or had any severe mental illness that prevented them from responding to the questionnaire were excluded. All adults included in the baseline were traced in 2012-2013 and 2014-2015 (second and third waves, respectively) (Figure 1). A total of 862 individuals were effectively evaluated in 2014-2015 (50.1% of the original cohort) at the premises of the Federal University of Santa Catarina (UFSC).

The baseline of the EpiFloripa Aging Cohort Study was conducted in 2009 (N=1,705; age range 60-104 years), and a second wave occurred in 2013/2014. The final sample size at baseline was estimated as 1,599 subjects and a similar two-stage cluster sampling strategy was employed. In this case, eight census tracts per decile of family income were selected in the first stage and 60 households in each of these sectors were selected during the second stage. This sampling method would yield a sample estimate of 1911, considering a mean of one elderly for every 2.51 households. All elderly people residing in the selected households were considered eligible for the study, except institutionalized ones. All these individuals were traced in 2013-2014, with a follow-up rate of 70.3% (n=1,197). Of these, 604 participants accepted to participate in clinical and imaging examinations and monitoring tests.

Ethics approvals for both studies were obtained from the Human Research Ethics Committees of the UFSC. All participants signed a consent form. In all cohort waves of the EpiFloripa Adult Cohort Study and the EpiFloripa Aging Cohort Study, equipment was previously calibrated, and interviewers were trained and standardized in the anthropometric measurement techniques (by inter- and intra-observer variability).¹⁶

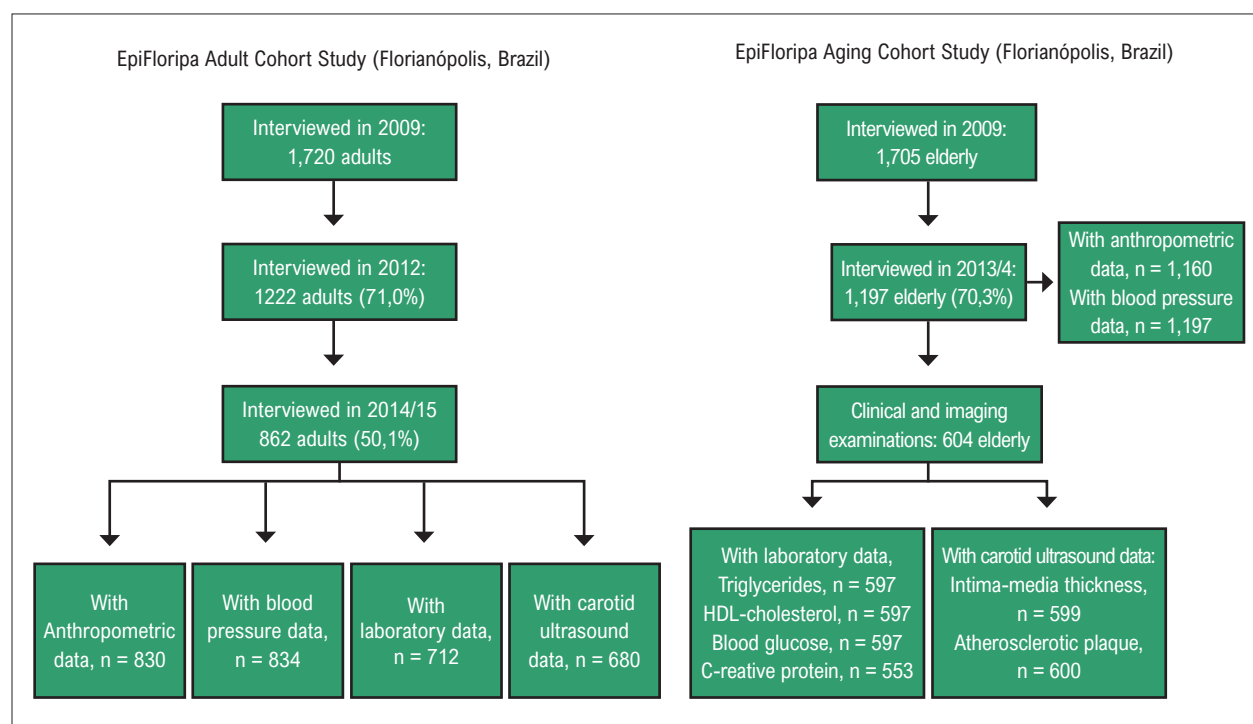


Figure 1 – Flowchart of the EpiFloripa Adult Cohort Study and EpiFloripa Aging Cohort Study and variables used in the present study.

Data collection, laboratory data, and imaging test

Anthropometric, laboratory and image data used in this article belong to the third wave of the EpiFloripa Adult Cohort Study and the second wave of the EpiFloripa Aging Cohort Study. Similar methods and equipment were used in both studies. Anthropometric measures (waist circumference [WC], height and body mass) were measured twice according to the recommendations of Lohman et al.,¹⁶ and the mean of two measurements was considered for the study.

WC was measured to the nearest 1 mm at the narrowest part of the trunk using an inextensible anthropometric tape, and height was measured to the nearest 1 mm using a stadiometer. Body mass was measured to the nearest 0,1 Kg using a digital scale (150 Kg capacity), calibrated before the study.

Blood pressure was measured in the sitting position, on the right arm using a pulse sphygmomanometer (Techline® digital read, São Paulo, Brazil), with the cuff at heart level. Blood pressure levels were measured twice, with a rest time of at least 15 minutes before and between measurements. When the difference between measurements was greater than 20 mmHg for systolic blood pressure or 10 mmHg for diastolic blood pressure, a third measurement was performed to replace the highest value. The mean of measurements was considered for analysis.

Blood samples were collected early in the morning after fasting for at least eight hours. Samples were stored and analyzed according to standard techniques of the Laboratory of Clinical Analysis (University Hospital, UFSC). Fasting blood glucose and lipid profile (triglycerides and high-density lipoproteins - HDL) were determined by colorimetric test, while CRP was determined by turbidimetry.

Carotid ultrasound was performed by a cardiologist using a portable ultrasound equipment Viamo™ (Toshiba Medical Systems, Tokyo, Japan) using a 5-11 MHz linear transducer. At least three IMT images of the common carotid artery were obtained on each side (right and left) and used the one with the best quality (quality index > 0.50). Carotid IMT measurements were analyzed using the M'Ath® software (version 3.1, METRIS Co., Argenteuil, France), which performs 100 automated measures per centimeter. The mean (in mm) of the left and right IMT was used in the analyses.¹⁷ The presence of atherosclerotic plaques (common carotid, carotid bulb, or ramifications in any side) was also identified during the imaging examination. Atherosclerotic plaque was defined as a focal structure encroaching at least 0.5 mm into the arterial lumen or having an arterial wall thickness ≥ 50% the surrounding IMT, with or without calcifications.^{18,19}

Outcomes

Three different outcomes were considered for this study: 1) carotid IMT (mean left and right IMT in millimeters, continuous symmetrical variable); 2) the presence of atherosclerotic plaque (binary variable, yes/no), and; 3) CRP levels (continuous variable analyzed as natural logarithm, $\ln$, due to its asymmetry).²⁰

Exposure: clusters of cardiometabolic risk factors

The joint criteria for definition of metabolic syndrome (MS) were used to establish the cutoff points of the different risk factors.²¹ Central obesity was defined as a WC > 80.0 cm in women and > 90.0 cm in men. High blood pressure was defined as a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg. Individuals who reported being diagnosed with hypertension by a physician and/or were taking antihypertensive drugs were also classified as hypertensive. Hyperglycemia was defined as a fasting blood glucose ≥ 100 mg/dl, self-report of a medical diagnosis of diabetes mellitus, and/or making use of antidiabetic medications.¹⁹ Participants were considered to have dyslipidemia when they had elevated triglycerides (≥ 150 mg/dL), low HDL (< 40 mg/dl in men and < 50 mg/dl in females), or reported use of antilipemic drugs.²¹

Each MS component was analyzed either as an independent exposure variable or as a cluster. Two different variables were generated to identify clusters. The first variable considered the number of positive cardiometabolic risk factors within the same individual (0, 1, 2, 3 or 4 MetS components). The second one combined the four independent variables into 16 possible combinations: negative for all risk factors, positive for only one factor (four possible combinations), two-factor cluster (six possible combinations), three-factor cluster (four possible combinations) or positive for all cardiometabolic risk factors.

Sociodemographic and lifestyle variables

Sociodemographic and lifestyle data were included as possible confounding factors. Most of these variables were collected during the third wave of the EpiFloripa Adult Cohort Study (2014/2015) and second wave of the EpiFloripa Aging Cohort Study (2013/2014): sex (male or female); age in years; education attainment (0-8, 9-11, ≥12 years of schooling); *per capita* family income (including all sources of income and divided by the number of family members) distributed in tertiles (1st tertile = <R\$ 900.00; 2nd tertile = R\$ 907.33 to R\$ 2,122.00; 3rd tertile = >R\$ 2,125.00 ; 1 USD = R\$ 3.14 in 2015). Smoking was analyzed as never smoked, former smoker or smoker, regardless of intensity and frequency. A validated questionnaire was used to evaluate physical activity in each cohort.^{22,23} The adults were considered active when they reported ≥ 30 minutes of moderate-intensity physical activity on five or more days per week or vigorous-intensity activities for at least 20 minutes on three or more days per week.²⁴ Older adults were considered physically active when performed ≥ 150 minutes of physical activity/week. Data on energy intake from alcohol, saturated fat, sugar, fiber and sodium intake were obtained by two 24-hour food recalls, and information was extracted using procedures recommended in the literature, with adjustments for intra- and inter-individual variability.²⁵ Consumption of saturated fats and fiber were transformed into $\ln$ due to their asymmetric distribution.

Statistical analysis

Symmetric, continuous variables were described as mean and standard deviation, and asymmetric variables as median and interquartile range (p25-p75). Geometric mean was also

estimated for CRP. Histograms and Q-Q plots were used to verify the normality of continuous variables. Categorical variables were presented as percentages (%). Depending on the nature of the investigated variables, the chi-square test, t-test for independent samples, or the Mann-Whitney test was used to identify possible differences between cohort members evaluated (or not) in the last wave, as compared to the baseline. Although the literature has reported an important relationship between increased years of life and cardiometabolic risk,²⁰ considering the outcomes of the present study (IMT, carotid plaque and CRP), interactions between all cardiometabolic risk variables (analyzed individually or as clusters) with age were tested. However, in the present study, a possible effect of age was detected only on CRP and dyslipidemia ($p = 0.61$).²⁶ Thus, to maintain statistical power to test the associations of interest in this study, the analyses were not stratified by age.

To evaluate the most prevalent clusters of cardiometabolic risk factors, the ratio between the observed and expected prevalence (O/E ratio) for each of the 16 possible combinations was estimated.²⁷ The expected prevalence was calculated by multiplying the observed probability of each risk factor, assuming that they occur independently in the population. An O/E ratio > 1.2 was used to identify highly prevalent clusters (i.e., higher than a random occurrence).²⁷

Linear regression models were used to test associations between the clusters of cardiometabolic risk factors (independent variables) and IMT and natural logarithm of CRP (lnCRP). Results were presented as regression coefficients (β) with the respective standard error (SE). For lnCRP, β was transformed into the exponential form ($_{\text{EXP}}\beta$) and was interpreted as the percentage increase in serum CRP levels in relation to the geometric mean of those without any cardiometabolic risk factor. Assumptions of linearity for continuous variables, constant variance of standardized residuals, and goodness of fit of the model were assessed by plotting residuals against fitted values.

Logistic regression was used to analyze the presence of atherosclerotic plaque as an outcome, and results were

expressed as odds ratio (OR) with their respective SE. All analyses were adjusted for all possible confounders (sociodemographic and lifestyle variables),²⁰ regardless of their level of statistical significance in the association with the outcomes.

Data analysis was conducted in the statistical software Stata 13.0 (StataCorp LP, College Station, USA), considering sampling weights, i.e., probability of selection at baseline and probability of location during follow-up, re-weighted to the estimated population of Florianópolis by sex and age group¹² and the survey design in each study. (A p value < 0.05 denoted statistical significance.

Results

Comparisons between cohorts

In the EpiFloripa Adult Cohort Study, 862 individuals were interviewed in 2014-15 (50.1% of the original cohort) (Table 1). Family income and smoking status of participants were comparable with those of the baseline sample (2009). In the EpiFloripa Aging Cohort Study, 1,197 elderly were interviewed in 2013/14 (70.3%), who showed comparable data of sex, family income and smoking status to the baseline sample (2009).

Data of the outcomes of the present study were available in 1,301 participants in both studies combined, and results are described below. The mean IMT was 0.64 mm (± 0.15) and the median CRP was 1.34 mg/L (p25-p75 0.61, 3.48; geometric mean 2.64 mg/L). Also, 27.7% of participants had carotid plaques.

Prevalence of cardiovascular risk factors and multivariate risk assessment

The prevalence of central obesity and elevated blood pressure levels was 56.8% and 71.5%, respectively; 17.7% of participants had dyslipidemia and 22.4% hyperglycemia (Table 2). Combined, 6.1% of the sample was positive for all four factors, while 21.8% had no MS component.

Table 1 – Comparison of baseline characteristics of participants in the EpiFloripa Adult Cohort Study in 2009 (n = 1720) versus participants recruited in 2014/15 (n = 862), and participants in the EpiFloripa Aging Cohort Study in 2009 (n = 1705) versus 2013/14 (n = 1197)

Variables*	EpiFloripa Adult Cohort Study			EpiFloripa Aging Cohort Study		
	2009 (n=1,720)	2014/15 (n=862)	p value	2009 (n=1,705)	2013/14 (n=1197)	p value
Sex: male	44.3	42.5	0.03 [†]	37.5	36.9	0.36 [†]
Age in years: mean $\pm$ SD	38.1 $\pm$ 11.6	39.9 $\pm$ 11.5	< 0.01 [†]	70.5 $\pm$ 7.9	69.7 $\pm$ 7.1	< 0.01 [†]
Per capita Family income (R\$): Median [p25-p75]	900 [500-1750]	900 [500-1667]	0.55 [§]	767 [380-1600]	800 [400-1667]	0.09 [§]
Smoking						
Never smoked	54.7	55.8	0.05 ^{//}	59.6	60.2	0.53 ^{//}
Former smoker	26.1	27.7		32.0	31.1	
Smoker	19.2	16.5		8.4	8.7	

*: Considering information obtained in 2009; †: 1 USD = R\$ 1.70 in 2009; ‡: T- test; §: Mann-Whitney test; //: Chi-square test.

Considering each MS component as an independent variable, high blood pressure and hyperglycaemia were associated with a higher IMT. High blood pressure and dyslipidemia were associated with the presence of atherosclerotic plaque, whereas central obesity and dyslipidemia were related to higher lnCRP levels.

Table 2 also shows there was a direct trend between the number of cardiometabolic risk factors present in the same individual and the three outcomes (p-value for trend < 0.05 in all cases) (Table 2).

Prevalence of combinations of MS components

The observed prevalence for the coexistence of the four risk factors in the same individual was 6.1%, 410% higher (O/E ratio = 5.1) than it would be expected at random. For the simultaneity of three risk factors, all combinations with central obesity presented an O/E ratio > 1.2. The simultaneous presence of central obesity and elevated blood pressure (20.5%) and the isolated presence of elevated blood pressure (19.5%) were the most frequent combinations of two and one risk factors, respectively. However, even among these combinations, the O/E ratio was < 1.0. Finally, the observed prevalence of patients with none of the cardiometabolic risk factors was 110% higher than the expected prevalence. (Table 3).

Associations between clusters of MS components and the investigated outcomes

Table 4 shows the association between the 16 combinations of cardiometabolic risk factors and the investigated outcomes. All clusters including central obesity and high blood pressure (i.e. clusters of two, three, or four factors) showed higher IMT

and lnCRP than individuals without any risk factor. On the other hand, central obesity was a common factor in the determination of systemic inflammation, since a higher lnCRP was observed in all combinations including that risk factor. Except for central obesity, the isolated presence of one risk factor was not associated with any of the investigated outcomes. Other clusters showed a low prevalence (< 1%) to allow robust conclusions. Conversely, although the highest O/E was for the coexistence of the four risk factors, the associations with the investigated outcomes were not stronger than the three-component clusters. None of the clusters was associated with a higher frequency of carotid plaque.

Discussion

According to the available literature, this is the first population-based study conducted in Latin America aiming to investigate the relationship between clusters of cardiometabolic risk factors and indicators of atherosclerosis and chronic inflammation. In agreement with our results, similar studies conducted in Iceland, Cyprus and Spain^{18,28,29} identified that specific MS components are associated with increased carotid IMT, presence of atherosclerotic plaque, and increased CRP levels. However, none of these studies addressed the effects of combinations of MS components.

According to our findings, IMT and CRP levels increased with the number of MS risk factors present in the same individual. Similar findings were reported in cross-sectional population-based studies investigating adults and older people in Cyprus (IMT)²⁹ and Spain (CRP).²⁸ Furthermore, a population-based cohort study carried out in Finland³⁰ and another study with employees from six public universities in Brazil³¹ reported that the “additive” effect of MS components on carotid IMT was stronger than the effect of

Table 2 – Results adjusted for the association of cardiometabolic risk factors with the carotid intima-media thickness, presence of carotid plaque and C-reactive protein levels among adults and older adults in the EpiFloriap Cohort Study (2014/15) and EpiFloriap Aging Cohort Study (2013/2014) (n= 1,301)

	%	IMT (mm)	Carotid plaque	lnCRP
		β (SE) [‡]	OR (SE)	β (SE) [§] _{EXP}
Individual risk factors*				
Central obesity (% yes)	56.8	0.6 (0.8)	0.69 (0.14)	1.86 (0.15) [¶]
Elevated blood pressure (% yes)	71.5	2.4 (0.7) [¶]	2.12 (0.51) [¶]	1.09 (0.12)
Dyslipidemia (% yes)	17.7	1.9 (1.1)	1.67 (0.43) [¶]	1.12 (0.11)
Hyperglycemia (% yes)	22.4	2.9 (0.9) [¶]	1.21 (0.24)	1.22 (0.10) [¶]
Number of positive risk factors [†]				
None//	21.8	59.1±8.8 [#]	27.7% [#]	0.88±1.5 [#]
1	27.6	1.6 (0.8)	1.02 (0.35)	1.37 (0.20)
2	27.1	3.0 (1.0)	1.53 (0.64)	2.07 (0.28)
3	17.4	5.5 (1.1)	1.88 (0.78)	2.76 (0.41)
4	6.1	7.5 (2.3)	2.01 (0.96)	2.17 (0.33)

IMT: carotid intima-media thickness; lnCRP: natural logarithm of C-reactive protein; SE: standard error; mm: millimetres. * – Results adjusted for sex, age, family income, educational level, smoking, nutritional variables (intake of saturated fat, sugar, alcohol, fibre, and sodium), physical activity level, and mutual adjustment between individual risk factors. † Results adjusted for sex, age, family income, educational level, smoking, nutritional variables (intake of saturated fat, sugar, alcohol, fibre, and sodium), and physical activity level ‡ – Results presented as power (10²). § – Results interpreted as increment percentage of geometric mean. // – Mean ± SD or prevalence in the reference category (“none”). ¶ – p-value <0.05 in comparison with the reference category. # – p-value for trend <0.05.

Table 3 – Prevalence of combinations of metabolic syndrome components among adults and older adults in the EpiFloripa Cohort Study (2014/15) and EpiFloripa Aging Cohort Study (2013/2014) (n= 1,301)

Risk Factor	Central obesity	Elevated blood pressure	Dyslipidemia	Hyperglycemia	n	Prevalence		
						Observed % (95% CI)	Expected %	O/E
4	+	+	+	+	112	6.1 (4.9-7.6)	1.2	5.1
3	+	+	+	-	68	5.9 (4.6-7.5)	4.3	1.4
	+	+	-	+	209	10.2 (8.1-12.6)	5.7	1.8
	+	-	+	+	09	0.7 (0.3-1.6)	0.5	1.4
	-	+	+	+	10	0.7 (0.3-1.5)	1.6	0.4
2	+	+	-	-	309	20.5 (17.5-23.8)	19.7	1.0
	+	-	+	-	10	0.8 (0.3-1.8)	1.7	0.5
	+	-	-	+	17	1.1 (0.6-2.1)	2.3	0.5
	-	+	+	-	19	2.4 (1.4-4.4)	5.6	0.4
	-	+	-	+	37	1.8 (1.1-2.9)	7.5	0.2
	-	-	+	+	05	0.4 (0.1-1.0)	0.6	0.7
1	-	-	-	+	17	1.5 (0.8-2.7)	3.0	0.5
	-	-	+	-	11	0.8 (0.4-1.4)	2.2	0.4
	-	+	-	-	202	19.5 (16.2-23.2)	25.9	0.8
	+	-	-	-	70	5.8 (4.4-7.6)	7.8	0.7
0	-	-	-	-	196	21.8 (18.7-25.1)	10.3	2.1

CI: confidence interval; + presence of risk factor; - absence of risk factor; O: observed prevalence; E: expected prevalence; O/E: ratio between observed and expected prevalence.

each single component. This may be due to the coexistence of harmful habits³²⁻³⁴ or genetic predisposition³⁵ that could facilitate the development of these factors and increase their atherogenic and inflammatory potential. Moreover, some of the two and three-component clusters had a stronger association with IMT and CRP than the coexistence of the four MS risk factors.

According to the literature, the deleterious effect of these clusters on the development of CVD results of the combination of diverse pathophysiological mechanisms, including 1) high concentration of local and systemic inflammatory markers as a consequence of body fat excess; 2) increased flow variation and oscillation of tensions within the vessel due to high blood pressure, with consequent endothelial dysfunction and arterial stiffness; 3) elevated circulating level of free fatty acids and low-density lipoprotein (LDL) cholesterol, which implies in increased toxicity to the endothelium and adjacent smooth muscle, and 4) blood vessel wall injury caused by lipoprotein glycation resulting from high blood glucose levels.³⁶ All these factors promote the attraction and accumulation of activated macrophages, mast cells and T-cells in the growing atherosclerotic lesion, as well as greater arterial stiffness and systemic inflammation.³⁶

Although the literature highlights that insulin resistance and obesity play a central role in the development of MS and CVD,^{18,36,37} high blood pressure was also found in our study as a central determinant of inflammation and atherosclerosis. Higher IMT or CRP levels were observed in all combinations that included

high blood pressure and abdominal obesity. From a public health perspective, these findings are worrisome as one-third of individuals (i.e., the combination of all clusters including these two factors: 18.3% + 6.6% + 5.2% + 4.3% = 34.4%) would be at increased risk of CVD due to higher IMT.

In addition, abdominal obesity was a common risk factor for systemic inflammation in this study. Similar results were observed among adults and elderly in Portugal, abdominal obesity was the most important determinant of systemic inflammation either individually or in combination with other cardiometabolic risk factors.³⁸ This finding reinforces the idea that chronic subclinical inflammation among individuals with central obesity contributes to atherosclerosis, regardless of the coexistence of insulin resistance or dyslipidemia.⁶

On the other hand, when assessed as individual risk factors rather than as clusters, the presence of atherosclerotic plaque was 1.7-2.1 more likely among those with dyslipidemia or high blood pressure. Other population-based studies have identified similar findings.^{18,39,40} Longitudinal studies not only showed that increased systolic pressure and dyslipidemia are independent risk factors for the development of atherosclerotic plaque,^{39,41} but vasodilation and prolonged use of lipid-lowering drugs have a protective effect on their progression.⁴¹

In cluster analysis, the reduced number of individuals in some clusters and the investigation of a binary outcome probably affected the power of the study to identify associations.⁴² However,

Table 4 – Adjusted association* of clusters of metabolic syndrome components with carotid intima-media thickness, presence of carotid plaque and C-reactive protein levels among adults and older adults in the EpiFloripa Cohort Study (2014/15) and EpiFloripa Aging Cohort Study (2013/2014) (n= 1301)

	n	%	IMT (mm)	Carotid plaque	lnCRP
			β (SE) [‡]	OR (SE)	β (SE) [§] _{EXP}
All negative	196	21.8	59.9±8.8 ^{//}	11.6% ^{//}	0.86±1.5 ^{//}
Positive for one risk factor only					
Central obesity	70	5.8	0.4 (1.3)	0.24 (0.13)	2.01 (0.38) [†]
Elevated blood pressure	202	19.5	1.7 (0.9)	1.48 (0.53)	1.19 (0.18)
Dyslipidemia	11	0.8	2.7 (1.9)	0.92 (0.85)	1.92 (0.76)
Hyperglycaemia	17	1.5	3.7 (2.3)	0.71 (0.66)	1.21 (0.37)
Two-components clusters					
Central obesity + elevated blood pressure	309	20.5	3.2 (0.9) [†]	1.31 (0.54)	2.18 (0.32) [†]
Central obesity + Dyslipidemia	10	0.8	-1.4 (1.9)	1.08 (1.04)	3.63 (0.90) [†]
Central obesity + Hyperglycemia	17	1.1	-1.7 (4.6)	0.69 (0.59)	2.24 (0.88) [†]
Elevated blood pressure + Dyslipidemia	19	2.5	5.3 (4.2)	3.14 (2.44)	1.03 (0.27)
Elevated blood pressure + Hyperglycemia	37	1.8	0.8 (3.4)	1.80 (0.88)	2.23 (0.74) [†]
Dyslipidemia + Hyperglycemia	05	0.4	9.4 (4.2) [†]	-	4.20 (1.31) [†]
Three-components clusters					
Central obesity + Elevated blood pressure + Dyslipidemia	68	5.9	3.9 (1.5) [†]	2.15 (1.07)	2.77 (0.48) [†]
Central obesity + Elevated blood pressure + Hyperglycemia	209	10.2	6.1 (1.4) [†]	1.58 (0.70)	2.83 (0.42) [†]
Central obesity + Dyslipidemia + Hyperglycemia	09	0.7	5.3 (7.3)	1.36 (1.81)	4.06 (1.44) [†]
Blood pressure + Dyslipidemia + Hyperglycemia	10	0.6	11.1 (4.6) [†]	3.01 (2.78)	1.88 (0.84)
Positives for the four risk factors	112	6.1	7.4 (2.3) [†]	1.92 (0.91)	2.21 (0.34) [†]

IMT: carotid intima-media thickness; CRP: natural logarithm of C-reactive protein; SE: standard error; mm: millimeters. *Results adjusted for sex, age, family income, educational level, smoking, nutritional variables (intake of saturated fat, sugar, fibre, and sodium) and physical activity level. † – p-value < 0.05 in comparison with the reference category, indicating a higher outcome in that group. ‡ – results presented as power (10-2). § – Results should be interpreted as increment percentage of geometric mean. // – Mean ± SD or prevalence in the reference category ("all negative").

previous studies have identified a consistent relationship between obesity, inflammation, and atherosclerosis.⁴³ Further research including longitudinal analyses and larger samples is necessary to corroborate these findings.

Despite the strengths of the study (population-based sample from a middle-income country, the use of measured data and not only self-reported, and calibrated equipment to increase data accuracy), some limitations need to be highlighted. First, the cross-sectional design limits causal inferences, although longitudinal studies have shown consistent results.^{39,41} Second, the insufficient number of individuals in some clusters reduced the statistical power of the study, especially for testing the associations with binary outcomes. Third, despite the considerable percentage losses to follow-up, it is unlikely that it biased our results, as the characteristics of the investigated sample were similar to those at the baseline.

Conclusion

In conclusion, our findings showed that the coexistence of elevated blood pressure and central obesity was associated with

increased IMT and CRP levels. Central obesity affected systemic inflammation either alone or in combination with other risk factors. Moreover, some two- and three-component clusters showed stronger associations with IMT and CRP levels compared with four-component clusters. The investigation of MS components as independent and unrelated variables could undermine the identification of risk factor cluster with greater atherogenic or inflammatory potential and, consequently, of individuals at a higher risk of CVD. These findings may help clinicians and public health policymakers to define better strategies to reduce morbidity and mortality associated with these conditions.

Author Contributions

Conception and design of the research: Lima TR, Silva DAS, González-Chica DA; Acquisition of data and Statistical analysis: Lima TR, Silva DAS, D'Orsi E, González-Chica DA; Analysis and interpretation of the data: Lima TR, Silva DAS, Giehl MWC, González-Chica DA; Obtaining financing: D'Orsi E, González-Chica DA; Writing of the manuscript: Lima TR, Silva DAS; Critical revision of the manuscript for intellectual content: Silva DAS, Giehl MWC, D'Orsi E, González-Chica DA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-88.
2. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1859-922.
3. World Health Organization. About cardiovascular diseases, 2019. Geneva: WHO; 2019. [acesso 19 dec. 2019]. Disponível em: <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-cvds>.
4. Chantler PD, Frisbee JC. Arterial function in cardio-metabolic diseases: from the microcirculation to the large conduits. *Prog Cardiovasc Dis*. 2015;57(5):489-96.
5. Labazi H, Trask AJ. Coronary microvascular disease as an early culprit in the pathophysiology of diabetes and metabolic syndrome. *Pharmacol Res*. 2017 Sep;123:114-21.
6. Wilson AM, Ryan MC, Boyle AJ. The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen. *Int J Cardiol*. 2006;106(3):291-7.
7. Kuo F, Gardener H, Dong C, Cabral D, Della-Morte D, Blanton SH, et al. Traditional cardiovascular risk factors explain the minority of the variability in carotid plaque. *Stroke*. 2012;43(7):1755-60.
8. Rosvall M, Persson M, Östling G, Nilsson P, Melander O, Hedblad B, et al. Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: The Malmö Diet and Cancer Study. *Atherosclerosis*. 2015;239(2):615-21.
9. Selvarajah S, Haniff J, Kaur G, Hiong TG, Cheong KC, Lim CM, et al. Clustering of cardiovascular risk factors in a middle-income country: a call for urgency. *Eur J Prev Cardiol*. 2013;20(2):368-75.
10. Wang X, Dalmeijer GW, den Ruijter HM, Anderson TJ, Britton AR, Dekker J, et al. Clustering of cardiovascular risk factors and carotid intima-media thickness: The USE-INT study. *PLoS One*. 2017;12(3):e0173393.
11. Hunter DJ, Reddy KS. Noncommunicable diseases. *N Engl J Med*. 2013;369(14):1336-43.
12. Atlas of Human Development in Brazil. United Nations Development Program. [acesso 17 dec. 2019]. Disponível em: <http://www.atlasbrasil.org.br/perfil>.
13. Boing AC, Peres KG, Boing AF, Hallal PC, Silva NN, Peres MA. EpiFloripa Health Survey: the methodological and operational aspects behind the scenes. *Rev Bras Epidemiol*. 2014;17(1):147-62.
14. Peres MA, Peres KG, Boing AF, Bastos JL, Silva DA, González-Chica DA, et al. Oral health in the EpiFloripa: a prospective study of adult health in Southern Brazil. *Rev Bras Epidemiol*. 2014;17(2):571-5.
15. Tessari AA, Giehl MWC, Schneider IJC, González-Chica DA. Anthropometric measures change and quality of life in elderly people: a longitudinal population-based study in Southern Brazil. *Qual Life Res*. 2016;25(12):3057-66.
16. Lohman T, Roche A, Martorell R. Anthropometric Standardization Reference Manual. 2nd ed. Champaign: Human Kinetics Books; 1998.
17. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21(2):93-111.
18. Sturlaugsdottir R, Aspelund T, Björnsdottir G, Sigurdsson S, Thorsson B, Eiriksdottir G, et al. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. *BMJ Open*. 2016;6(11):e012457.
19. Wang A, Wu L, Liu X, Su Z, Luo Y, Chen S, et al. The prevalence of carotid plaque with different stability and its association with metabolic syndrome in China: The Asymptomatic Polyvascular Abnormalities Community study. *Medicine*. 2016;95(34):e4619.
20. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Int J Behav Med*. 2012;19(4):403-88.
21. Alberti K, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-5.
22. Moura EC, Morais Neto OL, Malta DC, Moura L, Silva NN, Bernal R, et al. Surveillance of risk-factors for chronic diseases through telephone interviews in 27 Brazilian cities (2006). *Rev Bras Epidemiol*. 2008;11(suppl 1):20-37.
23. Benedetti TB, Mazo GZ, Barros MVG. Application of the International Physical Activity Questionnaire (IPAQ) for evaluation of elderly women: concurrent validity and test-retest reproducibility. *Rev Bras Ciênc. Mov*. 2004;12(1):25-34.

24. Florindo AA, Hallal PC, Moura EC, Malta DC. Practice of physical activities and associated factors in adults, Brazil, 2006. *Rev Saúde Pública*. 2009;43(Suppl 2):65-73.
25. Dodd KW, Guenther PM, Freedman LS, Subar AF, Kipnis V, Midthune D, et al. Statistical methods for estimating usual intake of nutrients and foods: a review of the theory. *J Am Diet Assoc*. 2006;106(10):1640-50.
26. Katz MH. *Multivariable analysis: a practical guide for clinicians and public health researchers*. Cambridge: Cambridge University Press; 2011.
27. Schuit AJ, Loon AJM, Tijhuis M, Ocké MC. Clustering of lifestyle risk factors in a general adult population. *Prev Med*. 2002;35(3):219-24.
28. Martínez MA, Puig JG, Mora M, Aragón R, O'Dogherty P, Antón JL, et al. Metabolic syndrome: prevalence, associated factors, and C-reactive protein: the MADRIC (MADrid Riesgo Cardiovascular) Study. *Metabolism*. 2008;57(9):1232-40.
29. Panayiotou AG, Griffin M, Kouis P, Tyllis T, Georgiou N, Bond D, et al. Association between presence of the metabolic syndrome and its components with carotid intima-media thickness and carotid and femoral plaque area: a population study. *Diabetol Metab Syndr*. 2013;5(1):44.
30. Koskinen J, Kähönen M, Viikari JS, Taittonen L, Laitinen T, Rönnemaa T, et al. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. *Circulation*. 2009;120(3):229-36.
31. Santos IS, Alencar AP, Rundek T, Goulart AC, Barreto SM, Pereira AC, et al. Low Impact of Traditional Risk Factors on Carotid Intima-Media Thickness: The ELSA-Brasil Cohort. *Arterioscler Thromb Vasc Biol*. 2015;35(9):2054-9.
32. Cena H, Fonte ML, Turconi G. Relationship between smoking and metabolic syndrome. *Nutri Rev*. 2011;69(12):745-53.
33. González-Chica DA, Dal Grande E, Bowden J, Musker M, Hay P, Stocks N. Are we reducing the risk of cardiovascular disease and improving the quality of life through preventive health care? Results of a population-based study in South Australia. *Prev Med*. 2017 Jun;99:164-70.
34. Strasser B. Physical activity in obesity and metabolic syndrome. *Ann N Y Acad Sci*. 2013;1281(1):141-59.
35. Lin HF, Boden-Albala B, Juo S, Park N, Rundek T, Sacco R. Heritabilities of the metabolic syndrome and its components in the Northern Manhattan Family Study. *Diabetologia*. 2005;48(10):2006-12.
36. Gallagher EJ, Leroith D, Karnieli E. The metabolic syndrome-from insulin resistance to obesity and diabetes. *Med Clin North Am*. 2011;95(5):855-73.
37. Lou Y, Li B, Su L, Mu Z, Sun M, Gu H, et al. Association between body mass index and presence of carotid plaque among low-income adults aged 45 years and older: a population-based cross-sectional study in rural China. *Oncotarget*. 2017;8(46):81261-72.
38. Santos A, Lopes C, Guimaraes JT, Barros H. Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. *Int J Obes*. 2005;29(12):1452-6.
39. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study. *Stroke*. 2012;43(7):1818-23.
40. Rundek T, Gardener H, Della-Morte D, Dong C, Cabral D, Tiozzo E, et al. The relationship between carotid intima-media thickness and carotid plaque in the Northern Manhattan Study. *Atherosclerosis*. 2015;241(2):364-70.
41. Herder M, Arntzen KA, Johnsen SH, Eggen AE, Mathiesen EB. Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008. *Arterioscler Thromb Vasc Biol*. 2013;33(4):858-62.
42. Martinez-Mesa J, Gonzalez-Chica DA, Bastos JL, Bonamigo RR, Duquia RP. Sample size: how many participants do I need in my research? *An Bras Dermatol*. 2014;89(4):609-15.
43. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6(6):399-409.



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The Importance of Recognizing the Co-Occurrence of Cardiometabolic Risk Factors in the Population to Establish Priorities in Public Policies

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Short Editorial related to the article: Clusters of Cardiometabolic Risk Factors and Their Association with Atherosclerosis and Chronic Inflammation among Adults and Elderly in Florianópolis, Southern Brazil

Cardiometabolic disease (CMD) is the leading cause of morbidity and mortality around the globe.¹ Metabolic syndrome (MS) is a collection of risk factors for metabolic disease, including elevated blood pressure, hypertension, hyperglycemia, dyslipidemia, and obesity. When these risk factors are present in combination, the likelihood of future cardiovascular issues increases more than when any of these risks is present alone.²

MS has an estimated frequency between 20% and 25% in the adult population worldwide, and the prevalence increases with age.^{3;4}

In a cross-sectional population-based investigation using laboratory data from the 2014–2015 National Health Survey, the prevalence of Metabolic Syndrome (MS) was estimated to be 38.4% in the Brazilian population.⁵ According to the National Health Survey, subgroups that are sociodemographically vulnerable and have unhealthy lifestyles have a higher prevalence of MS.^{6;7}

Previous research has established associations between inflammatory indicators, atherosclerosis, and MS components.^{8;9} It is critical to understand the co-occurrence of cardiometabolic risk factors and their association with chronic inflammation and atherosclerotic disease to better control risk factors in a multifaceted way.

Based on this, Lima et al.¹⁰ aimed to characterize clusters of cardiometabolic risk factors and their relationship with atherosclerosis and chronic inflammation in adults and the elderly living in southern Brazil. A census-based, cross-sectional analysis of data from two population cohorts of adults and elderly (EpiFloripa Adult and Aging Cohort Studies) was conducted to determine the association between variables such as blood pressure, waist circumference, laboratory tests of lipid and glucose profile, isolated or in combination, with the outcomes of carotid intima-media thickness, atherosclerotic plaques, and serum levels of – C-reactive protein.

Keywords

Metabolic Syndrome X; Morbimortality; Risk Factors; C- Reactive Protein; Carotid Intima-Media Thickness; Hypertension; Obesity; Diabetes Mellitus; Public Health.

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The study showed that individuals with the metabolic syndrome components in groups were related with increased carotid artery thickness and C-reactive protein levels, as compared to individuals without MS. Increased waist circumference was a prevalent predictor of inflammation, and the clustering of high waist circumference with arterial hypertension was associated with increased atherosclerosis and C-reactive protein levels. The intima-media thickness and associated protein C increased in proportion to the number of risk factors present in the same individual. The clusters of risk factors for inflammation and atherosclerosis included central obesity and hypertension, which are both modifiable.¹⁰

Cohort studies that assess cardiovascular risk factors are extremely important to establish public health priorities and the vital point is that this is a population-based study, where data were measured and collected using an appropriate method, which included middle-income adults and older adults in Brazil but should not be extrapolated to different populations.

The estimated prevalence of obesity in adults is 23.5% in southern Brazil,¹¹ and, according to the national health survey, this number has doubled in the last two decades.¹² According to the National Health Survey, the prevalence of hypertension in 2013 was 22.8% and increased with age.¹³

Population-based interventions for weight and blood pressure control are urgently needed. An estimate was carried out of the costs attributable to non-communicable chronic diseases based on the relative risks and population prevalence of hypertension, diabetes, and obesity, considering costs of hospitalizations, outpatient procedures, and drugs distributed by the public health system in Brazil (SUS) to treat these diseases in the adult population in Brazil. The SUS cost attributable to hypertension was R\$2.03 billion, and to obesity in 2018 was R\$1.42 billion.¹⁴ These costs together make up about 4.2% of the annual budget of the public health system in Brazil.

The key recommendations for MS prevention and treatment are lifestyle changes focused on education, frequent physical activity, and a nutritious diet, as well as drug interventions.^{15;16} Systematic reviews of randomized clinical trials indicate that lifestyle change programs have benefits for the control of MS and an impact on quality of life.^{15;17}

In a country that has a universal health system, and most of the population depends on public health financing, knowing where to allocate resources is crucial for better control of CMD morbidity and mortality.

References

1. World Health Organization. (WHO)_World health statistics 2018: monitoring health for the SDGs, sustainable development goals. 2018. Disponível em: < <https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/world-health-statistics> >. Acesso em: 2nd July 2019.
2. Sposito A, Caramelli B, Fonseca FA, Bertolami MC, Afiune Neto A, Souza AD, et al. [IV Brazilian Guideline for Dyslipidemia and Atherosclerosis prevention: Department of Atherosclerosis of Brazilian Society of Cardiology]. Arq Bras Cardiol.2007;88(supl1):2-19.
3. Alberti KG, Eckel R, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
4. Saad MAN, Cardoso GP, Martins WA, Velarde LG, Cruz Filho RA. Prevalence of metabolic syndrome in elderly and agreement among four diagnostic criteria. Arq Bras CARDIOL.2014;102(3):263-9.
5. Oliveira LVA, Santos BNS, Machado IE, Malta DC, Velasquez-Nelendez G, Felisbino Mendes MS. Prevalence of the Metabolic Syndrome and its components in the Brazilian adult population. Cien Saude Colet.2020;25(11):4269-80.
6. Ramires KN, Menezes RC, Longo-Silva G, Gama dos Santos T, Marinho PM, Silveira JAC. Prevalence and Factors Associated with Metabolic Syndrome among Brazilian Adult Population: National Health Survey - 2013. Arq Bras Cardiol. 2018;110(5):455-66.
7. Francisco PMS, Assumpção D, Malta DC. Co-occurrence of Smoking and Unhealthy Diet in the Brazilian Adult Population. Arq Bras Cardiol.2019;113(4):699-709.
8. Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, et al.. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adults with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. Am J Cardiol.2005;96(5):655-8.
9. Garcia VP, Rocha HN, sales AR, Rocha NG, Nobrega ACL. Sex Differences in High Sensitivity C-Reactive Protein in Subjects with Risk Factors of Metabolic Syndrome. Arq Bras Cardiol.2016;106(3):182-7.
10. Lima TR, Silva DAS, Giehl MWC, D'Orsi E, González-Chica DA. Clusters of Cardiometabolic Risk Factors and Their Association with Atherosclerosis and Chronic Inflammation among Adults and Elderly in Florianópolis, Southern Brazil. Arq Bras Cardiol. 2021; 117(1):39-48.
11. Vedana EH, Peres MA, Neves J, Rocha GC, Longo GZ. Prevalence of obesity and potential causal factors among adults in southern Brazil. Arq Bras Endocrinol Metabol.2008;52(7):1156-62.
12. Szwarcwald CL, Malta DC, Pereira CA, Vieira MLF, Conde WL, Souza Jr PRB, et al.. [National Health Survey in Brazil: design and methodology of application. Cien Saude Colet.2008;52(7):333-42.
13. Malta DC, Santos NB, Perillo RO, Szwarcwald CL. Prevalence of high blood pressure measured in the Brazilian population, National Health Survey, 2013. São Paulo Med J.2016;134(2):163-70.
14. Nilson EAF, Andrade RCS, Brito DA, Oliveira ML. Costs attributable to obesity, hypertension, and diabetes in the Unified Health System, Brazil, 2018. Costos atribuibles a la obesidad, la hipertensión y la diabetes en el Sistema Único de Salud de Brasil, 2018. Rev Panam Salud Publica.2020;44:e32.
15. Saboya PP, Bodanese LC, Zimmerman PR, Gustavo AS, Macagnan FE, Zimmerman PR, ety al. Lifestyle Intervention on Metabolic Syndrome and its Impact on Quality of Life: A Randomized Controlled Trial. Arq Bras Cardiol.2017;108(1):60-9.
16. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA.2001;285(19):2486-97.
17. Bassi N, Karogodin I, Wang S, Vassallo P, Priyanath A, Massaro E, et al. Lifestyle modification for metabolic syndrome: a systematic review. Am J Med. 2014;127(12):1242.e1-10.



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Temporal Trend of Mortality Due to Ischemic Heart Diseases in Northeastern Brazil (1996–2016): An Analysis According to Gender and Age Group

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Abstract

Background: Ischemic heart disease (IHD) is the leading cause of death among cardiovascular diseases (CVD).

Objective: To describe the sociodemographic profile and analyze the trend in the mortality rate due to IHD, according to sex and by age group, in the states of the Northeast region of Brazil, from 1996 to 2016.

Methods: Ecological study involving IHD mortality in the northeastern states. Variables analyzed: sex, age, education, marital status, ICD-10 category and state of residence. Crude and standardized rates were calculated. Death data were collected from the Mortality Information System (SIM) and population data from the Brazilian Institute of Geography and Statistics (IBGE). In temporal analyzes the regression model by inflection points was used, with the calculation of annual percent change (APC) and average annual percent change of the period (AAPC). A 95% confidence interval and a significance level of 5% were considered.

Results: 405916 deaths due to IHD were registered in the northeast region during the study period. The death profile is characterized by men (n=229006; 56,42%), elderly (n=301379; 74,25%), race/color brown (n=197936; 48,76%), elementary or <4 years at school (n=232599; 57,30%) and married (n=179599; 44,25%). There was an unusual highlight to the increase in the annual growth rate in the age group of adolescents (AAPC: 5,2%, p <0.01). The standardized regional mortality rate grew from 30,7 per 100,000 inhabitants in 1996 to 53.8 per 100,000 in 2016 (AAPC 2.8%; p<0.01). All nine states presented a statistically significant growth trend, with emphasis on Maranhão (AAPC 7,6%; p<0.01) and Piauí (AAPC 6,0%; p<0.01).

Conclusion: The prevalent observed profile was male, elderly, race/color brown, low education level and married. Mortality due to IHD presented an upward trend in all states, although with an uneven pattern among the federated units.

Keywords: Myocardial Ischemia/mortality; Epidemiology; Socioeconomic Factors; Deaths; Statistical Analysis; Demography; Public Health.

Introduction

Nursing has gained prominence regarding the application of technologies, with opportunities to implement and/or develop them for further evolution of the profession and benefits to the client-professional relationship.¹⁻³ In this scenario, Chronic Non-Communicable Diseases (CNCDs) - Cardiovascular Diseases (CVD), cancer, chronic respiratory diseases and Diabetes Mellitus (DM) - have gained space in the epidemiological and social context, constituting a global health problem responsible for 40 million deaths annually, 17 million of which as a result of CVD.⁴

In Brazil, in 2016, CNCDs resulted in 707,000 deaths, of which 362,000 were due to CVD.⁵ Due to the continental size of the country, the CNCD mortality dynamics between the regions and units of the Brazilian federation does not show homogeneous features. São Paulo, for example, follows the pattern of developed countries, with a reduction in the mortality rate,⁶ while in the Northeast, under different socioeconomic contexts (worse socioeconomic indicators and difficult access to health), the scenario is the opposite one.^{7,8}

Among the CVDs, the most prevalent is Ischemic Heart Disease (IHD), responsible for 116,000 deaths in Brazil in 2016 alone.⁵ IHD presents as insufficient blood flow and inadequate oxygen supply to the heart. This may be the effect of atheromatous plaque rupture, platelet adhesion, thrombosis, and vasospasm, the consequences of which will be ischemic myocardial injury, irreversible damage to cardiomyocytes, and overload hypertrophy in non-necrotic areas.⁹ In a pragmatic way, individuals have increased

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dependence on activities of daily living and mobility, that is, there is a decrease in functional capacity.¹⁰

The risk factors for these diseases are classified into two categories: modifiable and non-modifiable ones. The modifiable factors are Systemic Arterial Hypertension (SAH), obesity, sedentary lifestyle, inadequate eating habits, smoking, alcohol consumption, dyslipidemias, and insulin resistance; the non-modifiable factors refer to age, gender, ethnicity, and heredity.^{11,12} The control of modifiable risk factors greatly reduces morbidity and mortality from cardiovascular disease.¹³

Research on the temporal evolution of CVD mortality in the Northeast is fundamental for health decision-making, as it can contribute to the definition of priority areas for intervention and the development of strategies and actions aimed at improving the health of the population, especially with regard to risk factors.¹⁴

The Northeast region lacks descriptive studies on its detailed epidemiological characteristics. Based on the above, this study aimed to describe the sociodemographic profile and analyze the trend of the mortality rate from IHD, according to gender and age group, in the states of the Northeast region of Brazil, from 1996 to 2016. Thus, it broadens the scientific range about their health situation and the social determinants that constitute it.

Methods

Data Source and Collection

Death records were obtained from the Mortality Information System (MIS) of the Department of Informatics of the Unified Health System of the Brazilian Ministry of Health (<http://www.datasus.gov.br/>). During the collection process, the codes I20 to I25 of the International Classification of Diseases (ICD-10) were considered: I20 - Angina pectoris; I21 - Acute myocardial infarction; I22 - Recurrent myocardial infarction; I23 - Some current complications subsequent to acute myocardial infarction; I24 - Other acute ischemic heart disease; I25 - Chronic ischemic heart disease. The population data necessary to calculate the indicators were collected from the 2010 IBGE census.

Study area

The Northeast region of Brazil comprises nine states (Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe and Bahia) and has an estimated population of 57 million inhabitants, which corresponds to 28% of the national population – being the second most populous region of Brazil.¹⁵

Study variables

The study included sociodemographic variables (age group, education, marital status, skin color/ethnicity and states), International Classification of Diseases (ICD-10) category and the crude and standardized mortality rates, according to gender and age group.

To calculate the rates, the following equations were used:

a) Annual mortality rate = (Number of deaths from IHD at the site and in the year / Resident population at the site and in the year) x 100,000

b) Mortality rate for the period = (Simple average of the number of deaths from IHD at the site in the period / Mid-period resident population at the site) x 100,000

The direct method was adopted for the standardization of mortality rates, considering the Brazilian population of the year 2010 as the standard population. The following age groups were used in the standardization process: 0 to 9 years, 10 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years and 60 years or older.

Statistical Treatment

Initially, the sociodemographic variables were analyzed using simple descriptive statistics (absolute and relative frequencies). The temporal analysis was performed using the joinpoint regression model. The model analyzes whether a line with multiple segments is better suited to explain the temporal behavior of a data set when compared to a straight line or one with fewer segments. Thus, the trend of each indicator is classified as stationary, increasing or decreasing, according to the slope of the regression line. The Annual Percent Change (APC) and Average Annual Percent Change (AAPC) were calculated.¹⁶

The following parameters were adopted in the analysis: i) minimum of zero joins, ii) maximum of four joins, iii) model selection by Monte Carlo method (n= 4499 permutations), iv) error autocorrelation method based on date, v) 95% confidence interval (95%CI) and vi) 5% significance level. These analyses were performed with the help of the Joinpoint regression program (version 4.5.0.1, National Cancer Institute, Bethesda, MD, USA).

Ethical aspects

This study used secondary data from the public domain, in which it is not possible to identify the subjects.

Results

From 1996 to 2016, 405,916 deaths from IHD were recorded in the Northeast region of Brazil. Of these deaths, 56.42% (n=229006) occurred in males, 74.25% (n=301379) were elderly, 48.76% (n=197936) were brown, 57.30% (n=232599) had elementary school education or <4 years in school, and 44.25% (n=179599) were married. The proportion of blank fields in the variables level of schooling (33.54%), marital status (8.95%) and ethnicity/skin color (15.84%) stood out. As for the cause of death, 85.07% (n=345329) were due to acute myocardial infarction (I21) and 46.37% (n=188217) of the deaths occurred in the states of Pernambuco and Bahia (Table 1).

The regional standardized mortality rate increased from 30.7/100,000 inhabitants in 1996 to 53.8/100,000 in 2016 (AAPC 2.8%; 95%CI: 1.9 to 3.7; p<0.01). All nine states showed a significant growth trend, especially the state of Maranhão, of which rate increased from 14.8/100,000 in 1996 to 64.0/100,000 inhabitants in 2016 (AAPC 7.6%; 95%CI: 5.7 to 9.6; p<0.01), followed by Piauí, in which the rate increased from 18.7/100,000 in 1996 to 61.5/100,000 inhabitants in 2016 (AAPC 6.0%; 95%CI: 4.3 to 7.8; p<0.01). Pernambuco stood out with the highest number of temporal segments, with four inflections, five temporal segments and AAPC equal to 1.2% (95%CI: 0.0 to 2.5; p<0.01).

Table 1 – Sociodemographic characterization and ICD-10 category of deaths from ischemic heart disease (IHD) in Northeast Brazil, 1996-2016

Variable	Male n=229006 (56.42%)		Female n=176766 (43.55%)		Unknown n=144 (0.03%)		Total n=405916 (100%)	
	n	%	n	%	n	%	n	%
Age Range								
<10 years	72	0.05	49	0.02	0	0.00	121	0.03
10 to 19	469	0.20	215	0.12	1	0.70	685	0.17
20 to 29	2197	0.96	815	0.46	0	0.00	3012	0.74
30 to 39	7086	3.09	3197	1.81	3	2.08	10286	2.53
40 to 49	19380	8.46	10763	6.09	14	9.72	30157	7.43
50 to 59	38131	16.65	21493	12.16	17	11.81	59641	14.69
60 years or older	161295	70.43	139991	79.20	93	64.58	301379	74.25
Ignored	376	0.16	243	0.14	16	11.11	635	0.16
Skin color/ ethnicity								
White	58574	25.58	53120	30.05	10	6.94	111704	27.52
Black	17345	7.57	11975	6.77	1	0.70	29321	7.22
Yellow	1062	0.46	928	0.53	2	1.39	1992	0.49
Brown	115714	50.53	82208	46.51	14	9.72	197936	48.76
Indigenous	385	0.17	301	0.17	0	0.00	686	0.17
Unknown	35926	15.69	28234	15.97	117	81.25	64277	15.84
Level of schooling								
Elementary or < 4 years at school	129138	56.39	103426	58.51	35	24.30	232599	57.30
High school	15866	6.93	9088	5.14	4	2.78	24958	6.15
Higher education	8303	3.62	3909	2.21	0	0.00	12212	3.01
Unknown	75699	33.06	60343	34.14	105	72.92	136147	33.54
Marital status								
Single	45124	19.7	41989	23.75	21	14.58	87134	21.47
Married	125600	54.85	53953	30.52	46	31.94	179599	44.25
Widowed	26413	11.53	58356	33.01	26	18.06	84795	20.89
Divorced	6930	3.03	3642	2.06	1	0.70	10573	2.60
Other	5254	2.29	2228	1.27	2	1.39	7484	1.84
Unknown	19685	8.60	16598	9.39	48	33.33	36331	8.95
ICD-10 Category								
I20	885	0.39	875	0.5	0	0.00	1760	0.43
I21	196621	85.86	148585	84.06	123	85.42	345329	85.07
I22	591	0.25	386	0.21	0	0.00	977	0.25
I23	3	<0.01	0	0.00	0	0.00	3	<0.01
I24	6745	2.95	6320	3.58	7	4.86	13072	3.22
I25	24161	10.55	20600	11.65	14	9.72	44775	11.03
States								
Maranhão	21847	9.54	13792	7.8	24	16.67	35663	8.79
Piauí	14539	6.35	9446	5.34	16	11.11	24001	5.91
Ceará	33500	14.63	26623	15.06	26	18.06	60149	14.82
Rio Grande do Norte	17347	7.57	13335	7.54	4	2.78	30686	7.56
Paraíba	18825	8.22	14945	8.45	11	7.64	33781	8.32
Pernambuco	59385	25.93	48909	27.67	34	23.61	108328	26.69
Alagoas	11957	5.22	9034	5.11	2	1.38	20993	5.17
Sergipe	6797	2.97	5624	3.20	5	3.47	12426	3.06
Bahia	44809	19.57	35058	19.83	22	15.28	79889	19.68

I20- Angina pectoris; I21- Acute myocardial infarction; I22- Subsequent myocardial infarction; I23- Certain current complications following acute myocardial infarction; I24- Other acute ischemic heart diseases; I25- Chronic ischemic heart disease.

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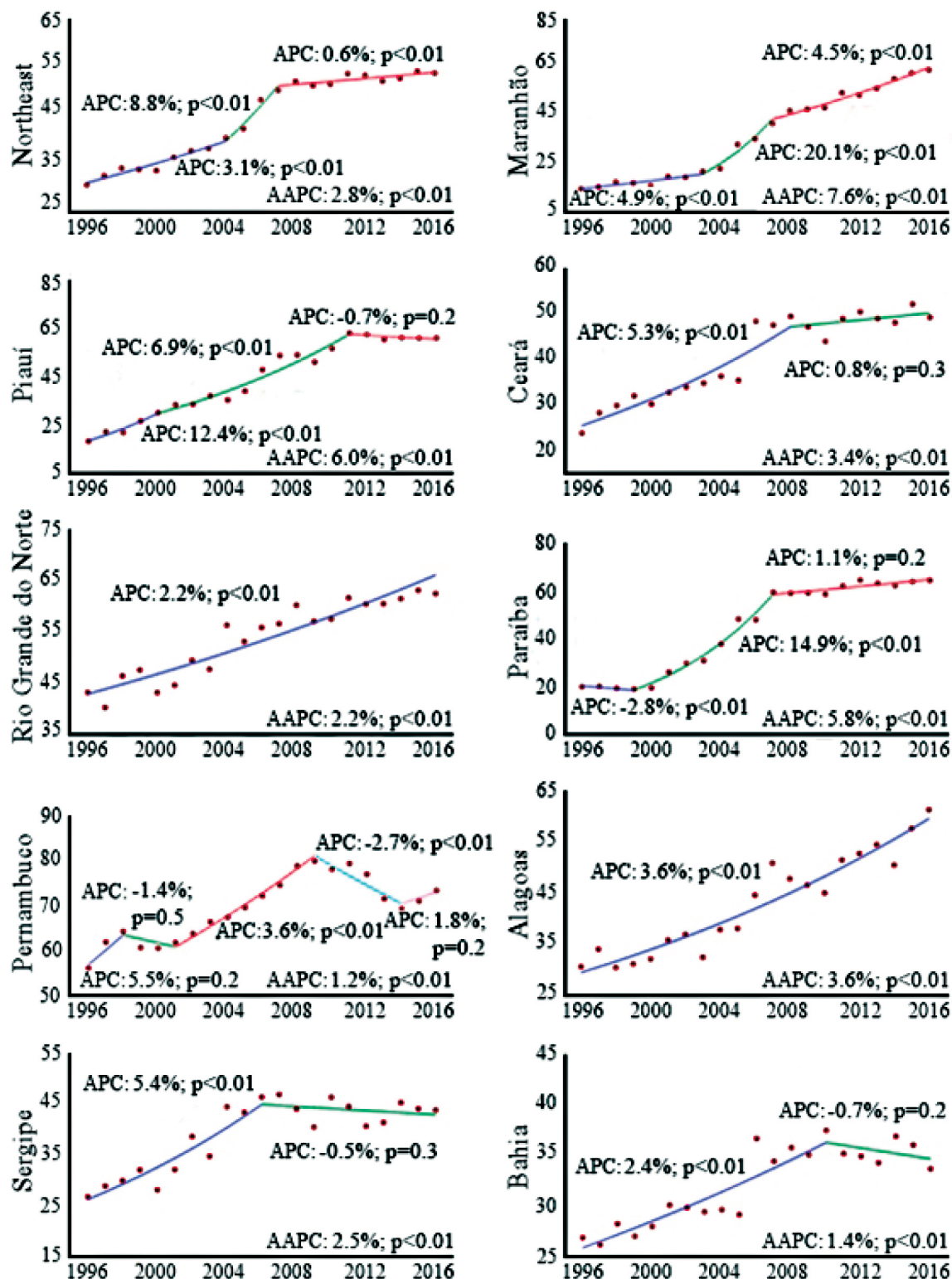


Figure 1 – Time trend of the standardized mortality rate from Ischemic Heart Disease (IHD), according to state of residence. Northeast Brazil, 1996-2016. APC: Annual Percent Change. AAPC: Average Annual Percent Change. *Confidence Interval values have been suppressed in the illustration for better visualization and understanding of the trend lines.

The states of Rio Grande do Norte and Alagoas showed a linear trend of mortality growth (2.2% in Rio Grande do Norte and 3.6% in Alagoas) (Figure 1).

The mean mortality rate in males (42.05/100,000) was 32% higher than in females (31.6/100,000), although with the same mean variation (AAPC 4.4%; 95%CI: 3.4 to 5.4; $p < 0.01$). The adolescent age group showed a statistically significant increase, greater than in the other age groups (AAPC: 5.2%, $p < 0.01$) (Table 2). All states showed an upward trend in both genders, with Maranhão (AAPC 8.7% for men and 9.3% for women) and Piauí (AAPC 7.9% for men and 8.4% for women) standing out (Table 3).

In the stratification according to the age group, the regression model showed a tendency for mortality growth in all age segments, with the exception of the group aged 30 to 39 years (AAPC 0.9%; 95%CI: -0.8 to 2.5; $p = 0.4$) (Table 2). The regional mortality rate in individuals aged

60 years or older increased from 202.0/100,000 in 1996 to 382.3/100,000 inhabitants in 2016, with an average annual growth of 3.3% (95%CI: 2.5 to 4.1; $p < 0.01$). The age group 60 years or older was the only one with a statistically significant growth in all states, especially the states of Maranhão (AAPC 8.4%; 95%CI: 6.3 to 10.5; $p < 0.01$) and Piauí (AAPC 6.5%; 95%CI: 5.3 to 7.7; $p < 0.01$) (Table 4).

Finally, a divergence in the trend by age group was observed when comparing the states. In Piauí, for example, there was an increase in all age groups starting from ten years of age, while in Bahia, the increase was observed only in the elderly segment (60 years or older) (Table 4).

Discussion

This study analyzed the socio-demographic profile and the temporal behavior of mortality from IHD in the Northeast region of Brazil from 1996 to 2016. The profile of deaths

Table 2 – Time trend of crude mortality rate from Ischemic Heart Disease (IHD), according to gender and age group. Northeast, Brazil, 1996-2016

Variable	Mortality Rate/100,000			Trend		
	1996	2016	1996-2016	Time period	APC (95%CI; p value)	AAPC (95%CI; p value)
Gender						
Male	25.52	60.88	42.05	1996-2004	3.7% (3.0 to 4.5; p<0.01)	4.4% (3.4 to 5.4; p<0.01)
				2004-2007	10.6% (3.4 to 18.3; p<0.01)	
				2007-2016	3.0% (2.4 to 3.6; p<0.01)	
Female	18.78	44.24	31.69	1996-2003	4.0% (3.1 to 5.0; p<0.01)	4.4% (3.6 to 5.2; p<0.01)
				2003-2007	9.2% (5.5 to 13.1; p<0.01)	
				2007-2016	2.6% (2.0 to 3.2; p<0.01)	
Age Range						
0 to 9	0.01	0.10	0.05	-	-	-
10 to 19	0.21	0.39	0.31	1996-2016	5.2% (3.0 to 7.5; p<0.01)	5.2% (3.0 to 7.5; p<0.01)
20 to 29	1.00	1.96	1.42	1996-2016	2.8% (2.0 to 3.6; p<0.01)	2.8% (2.0 to 3.6; p<0.01)
30 to 39	5.79	7.18	6.66	1996-2003	-1.5% (-3.5 to 0.5; p=0.2)	0.9% (-0.8 to 2.5; p=0.4)
				2003-2007	6.8% (-1.1 to 15.4; p=0.3)	
				2007-2016	0.2% (-1.2 to 1.6; p=0.2)	
40 to 49	20.44	26.84	25.38	1996-1998	9.8% (1.1 to 19.2; p<0.01)	1.5% (0.1 to 2.9; p<0.01)
				1998-2001	-4.6% (-12.1 to 3.6; p=0.2)	
				2001-2008	4.4% (3.0 to 5.9; p<0.01)	
				2008-2016	-0.7% (-1.6 to 0.2; p=0.2)	
50 to 59	52.99	78.25	74.40	1996-2008	3.3% (2.7 to 3.9; p<0.01)	1.6% (1.1 to 2.2; p<0.01)
				2008-2016	-0.7% (-1.8 to 0.3; p=0.3)	
60 or older	202.03	382.28	323.15	1996-2003	3.3% (2.2 to 4.3; p<0.01)	3.3% (2.5 to 4.1; p<0.01)
				2003-2007	8.5% (4.6 to 12.6; p<0.01)	
				2007-2016	1.0% (0.4 to 1.7; p<0.01)	
Overall population	22.14	52.40	36.82	1996-2004	4.0% (3.3 to 4.7; p<0.01)	4.4% (3.5 to 5.3; p<0.01)
				2004-2007	10.5% (3.9 to 17.4; p<0.01)	
				2007-2016	2.8% (2.2 to 3.4; p<0.01)	

APC: Annual Percent Change. AAPC: Average Annual Percent Change.

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Table 3 – Average Annual Percent Change (AAPC) of the mortality rate from Ischemic Heart Diseases (IHD), according to gender and state of residence. Northeast, Brazil, 1996-2016

State	Male			Female		
	1996	2016	AAPC (95%CI; p value)	1996	2016	AAPC (95%CI; p value)
Maranhão	12.06	62.75	8.7% (7.0 to 10.5; p<0.01)	6.20	38.89	9.3% (7.1 to 11.7; p<0.01)
Piauí	16.16	75.49	7.9% (4.4 to 11.5; p<0.01)	9.98	45.16	8.4% (7.3 to 9.5; p<0.01)
Ceará	20.65	56.89	5.1% (4.5 to 5.8; p<0.01)	15.55	41.70	5.0% (3.9 to 5.1; p<0.01)
Rio Grande do Norte	39.61	74.56	3.5% (3.1 to 3.9; p<0.01)	27.88	53.24	3.9% (3.4 to 4.4; p<0.01)
Paraíba	20.88	78.08	6.8% (5.5 to 8.1; p<0.01)	15.53	60.00	7.1% (5.2 to 9.1; p<0.01)
Pernambuco	49.59	85.82	2.4% (1.5 to 3.3; p<0.01)	36.93	64.36	2.3% (1.3 to 3.3; p<0.01)
Alagoas	23.73	61.02	4.7% (3.1 to 6.3; p<0.01)	15.95	47.96	5.3% (4.5 to 6.1; p<0.01)
Sergipe	19.25	42.47	4.4% (3.1 to 5.7; p<0.01)	18.58	35.80	2.7% (0.5 to 4.9; p<0.01)
Bahia	21.35	39.39	3.6% (3.2 to 4.1; p<0.01)	16.32	29.05	3.6% (2.7 to 4.4; p<0.01)

APC: Annual Percent Change. AAPC: Average Annual Percent Change.

Table 4 – Average Annual Percent Change (AAPC) of crude mortality rate from Ischemic Heart Disease (IHD), according to age range and state of residence. Northeast, Brazil, 1996-2016

Age Range	Maranhão			Piauí			Ceará		
	Rates		AAPC	Rates		AAPC	Rates		AAPC
	1996	2016	(95%CI)	1996	2016	(95%CI)	1996	2016	(95%CI)
0 to 9	0.00	0.14	-	0.00	0.19	-	0.00	0.07	-
10 to 19	0.00	0.50	-	0.15	0.84	7.0% (2.9 to 11.3; p<0.01)	0.51	0.56	4.9% (-0.3 to 10.4; p=0.5)
20 to 29	0.12	3.25	9.0% (4.9 to 13.2; p<0.01)	0.93	3.42	6.2% (3.6 to 8.9; p<0.01)	1.16	1.39	0.7% (-0.6 to 2.1; p=0.3)
30 to 39	3.17	11.62	5.8% (4.7 to 7.0; p<0.01)	6.09	10.00	3.5% (2.0 to 5.1; p<0.01)	5.80	5.31	0.8% (-0.3 to 1.9; p=0.3)
40 to 49	10.46	35.96	6.1% (1.5 to 11.0; p<0.01)	14.71	31.10	3.5% (2.5 to 4.5; p<0.01)	15.29	20.40	2.1% (1.2 to 3.1; p<0.01)
50 to 59	29.12	90.17	5.7% (3.2 to 8.1; p<0.01)	34.61	87.61	3.5% (1.4 to 5.6; p<0.01)	38.07	66.06	1.9% (0.5 to 3.4; p<0.01)
60 +	94.19	446.37	8.4% (6.3 to 10.5; p<0.01)	114.40	432.41	6.5% (5.3 to 7.7; p<0.01)	157.12	361.26	3.9% (2.8 to 5.1; p<0.01)
Age Range	Rio Grande do Norte			Paraíba			Pernambuco		
	Rates		AAPC	Rates		AAPC	Rates		AAPC
	1996	2016	(95%CI)	1996	2016	(95%CI)	1996	2016	(95%CI)
0 to 9	0.18	0.00	-	0.00	0.16	-	0.00	0.07	-
10 to 19	0.34	0.34	-	0.51	0.15	-	0.23	0.54	4.5% (0.9 to 8.3; p<0.01)
20 to 29	1.14	1.83	4.7% (0.8 to 8.7; p<0.01)	0.92	2.42	5.1% (2.7 to 7.5; p<0.01)	2.10	2.75	1.5% (-0.3 to 3.2; p=0.4)
30 to 39	7.16	7.45	2.0% (0.2 to 3.7; p<0.01)	4.12	7.30	4.7% (3.5 to 5.9; p<0.01)	9.65	9.13	-1.1% (-5.9 to 4.1; p=0.4)
40 to 49	23.52	28.02	1.1% (0.2 to 2.0; p<0.01)	14.54	34.14	4.2% (1.4 to 7.1; p<0.01)	33.08	35.25	-0.2% (-3.3 to 3.0; p=0.2)
50 to 59	69.14	88.46	1.3% (0.4 to 2.2; p<0.01)	31.84	84.49	5.7% (3.9 to 7.4; p<0.01)	98.89	114.28	0.6% (-0.8 to 2.0; p=0.2)
60 +	298.31	452.97	2.4% (1.8 to 3.0; p<0.01)	138.19	469.44	6.3% (4.8 to 7.7; p<0.01)	378.85	520.30	1.2% (0.4 to 1.9; p<0.01)
Age Range	Alagoas			Sergipe			Bahia		
	Rates		AAPC	Rates		AAPC	Rates		AAPC
	1996	2016	(95%CI)	1996	2016	(95%CI)	1996	2016	(95%CI)
0 to 9	0.00	0.17	-	0.00	0.00	-	0.00	0.08	-
10 to 19	0.00	0.15	-	0.00	0.00	-	0.13	0.23	-
20 to 29	0.66	2.13	3.2% (0.7 to 5.7; p<0.01)	0.35	0.50	-2.9% (-7.1 to 1.5; p=0.4)	0.75	0.99	0.8% (-0.7 to 2.3; p=0.6)
30 to 39	6.73	5.34	-0.8% (-2.3 to 0.6; p=0.2)	5.59	4.21	1.1% (-0.9 to 3.1; p=0.3)	4.31	5.34	0.4% (-0.5 to 1.2; p=0.6)
40 to 49	31.05	36.91	0.3% (-2.2 to 2.9; p=0.2)	12.47	26.10	2.9% (-0.3 to 6.1; p=0.3)	20.10	16.87	-0.1% (-0.8 to 0.6; p=0.7)
50 to 59	61.26	95.11	1.6% (-1.6 to 4.8; p=0.3)	55.05	67.15	1.6% (0.6 to 2.7; p<0.01)	45.72	50.89	0.3% (-0.7 to 1.3; p=0.2)
60 +	182.72	428.16	4.3% (3.8 to 4.9; p<0.01)	177.36	308.36	2.9% (1.7 to 4.0; p<0.01)	177.50	236.80	2.2% (1.7 to 2.7; p<0.01)

APC: Annual Percent Change. AAPC: Average Annual Percent Change.

was characterized by a predominance of males, involvement of the elderly, brown ethnicity/skin color, and low level of schooling. The temporal analysis showed an increase in the mortality rate in the region and in all states, especially in Maranhão and Piauí.

The profile observed in this study is in line with that observed in the literature.^{1,7,17-20} The population's aging process brings with it an increase in risk factors for cardiovascular diseases, especially dyslipidemia, obesity, and SAH.² A study conducted in the city of São Paulo shows that the odds ratio of developing CVD is higher in diabetics (Odds Ratio - OR 1.90), smokers (OR 1.49), overweight individuals (OR 1.57), and hypertensive individuals (OR 2.22).²⁰ It is estimated that the prevalence of SAH in the elderly is six to eight times higher than in young adults, justified by poor blood pressure control, due to the chronicity of the disease and sensitivity and restrictions in pharmacotherapy. In a study carried out in Goiânia, state of Goiás, of the 912 individuals with SAH that were interviewed, 72.6% were undergoing treatment and only 50.8% had achieved blood pressure control.²¹

It is pertinent to highlight the growth of mortality in adolescence, as observed in this investigation. In this population, studies point to a wide range of factors associated with overweight and obesity, such as i) excessive intake of simple sugars and fats, ii) insufficient consumption of fruits and vegetables, and iii) sedentary lifestyle, which may result in early mortality.²² The Study of Cardiovascular Risks in Adolescents (ERICA) carried out from 2013 to 2014 reported the prevalence of metabolic syndrome in 3.3% of those who were overweight and 21.7% of those who were obese in the Northeast region.²³

The medical importance of lipid profile alterations is related to the presence of subclinical atherosclerosis and the possibility of predicting dyslipidemia in adulthood; in the ERICA study, we observed a higher prevalence of low HDL (High Density Lipoprotein) levels in the North and Northeast regions of Brazil.²⁴ A study conducted in Belém, state of Pará in 2006, involving 437 children and adolescents, showed that 28.8% were overweight and 36% had high body fat percentage. Of these, 49% showed changes in lipid profile, especially low HDL levels.²⁵ Similar results were observed in Porto Alegre, state of Rio Grande do Sul, where an increase in dyslipidemia secondary to obesity was observed, characterized by low HDL levels and increased triglyceride levels, secondary to insulin resistance.²⁶

The cardiovascular risk is also influenced by gender, being higher in the male population. A study on hypertension in Goiânia - GO, conducted in 2010, showed that the rate of control of blood pressure levels is lower in the male population (44.0% in men and 54.8% in women).²¹ In Montes Claros, state of Minas Gerais, 62.8% of diabetes mellitus cases are identified in women, justified by the greater demand for medical care by this population. Women also show greater and better adherence to treatment.²⁷ Moreover, women have biological and behavioral characteristics capable of reducing the risk of cardiovascular disease, highlighting the protective role of estradiol on the vascular endothelium, greater access to health services and better performance in the control of risk factors.¹⁷

The influence of socioeconomic development and access to health services on the pattern of mortality has been evidenced in different studies.²⁸⁻³⁰ Research conducted in 2012 in the states of Rio de Janeiro, Rio Grande do Sul, and São Paulo showed a correlation between increased *per capita* GDP and educational accomplishments with decreased mortality from IHD.³¹ In the Northeast, Maranhão, at the same time that it showed the highest average percentage growth (7.6%) in mortality from IHD, it is characterized by being the state with the lowest *per capita* GDP - R\$400.97 - and the second state with the highest illiteracy rate among people aged 18 or over (20.56%), second only to the state of Alagoas (21.47%).³²

In Rio Grande do Sul, a statistically significant positive correlation was found for the GINI index and education, in addition to geographic distance. The distance shows that the geographical distributions of cardiac intervention reference centers directly influence, as an independent predictor of death, the mortality rate from IHD.³³ Another study also reports that, in line with socioeconomic disparities, the geographic distance factor becomes even more serious. Nevertheless, the creation of new reference services in cardiology is a possibility to solve the problem.³⁴

Brazil has undertaken efforts to reduce the occurrence of IHD. In 2000, the Ministry of Health implemented the Reorganization Care Plan for Hypertension and Diabetes Mellitus. Its objectives are to have a computerized system to help with the registration and follow-up of patients with SAH and DM - HiperDia -, as well as to know the magnitude of the diseases, plan the acquisition of medicines, and train professionals in the Brazilian health network to act in the health care profile of the unified health system (UHS).³⁵

In this context, a study conducted in Maringá, state of Paraná, showed that the impact of public policies, such as the Family Health Strategy (FHS), are associated with lower rates of hospitalization from Cardiovascular Conditions Sensitive to Primary Care (CCSPC). The success of the Primary Health Care (PHC) strategy is based on its approach to CVD risk factors, on the support to the self-management of health, along with longitudinal monitoring by health teams, in addition to their empowerment and autonomy.³⁶

PHC contributes to the fight against smoking, to the expansion of access to health services, and to the distribution of medicines to control the IHD risk factors.³⁷ In a survey regarding the access to medication by PHC users, the medication availability dimension was low, around 46.3% to 64.3%, well below the 80% recommended by the World Health Organization (WHO).³⁸ The proposed alternative is to replace the non-available drug and refer patients to the "People's Pharmacy", although the control of chronic diseases may be jeopardized by this measure.³⁹

The mortality growth trend is not homogeneous among the Northeastern states: there is a linear growth in the states of Alagoas and Rio Grande do Norte, rate instability in Pernambuco, and a stationary pattern in most states from the second half of the first decade of the 21st century. Different factors may justify these findings, such as intra-regional socioeconomic differences, the influence of public policies, and the quality of information records.^{3,40-43}

Even when considering the adopted methodological care, this study has limitations, especially the quality of mortality records, which is a challenge for the adequate monitoring of the health status and aid in decision-making. Additionally, the existence of garbage codes and operational difficulties in death surveillance are additional factors that compromise the quality of the records.

Conclusion

The mortality rates in the Northeast region of Brazil showed significant growth in all its states, being higher in Maranhão and Piauí. The profile of deaths was characterized by a predominance of elderly men, mixed race ethnicity/skin color, elementary school or <4 years in school, and married individuals. During the period, the male gender showed significantly higher rates than the female gender, although with the same percentage of growth. The rate inequalities between the states demonstrate the need for strategies consistent with the local reality and particularities and the possible influence of living conditions of the population, with this being a recommendation for future studies. Considering the finding of a higher annual rate of increase in the adolescent age group, which is a matter of concern, further investigations on cardiovascular mortality in adolescents are required.

References

1. Guimarães RM, Andrade SSCA, Machado EL, Bahia CA, Oliveira MM, Jacques FVL. Diferenças regionais na transição da mortalidade por doenças cardiovasculares no Brasil, 1980 a 2012. *Rev Panam Salud Publica*. 2015; 37(2):83-9.
2. Vasconcelos AMN, Gomes MMF. Transição demográfica: a experiência brasileira. *Epidemiol Serv Saúde*, Brasília. 2012; 21(4):539-48.
3. Santos JP, Paes NA. Associação entre condições de vida e vulnerabilidade com a mortalidade por doenças cardiovasculares de homens idosos do Nordeste. *Rev Bras Epidemiol*. 2014; 17(2):407-20.
4. World Health Organization (WHO). Health statistics and information systems. Estimates for 2000-2016. [Online]. Geneva. 2018. [Acesso em julho de 2019]. Disponível em: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.
5. Ministério da Saúde (BR). Sistema de informações sobre mortalidade (SIM). [Acesso em 13 de setembro de 2018]. Disponível em <http://datasus.saude.gov.br/>.
6. Lotufo PA, Fernandes TG, Bando, DH, Alencar AP, Benseñor, IM. Income and heart disease mortality trends in Sao Paulo, Brazil, 1996 to 2010. *Int J Cardiol*. 2013; 167(6):2820-3.
7. Gauri EM, Klein CH, Oliveira GMM. Mortalidade proporcional por insuficiência cardíaca e doenças isquêmicas do coração nas regiões do Brasil de 2004 a 2011. *Arq Bras Cardiol*. 2016; 107(3):230-8.
8. Ribeiro ALP, Duncan, BB, Brant LCC, Lotufo PA, Mill JC, Barreto SM, et al. Cardiovascular health in Brazil trends and perspectives. *American Heart Association, Circulation*. 2016; 133:422-33.
9. Perricone AJ, Heide RSV. Novel therapeutic strategies for ischemic heart disease. *Pharmacol Research* 89 (2014) 36-45.
10. Alves LC, Leimann BCQ, Vasconcelos MEL, Carvalho MS, Vasconcelos AGG, et al. The effect of chronic diseases on functional status of the elderly living in the city of São Paulo, Brazil. *Cad. Saúde Pública*, Rio de Janeiro, 23(8):1924-30.
11. Simão M, Nogueira MS, Hayashida M, Cesarino EJ. Doenças cardiovasculares: perfil de trabalhadores do sexo masculino de uma destilaria do interior paulista. *Rev Eletr Enfer*. 2002; 4(2):27-35.
12. Magalhães FJ, Mendonça LBA, Rebouças CBA, Lima FET, Custódio IL, Oliveira SC. Fatores de risco para doenças cardiovasculares em profissionais de enfermagem: estratégias de promoção da saúde. *Rev Bras Enferm*. 2014; 67(3):394-400.
13. Sociedade Brasileira de Cardiologia. I Diretriz Brasileira de Prevenção Cardiovascular. *Arq Bras Cardiol*. 2013; 101(6):1-63.
14. Moraes IHS, Santos SRFR. Informações em saúde: os desafios continuam. *Cienc Saúde Coletiva*. 1998; 3(1):37-51.
15. Instituto Brasileiro de Geografia e Estatística (IBGE). Sistema de Recuperação automática de dados-SIDRA. Acesso em 08 setembro 2018. Disponível em <https://sidra.ibge.gov.br/home/pms/brasil>.
16. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-51
17. Soeiro AM, Barros e Silva PGM, Roque EAC, Bossa AS, Biselli B, Leal TCAT, et al. Diferenças prognósticas entre homens e mulheres com síndrome coronariana aguda, dados de um registro brasileiro. *Arq Bras Cardiol*. 2018; 111(5):648-53.
18. Brant LCC, Nascimento BR, Passos VMA, Duncan BB, Benseñor IJM, Malta DC, et al. Variações e diferenciais da mortalidade por doença cardiovascular no Brasil e em seus estados, em 1990 e 2015: estimativas do Estudo Carga Global de Doença. *Rev Bras Epidemiol*. 2017; 20:116-28.
19. Mansur AP, Favarato D. Mortalidade por doenças cardiovasculares em mulheres e homens nas cinco regiões do Brasil, 1980-2012. *Arq Bras Cardiol*. 2016; 107(2):137-46.
20. Massa KHC, Duarte YAO, Filho ADPC. Análise da prevalência de doenças cardiovasculares e fatores associados em idosos, 2000-2010. *Cienc Saúde Coletiva*. 2019; 24(1):105-14.

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Conception and design of the research and Acquisition of data: Santana GBA, Paiva JPS, Oliveira TF, Mesquita RR, Gomes JA, Souza CDF, Rodrigues AKB; Analysis and interpretation of the data: Santana GBA, Leal TC, Silva LF, Santos LG, Gomes JA, Souza CDF, Rodrigues AKB; Statistical analysis: Santana GBA, Silva LF, Santos LG, Souza CDF, Rodrigues AKB; Writing of the manuscript: Santana GBA, Leal TC, Paiva JPS, Silva LF, Oliveira TF, Gomes JA, Souza CDF, Rodrigues AKB; Critical revision of the manuscript for intellectual content: Santana GBA, Leal TC, Paiva JPS, Silva LF, Santos LG, Souza CDF, Rodrigues AKB.

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21. Sousa ALL, Batista SR, Sousa AC, Pacheco JAS, Vitorino PVO, Pagotto V. Prevalência, tratamento e controle da hipertensão arterial em idosos de uma capital brasileira. *Arq Bras Cardiol.* 2019; 112(3):271-8.
22. Enes CC, Slater B. Obesidade na adolescência e seus principais fatores determinantes. *Rev Bras Epidemiol* 2010; 13(1):163-71.
23. Kuschmir MCC, Bloch KV, Szklo M, Klein CH, Barufaldi LA, Abreu GA, et al. ERICA: prevalência de síndrome metabólica em adolescentes brasileiros. *Rev Saúde Pública.* 2016; 50:11s.
24. Faria-Neto JR, Bento VFR, Baena CP, Olandoski M, Gonçalves LGO, Abreu GA, et al. ERICA: prevalência de dislipidemia em adolescentes brasileiros. *Rev Saúde Pública.* 2016; 50:10s.
25. Ribas SA, Silva LCS. Dislipidemia em escolares na rede privada de Belém. *Arq Bras Cardiol.* 2009; 92(6):446-51.
26. Radaelli G, Sausen G, Cesa CC, Portal VL, Pellanda LC. Dislipidemia secundária em crianças obesas – há evidências para tratamento farmacológico? *Arq Bras Cardiol.* 2018; 111(3):356-61.
27. Machado APMC, Santos ACG, Carvalho KKA, Gondim MPL, Bastos NP, Rocha JVS, et al. Avaliação da adesão ao tratamento de pacientes com diabetes mellitus e seus fatores associados. *REAS.* 2019; 19:e565.
28. Mansur AP, Favarato D. Tendências da taxa de mortalidade por doenças cardiovasculares no Brasil, 1980-2012. *Arq Bras Cardiol.* 2016; 107(1):20-5.
29. Gauri EG, Oliveira GMM, Klein CH. Mortalidade por insuficiência cardíaca e doença isquêmica do coração no Brasil de 1996 a 2011. *Arq Bras Cardiol.* 2014; 102(6):557-65.
30. Ishitani LH, Franco GC, Perpétuo IHO, França E. Desigualdade social e mortalidade precoce por doenças cardiovasculares no Brasil. *Rev Saúde Pública* 2006; 40(4):684-91.
31. Soares GP, Brum JD, Oliveira GMM, Klein CH, Souza e Silva NA, et al. Evolução de indicadores socioeconômicos e da Mortalidade Cardiovascular em três Estados do Brasil. *Arq Bras Cardiol.* 2013; 100(2):147-56.
32. Instituto de Pesquisa Econômica Aplicada (IPEA). Atlas de vulnerabilidade social. Disponível em <http://ivs.ipea.gov.br/index.php/pt/>. Acesso em: 10 agosto, 2019.
33. Andrade L, Lynch C, Barbeito A, Spiecker EM, Vissoci JR, et al. Spatial distribution of ischemic heart disease mortality in Rio Grande do Sul, Brazil: ACM digital library, 2013. p.1-17.
34. Andrade LD, Zanini V, Batilana AP, Carvalho ECAd, Pietrobon R, Nihei OK, Carvalho MDB. Regional disparities in mortality after ischemic heart disease in a Brazilian state from 2006 to 2010. *PLoS ONE.* 2013; 8(3): e59363
35. Ribeiro AG, Cotta RMM, Ribeiro SMR. A promoção da saúde e a prevenção integrada dos fatores de risco para doenças cardiovasculares. *Cienc Saúde Coletiva.* 2012; 17(1):7-1.
36. Lentsck MH, Saito AC, Mathias TAF. Tendência de declínio da hospitalizações por doenças cardiovasculares sensíveis à atenção primária. *Texto Contexto Enferm.* 2017; 26(2):e03170015.
37. Villela, LCM, Gomes FE, Meléndez JGV. Tendência da mortalidade por doenças cardiovasculares, isquêmicas do coração e cerebrovasculares. *Rev enferm UFPE (on line)* Recife 2014; 8(9): 3134-41
38. Álvares J, Guerra Junior AA, Araújo VE, Almeida AM, Dias CZ, Oliveira BA, et al. Acesso aos medicamentos pelos usuários da atenção primária no Sistema Único de Saúde. *Rev Saúde Pública.* 2017;51 (Supl 2):20s.
39. Nascimento RCRM, Álvares J, Guerra Junior AA, Gomes IC, Costa EA, Leite SN, et al. Disponibilidade de medicamentos essenciais na atenção primária do Sistema Único de Saúde. *Rev Saúde Pública.* 2017;51 (Supl 2):10s.
40. Santo AH. Causas mal definidas de morte e óbitos sem assistência. *Rev Assoc Med Bras* 2008; 54(1): 23-8.
41. Nogueira MC, Ribeiro LC, Cruz OG. Desigualdades sociais na mortalidade cardiovascular precoce em um município de médio porte no Brasil. *Cad Saúde Pública.* 2009; 25(11):2321-32.
42. Carvalho FCD, Vasconcelos TB, Arruda GMMS, Macena RHM. Modificações nos indicadores sociais da região Nordeste após a implementação da atenção primária. *Trab Educ Saúde.* 2019; 17(2):e0018925.
43. Soares GP, Brum JD, Oliveira GMM, Klein CH, Souza e Silva NA. Mortalidade por todas as causas e por doenças cardiovasculares em três estados do Brasil, 1980 a 2006. *Rev Panam Salud Publica.* 2010; 28(4):258-66.



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Mortality Due to Ischemic Heart Disease in Brazil – Northeast Disparities

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Short Editorial related to the article: Temporal Trend of Mortality Due to Ischemic Heart Diseases in Northeastern Brazil (1996–2016): An Analysis According to Gender and Age Group

Cardiovascular Diseases (CVD) have emerged as a global health concern responsible for more than 17 million deaths annually, representing the main cause of death since the 1960s. In particular, Ischemic Heart Diseases (IHD) constitute the most prevalent CVD, occupying the position of leading cause of death worldwide considering data until 2019, having been responsible for 8.9 million deaths in 2019 (16% of all causes of death) associated with an increase of more than 2 million deaths in the past two decades.¹

In Brazil, it has been undertaken an effort to provide more comprehensive statistics of the national panorama of CVD, with the production of an annual report 2 which includes the Ministry of Health official statistics and data from epidemiological studies, including the Global Burden of Disease Study (GBD), among other sources. It was verified a rate of 83 deaths due to IHD per 100 thousand inhabitants in 2017,³ with IHD being the main cause of death in all Brazilian states that year, differently from 1990, when stroke was still leading in some states in the northeast region.³

Being a country of continental dimensions and marked by social inequalities, in Brazil, the importance of conducting population investigations that address the great regional disparities is emphasized, mainly focusing on less developed regions (north, northeast and center-west), in order to establish priorities for public health interventions.^{4,5} In this sense, the article by Santana et al.⁶ evaluated the socio-demographic profile and the temporal behavior of IHD mortality in northeastern Brazil from 1996 to 2016.

Regarding the temporal evolution of the mortality rate, the study found a significant increase in IHD mortality in

all nine states in the northeast, although with inequalities in rates among the states, especially Maranhão and Piauí, where the highest mortality percentages were observed. This result clearly highlights the disparity in relation to what is observed in more developed regions in Brazil, such as the south and southeast, where there is a decreasing trend in that index, while in the north and midwest regions there is a tendency towards stabilization.⁷

This difference in the mortality slope due to IHD among Brazilian regions, with greater disadvantage in the northeast region, was already observed in a study involving data from more than two decades ago - 1981 to 2001.⁸ This heterogeneity persisted in subsequent analyzes, although there has been a convergence of trends among regions,^{7,9} reflecting the weight of socioeconomic development and access to health services in controlling mortality from IHD, and other CVDs. Serious and worrying is the fact that the problem still remains and strongly impacts the northeast region, as verified by Santana et al.⁶

The author discussed the importance of public policies, especially in Primary Health Care, with emphasis on the relevance of the Family Health Program and, in this context, concluded that the higher mortalities verified, particularly in the states of Maranhão and Piauí, could reflect local particularities and the living conditions of the population, which is marked by low education and lower GDP *per capita*.

It should also be noted, as an important finding in the study⁶, and that deserves attention, the highest annual increase of IHD mortality in the age group of adolescents. This point still needs further scientific elucidation, however, it should be considered the likely effect of the growth of overweight, obesity and dyslipidemia in this age group, which is already present in a significant way in the northeast region.¹⁰⁻¹³

Given the difference of development among Brazilian regions and states, which reflects on health disparities, the need to intensify public prevention policies in the northeast is reinforced. These undergo educational measures to control the main risk factors for IHD: hypertension, dyslipidemia, diabetes, smoking, a strong stimulus to healthy eating to maintain adequate weight, in addition to improving access and quality of health services, to reverse the trend in IHD mortality and other CVDs in this region.

Keywords

Myocardial Ischemia; Mortality; Cardiovascular Diseases; Brazil.

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References

1. World Health Organization [Internet]. Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019 [cited 2021 May 11]. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death>
2. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. *Arq Bras Cardiol.* 2020;115(3):308-439. doi: 10.36660/abc.20200812.
3. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1736-1788. doi: 10.1016/S0140-6736(18)32203-7.
4. Ribeiro ALP, Duncan BB, Brant LC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular Health in Brazil: Trends and Perspectives. *Circulation.* 2016;133(4):422-33. doi: 10.1161/CIRCULATIONAHA.114.008727.
5. GBD 2016 Brazil Collaborators. Burden of disease in Brazil, 1990-2016: a systematic subnational analysis for the Global Burden of Disease Study 2016. *Lancet.* 2018;392(10149):760-775. doi: 10.1016/S0140-6736(18)31221-2.
6. Santana GBA, Leal TC, Paiva JPS, Silva LF, Santos LG, Oliveira TF, et al. Temporal Trend of Mortality Due to Ischemic Heart Diseases in Northeastern Brazil (1996–2016): An Analysis According to Gender and Age Group. *Arq Bras Cardiol.* 2021; 117(1):51-60.
7. Mansur P, Favarato D. Mortality due to Cardiovascular Diseases in Women and Men in the Five Brazilian Regions, 1980-2012. *Arq Bras Cardiol.* 2016;107(2):137-46. doi: 10.5935/abc.20160102.
8. Souza MF, Alencar AP, Malta DC, Moura L, Mansur AP. Serial temporal analysis of ischemic heart disease and stroke death risk in five regions of Brazil from 1981 to 2001. *Arq Bras Cardiol.* 2006;87(6):735-40. doi: 10.1590/s0066-782x2006001900009.
9. Baena CP, Chowdhury R, Schio NA, Sabbag AE Jr, Guarita-Souza LC, Olandoski M, et al. Ischaemic heart disease deaths in Brazil: current trends, regional disparities and future projections. *Heart.* 2013;99(18):1359-64. doi: 10.1136/heartjnl-2013-303617.
10. Jesus GDS, Costa PRF, Oliveira LPM, Queiroz VAO, Cunha CM, Pereira EM, et al. Body Adiposity and Apolipoproteins in Children and Adolescents: A Meta-Analysis of Prospective Studies. *Arq Bras Cardiol.* 2020;115(2):163-171. doi: 10.36660/abc.20190331.
11. World Health Organization [Internet]. Obesity and overweight [cited 2021 May 11]. Available from: <https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight>
12. Ribas SA, Silva LC. Dyslipidemia in schoolchildren from private schools in Belém. *Arq Bras Cardiol.* 2009;92(6):412-7. doi: 10.1590/s0066-782x2009000600006.
13. Faria Neto JR, Bento VF, Baena CP, Olandoski M, Gonçalves LC, Abreu GA, et al. ERICA: prevalence of dyslipidemia in Brazilian adolescents. *Rev Saude Publica.* 2016;50(Suppl 1):10s. doi: 10.1590/S01518-8787.2016050006723.



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HDI, Technological and Human Resources in the Diagnosis and Treatment of Malformations of the Circulatory System in Brazil

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Abstract

Background: In 2015, the number of infants with congenital malformations (CMs) per 100 000 live births (LBs) was 2368 (7.6%) worldwide, of whom 10.6% died in the first year of life, 43% due to malformations of the circulatory system (MCSs), a scenario similar to what occurs in Brazil.

Objective: To assess, per Brazilian macroregion, whether diagnosis of MCS at birth and death due to MCS in the first year of life associate with human development index (HDI) and with technological and human resources.

Methods: Ecological study including data available in 2000–2015. Data of LBs, deaths and availability of echocardiography devices were obtained from the DATASUS website. The HDI was obtained from the Atlas of Human Development in Brazil, while other variables were obtained from medical demographic data. Correlation measures between the variables were performed using the Kendall index.

Results: The CM rate was 660.8/100 000 LBs, of which 18 444 were due to MCS (diagnosis rate, 38.55/100 000 LBs). Of all Brazilian macroregions, the Southern and Southeastern regions, with the highest HDI values and resources, had the highest MCS diagnosis rates (56.94/100 000 and 62.83/100 000 LBs, respectively). The Northern and Northeastern regions, with the lowest HDI values and resources, had the lowest MCS diagnosis rates (9.77/100 000 and 13.43/100 000 LBs, respectively). The MCS diagnosis rate was 6.4-fold higher in the Southeastern region as compared to the Northern region, but mortality rates were similar in both regions.

Conclusion: Of the CMs, the MCS accounted for the highest number of deaths in children under the age of 1 year in Brazil.

Keywords: Congenital Abnormalities; Cardiovascular Abnormalities; Heart Defects, Congenital/diagnosis; Infant Mortality; Epidemiology.

Introduction

Congenital malformation (CM) is defined as any defect in the formation of an organ or set of organs that determines the presence of a morphological abnormality at birth.¹ In 2015, the number of infants with CMs per 100 000 live births (LBs) worldwide was 2368 (7.6%), of whom 10.6% died in the first year of life, 43% due to malformations of the circulatory system (MCSs).²

The clinical presentation of MCSs varies from absence of malformation-related symptoms to symptomatic cardiac disease and risk of death. Approximately 25% of all MCSs are deemed critical and require intervention in the first year of life because they are often incompatible

with life and highly dependent on adequate medical and hospital support.³ Most deaths due to MCSs could be prevented with early diagnosis and appropriate treatment; therefore, MCSs are considered to be preventable causes of death.⁴

In 2015 in Brazil, 7.4% of the LBs were diagnosed with some CM at birth, and the percentage distributions of the types of CM and mortality were similar to those reported in the *Global Burden of Disease Study*.² Geopolitically, Brazil is subdivided into five “macroregions” (North, Northeast, West-Central, Southeast, and South), highly unequal in terms of distribution of resources and access to health care. Since those inequalities affect resources dedicated to the diagnosis and treatment of MCSs, it is important to investigate whether those inequalities impact the risk of death from MCSs in the first year of life.

Based on the above observations, the aim of this study was to assess the association of the diagnosis of MCS at birth and death from MCS in the first year of life with the human development index (HDI) and the availability of technological and human resources dedicated to the diagnosis and treatment of MCSs per Brazilian macroregion.

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Methods

Ecological study of the associations of MCS diagnosis at birth and MCS mortality in children younger than 1 year of age with (1) distribution of pediatricians, (2) distribution of cardiovascular surgeons, (3) availability of centers providing pediatric cardiac surgery, (4) number of echocardiography devices, and (5) HDI of the Brazilian macroregions, from 2000 to 2015. The study was approved by the Research Ethics Committee of the Clementino Fraga Filho University-affiliated Hospital (number 44662215.4.0000.5257).

Data regarding LBs, as well as the presence of malformations at birth, were obtained from the Brazilian Information System on Live Births (in Portuguese, *Sistema de Informações sobre Nascidos Vivos - SINASC*),⁵ which contains information of all live birth certificates registered in each Brazilian federative unit and is available on annual datasets from the Brazilian Unified Health System database (DATASUS) (<http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinasc/cnv/nvuf.def>). We chose to study the period between 2000 and 2015 because of the completeness of information available since 2000, especially in the Northern and Northeastern regions.

Death-related data were obtained from the DATASUS website (<http://datasus.gov.br/informacoes-de-saude/servicos2/transferencia-de-arquivos>). These sets of information comprise a combination of all death certificates registered in Brazil between 2000 and 2015, year by year, per place of residence, and per federative unit. From each database, we selected only deaths of children under the age of 1 year.⁵

The malformations identified at birth and the deaths whose underlying causes related to the ICD-10 chapter XVII were subdivided into "MCSs" and "other congenital malformations (OthCMs)".⁶ According to the anatomic location of the malformation, MCSs were distributed into the categories "cardiac chambers and septa" (Q20-21), "valves" (Q22-23), "others" (Q24 except 9) and "unspecified" (Q24.9), and "vessels" (Q25-28). The OthCMs were classified as follows: "nervous system" (Q00-07); "eye, ear, face, and neck" (Q10-18); "respiratory system" (Q30-34); "cleft lip and palate" (Q35-37); "digestive system" (Q38-45); "genital organs and urinary system" (Q50-56 and Q60-64); "musculoskeletal system" (Q65-79); "integument" (Q80-85); "other congenital malformations" (Q86-89); "chromosomal abnormalities" (Q90-99); "congenital syphilis" (A50, chapter I); and "lymphangioma and hemangioma" (D18, chapter II).

The distributions of pediatricians and cardiovascular surgeons across the country were obtained from the study on medical demography based on the medical censuses of the years 2011, 2013, and 2015.⁷⁻⁹ The variables used to assess the healthcare for the diagnosis and treatment of MCS were obtained from the DATASUS website and have been made available monthly since August 2005. Those variables included the number of centers classified as providing pediatric cardiovascular surgery and the number of echocardiography devices in use. Admissions due to MCSs in each macroregion have been made available from January 2000 onwards.¹⁰

The HDI of each federative unit for the year 2010 was obtained from the *Atlas of Human Development in Brazil*.¹¹ The HDI of each federative unit was weighted by each

unit's population size to yield the HDI of each macroregion. Information regarding the populations was obtained from the website of the Brazilian Institute of Geography and Statistics (<https://www.ibge.gov.br/apps/populacao/projecao>), which provides projections for the years 2000 to 2060.

This study was carried out using official databases, available on the DATASUS website, which provide anonymized information, thus not allowing the identification of the individuals.

Statistical analysis

For each Brazilian macroregion, we calculated the following rates related to children under the age of 1 year: (A) diagnostic rates of MCSs and OthCMs per 100 000 LBs, (B) mortality rates, and (C) proportional mortality from specific MCSs and from circulatory system diseases (CSDs). The estimates were calculated for each year and for the entire study period.

Data of the variables used to assess the healthcare units providing the diagnosis and treatment of MCSs were not available for the entire study period. Therefore, we calculated an annual estimate of these data using the mean of the available periods. The indicators corresponding to each of these variables, with the numbers of LBs used as denominators, were calculated by macroregion. The coefficients used for pediatricians, cardiovascular surgeons, centers providing pediatric cardiovascular surgery, and echocardiographic devices were calculated in relation to 1000 LBs and the coefficients for hospitalizations were calculated in relation to 100 000 LBs. Correlation measures were performed using the Kendall index, with a 95% significance index.

The data obtained from the DATASUS were analyzed with Stata,¹² version 14 (StataCorp LP, College Station, TX, USA), in tables exported to spreadsheets (Microsoft Excel, Microsoft, Seattle, WA, USA).¹³

Results

A total of 47 715 968 LBs were registered in Brazil between 2000 and 2015. The presence of CM in any organ or system was detected in 315 322 (0.66%) births, resulting in a rate of 660.8/100 000 LBs. Of all CMs, 18 444 were MCSs, with a rate of diagnosis of 38.55/100 000 LBs.

The distribution of the Brazilian population by macroregion is as follows: 14.4% inhabitants in the Southern region, 42.2% in the Southeastern, 8.3% in the Northern, 27.9% in the Northeastern, and 7.3% in the West-Central region.⁵ The highest rates of diagnosis of CMs per 100 000 LBs occurred in the Southern (719.47) and Southeastern (694.96) regions, while the Northern (464.02), West-Central (546.73) and Northeastern regions (559.29) showed lower rates with some oscillations over time. As shown in Figure 1, MCSs diagnosed at birth were more frequent in the Southeastern region (62.83/100 000 LBs) and less frequent in the Northern region (9.77/100 000 LBs). Regional differences in the rates of diagnosis of MCSs have become wider in the last 5 years, especially due to higher rates of MCSs in the Southeastern region, while diagnostic rates of OthCMs increased until 2011, with reasonable differences between regions, and stabilized

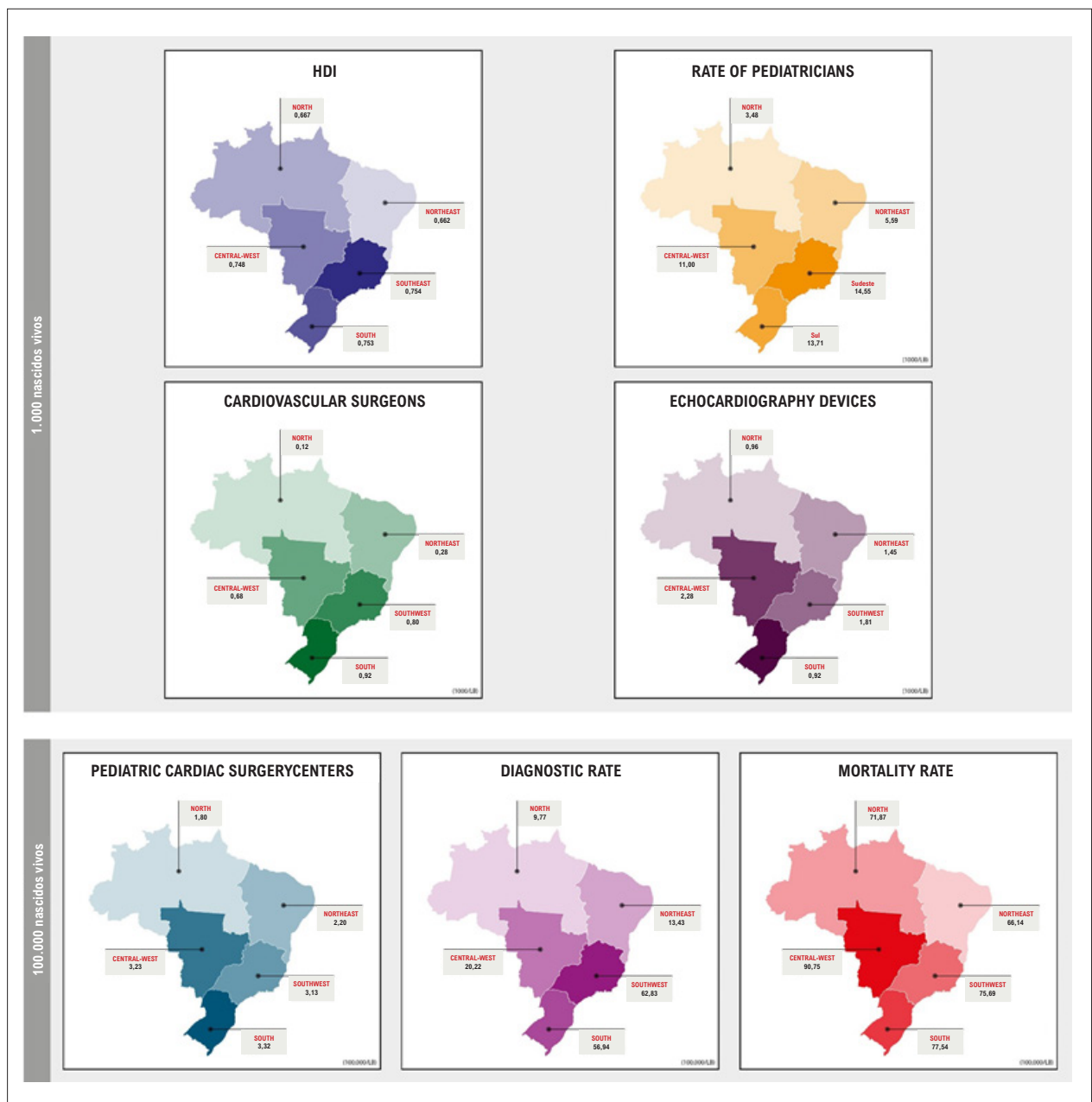


Figure 1 – Technological and human resources for the diagnosis and treatment of malformations of the circulatory system by Brazilian macroregion. HDI: human development index; LB: live births

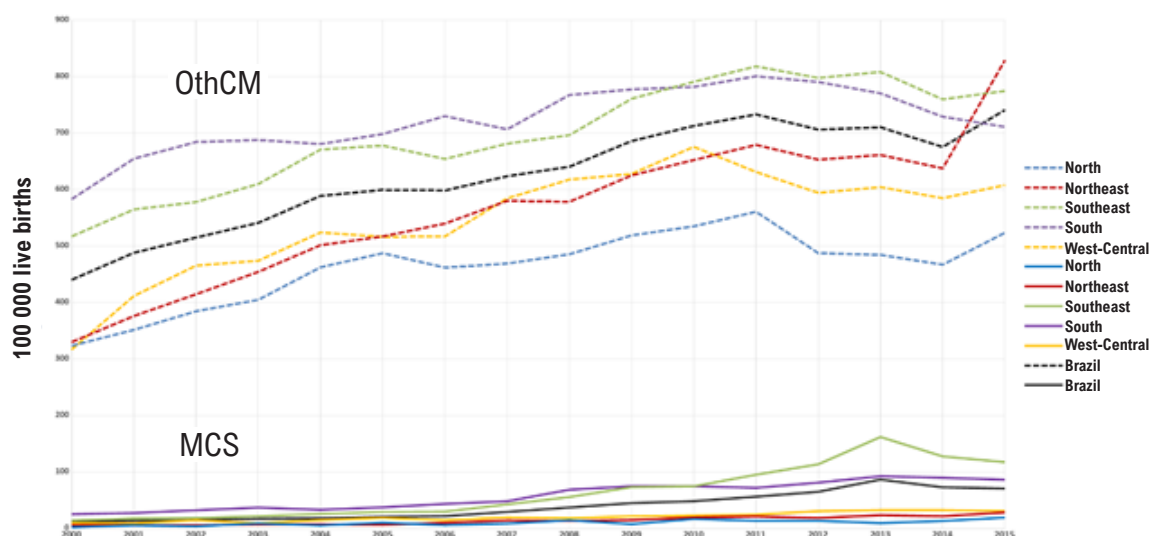
from then on, except for the Northeastern region (Figure 2a). All correlations between the variables studied were positive, that is, increases or decreases were concomitant in each pair of variables (Table 1).

In the period from 2000 to 2015, there were 756 201 deaths in children under the age of 1 year in Brazil. Of these, 126 877 occurred due to CM in any organ or system, with a mortality rate of 119.76/100 000 LBs. The MCSs corresponded to 38.2% of the deaths from CMs, with a mortality rate of 73.98/100 000 LBs. Figure 2b shows that the differences in the mortality rates from MCSs between the regions decreased

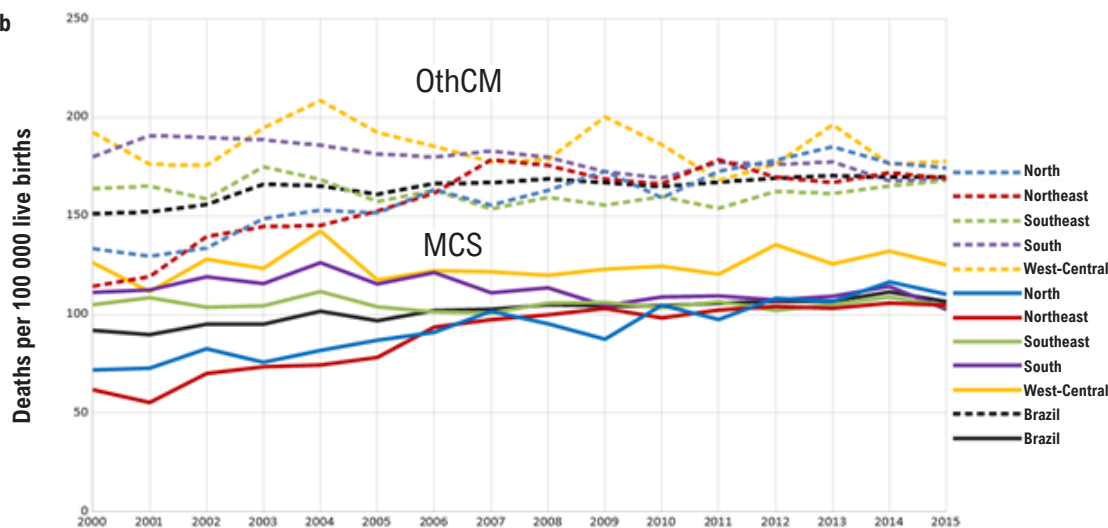
over the study period, except for the West-Central region, where those rates remained the highest throughout the period. The same occurred with mortality due to OthCMs, in which the West-Central region remained with the highest rates throughout the period.

As shown in Figure 3a, the type of CM per organ or set of organs affected most frequently diagnosed at birth in all regions was “malformation of the musculoskeletal system” (41.5%) followed by “other congenital malformations” (10.1%). The MCSs corresponded to 5.9% of all CM diagnoses, and 63.8% of the MCS diagnoses occurred in the Southeastern region.

Figure 2.a



2.b



Figures 2 – A) Diagnosis at birth of malformations of the circulatory system (MCS) and other congenital malformations (OthCM) in live births in Brazil. **B)** Mortality due to malformations of the circulatory system and other congenital malformations in children younger than 1 year, Brazil.

It is worth noting that 39.2% of the LBs in the country in the study period occurred in the Southeastern region, while in other regions the distribution of LBs was as follows: 10.71%, in the North; 29.02%, Northeast; 13.07%, South; and 7.86% West-Central. Figure 3b shows that from 2000 to 2015, in Brazil, MCSs were the most frequent cause of death from CM (38.2%), while malformations of the musculoskeletal system corresponded to 7.9% of those deaths. The West-Central region had the highest mortality rate attributed to MCS (90.75/100 000 LBs) in the same period.

Table 2 shows the proportional mortality in children under the age of 1 year attributed to CSD and MCS, with subdivision for specific causes. More than 83% of the deaths attributed to

circulatory system causes were due to MCS in all regions, with emphasis on the Southern region, where that rate was 93%. In this set of CSD and MCS, unspecified MCSs accounted for half of the deaths of children under 1 year of age in Brazil, of which less than half (44%) occurred in the Southeast alone. The Northern region showed a proportional mortality due to CSD 2.5 times higher than that of the Southern region. Cardiomyopathy corresponded to 32% of the deaths from CSD and emerged as the main cause of death in this subset in all regions.

Between 2000 and 2015, the rate of diagnosis of MCS at birth was 6.4 times higher in the Southeast than in the North, but the mortality rates were similar in both macroregions. Compared with the Southeast, the West-Central had almost

Table 1 – Correlations of diagnostic and mortality rates of malformations of the circulatory system with human development index (HDI) and rates of pediatricians, of cardiovascular surgeons, of echocardiographic devices and of pediatric cardiac surgery centers (Kendall index)

	HDI-M	Rate of pediatricians	Cardiovascular surgeons	Echocardiography devices	Pediatric cardiac surgery centers	diagnostic rate	Mortality rate
HDI-M	1.00						
Rate of pediatricians	0.80	1.00					
Cardiovascular surgeons	0.60	0.80	1.00				
Echocardiography devices	0.40	0.60	0.80	1.00			
Pediatric cardiac surgery centers	0.40	0.60	0.80	1.00	1.00		
Diagnostic rate	0.80	1.00	0.80	0.60	0.60	1.00	
Mortality rate	0.40	0.20	0.40	0.60	0.60	0.20	1.00

the same amount of resources (pediatricians, cardiovascular surgeons, centers providing pediatric cardiovascular surgery, and number of echocardiography devices) but made 3 times less MCS diagnoses and had a 1.2-fold higher mortality rate (Figure 1).

Discussion

Across the five Brazilian macroregions, between 2000 and 2015, we observed three patterns of association of the diagnosis of MCS at birth and death from MCS with HDI and technological and human resources dedicated to MCS diagnosis and treatment. The Southern and Southeastern regions, with the highest values of HDI and technological and human resources, showed the highest rates of diagnosis of MCSs at birth and of death attributed to MCSs, the latter consequent to better diagnostic ability. The Northern and Northeastern regions, with the lowest values of HDI and resources, had the lowest diagnostic rates of MCS at birth and death in the first year of life. On the other hand, the West-Central region, which had resources similar to those in the Southern and Southeastern regions, had a low rate of MCS diagnosis at birth and an improvement in the diagnosis of MCS by the time of death.

Comparing the diagnostic rates of CMs and MCSs at birth in Brazil with the global rates according to data provided by the *Global Burden of Disease Study* in the same period and age range of our study, we found the diagnostic rates of CM and MCS to be 1.40 and 1.78 times lower, respectively, than the global rates.² Even in the Southern region, which performed better than the other Brazilian regions, the diagnostic rates for CMs and MCS were 1.30 times and 1.70 times lower, respectively, compared with the global rates. When comparing the rates of the Northern region with those of countries in North America, Western Europe, Australia, and Japan, ours were even lower: 1.42 times for CMs and 1.83 times for MCSs.^{2,14}

The difference in the diagnostic rates of MCSs among countries is related to variations in investment in health care resources. Countries with higher gross domestic product and HDI have higher rates of MCS diagnosis.^{15,16} Similar

relationships have been found with the HDI and the diagnosis rate of MCS among regions and countries with similar HDI.² Caneco et al.¹⁶ have compared the need for cardiac surgery and the number of such surgeries performed in the first year of life in 2010 between the state of São Paulo and Poland, which had similar HDI and population size at that time.¹⁶ The authors have observed that, in children under the age of 1 year in Poland, 100% of the required surgeries were performed, whereas in the state of São Paulo, this rate was only 50%. This can be explained by the availability of access to health care resources, which occurs heterogeneously in Brazil due to geographical, sociocultural, and economic differences.¹⁶⁻¹⁸

Between 2000 and 2015, there was an increase in the diagnostic rates of OthCMs and MCS at birth in all Brazilian regions, and the percent differences between them remained constant in the period. In the Southern and Southeastern regions, the decrease in deaths was accompanied by an improvement in diagnostic rates over time, whereas in the Northern and Northeastern regions, there was an improvement in the diagnostic ability around the time of death, which resulted in an increased mortality rate for both OthCM and MCS. The Southeastern region, with the highest rates of MCS diagnosis at birth, showed death rates due to MCS similar to those of the Northern region; thus, as compared to the Northern region, the resources in the Southeastern region could more successfully prevent deaths from MCS at the time of birth. Over the study period, the differences in the mortality rates from OthCM and MCS in the Northern and Northeastern regions were reduced as compared to the other regions. This fact can be attributed to the results of the "Pact for the Reduction of Maternal and Neonatal Mortality",¹⁹ signed in 2004 among the three Brazilian federative health care levels to reduce neonatal mortality. The strategies to achieve that goal were designed to reduce mortality with more emphasis on the Northern and Northeastern regions, resulting in a greater contribution of resources and personnel to those regions. In addition, the accentuated slope in the OthCM curve between 2014 and 2015 in the Northeastern region might have been caused by the outbreak of the Zika virus that contributed to malformations of the nervous system.²⁰

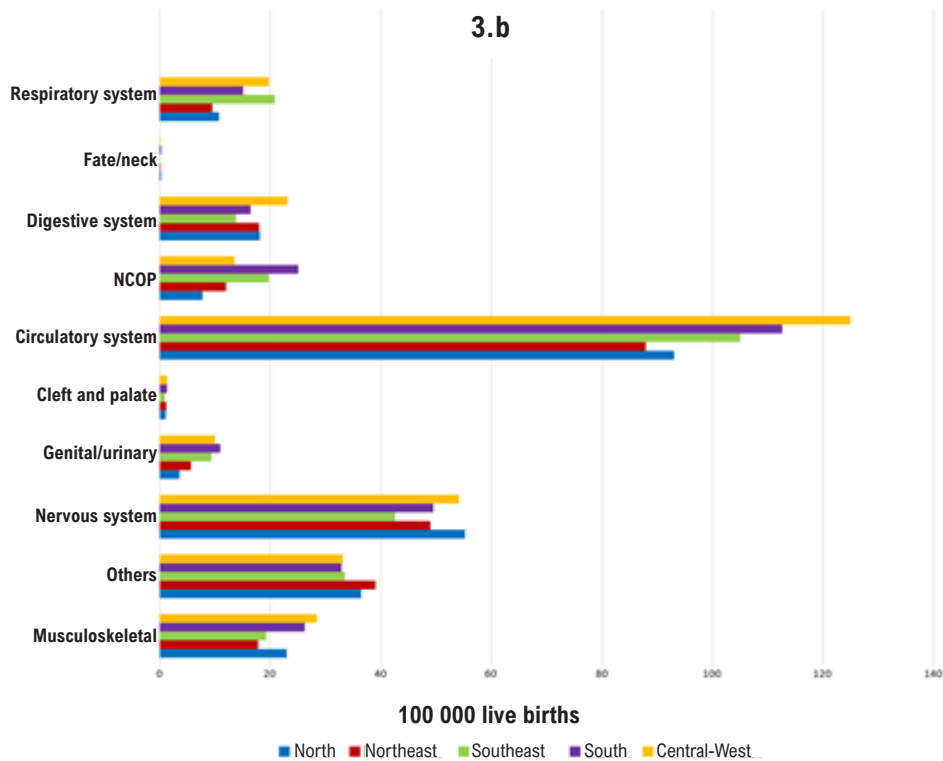
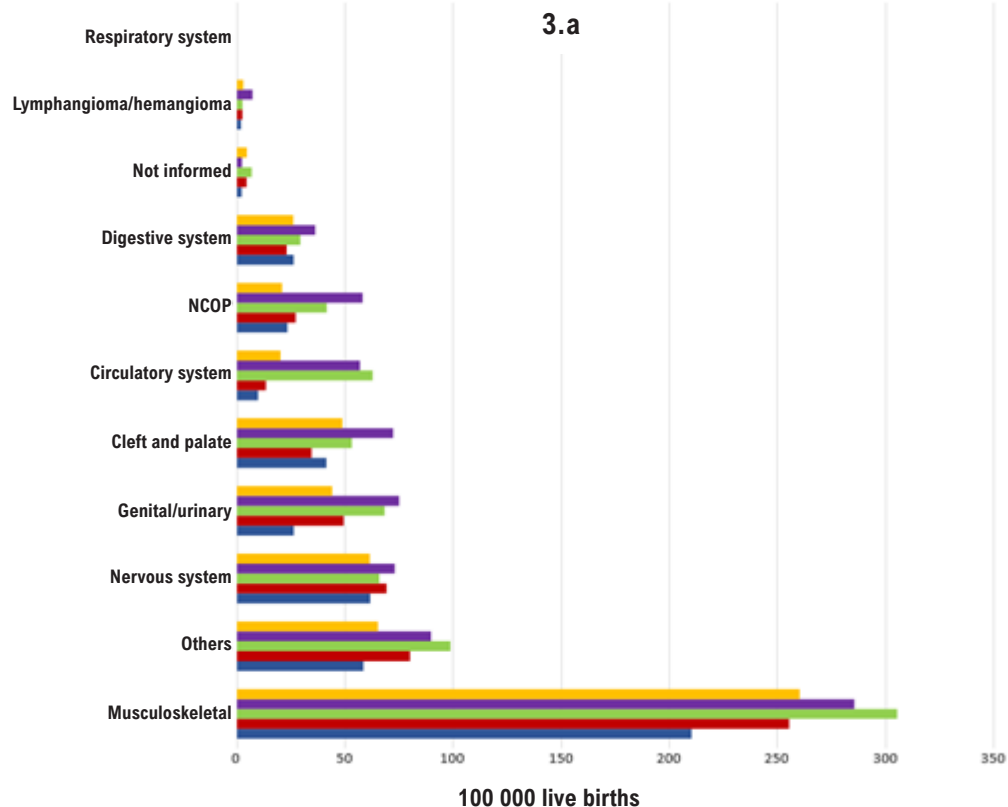


Figure 3 – A) Diagnosis by groups of types of congenital malformations present at birth between 2000 and 2015, Brazil; B) Childhood mortality by groups of types of congenital malformations between 2000 and 2015, Brazil.

Table 2 – Proportional mortality from circulatory system diseases and malformations of the circulatory system in children younger than 1 year between 2000 and 2015 subdivided by specific cause and distributed by Brazilian macroregions

Cause of death		North	Northeast	Southeast	South	West-Central	Total
Pulmonary heart disease and disease of the pulmonary circulation	Deaths PM (%)	84 1.51	189 1.31	396 1,76	62 0,83	76 1,49	807 1,46
Pericarditis and endocarditis	Deaths PM (%)	27 0,49	60 0,41	142 0,63	21 0,27	27 0,53	277 050
myocarditis	Deaths PM (%)	10 0,18	25 0,17	84 0,37	49 0,65	8 0,16	176 0,32
Cardiomyopathies	Deaths PM (%)	277 4,99	713 4,93	933 4,14	122 1,63	171 3,36	2216 4,02
Heart failure	Deaths PM (%)	163 2,94	347 2,40	276 1,22	73 0,97	56 1,10	915 1,66
Cerebrovascular diseases and diseases of other vessels	Deaths PM (%)	121 2,18	249 1,72	459 2,03	66 0,88	83 1,63	978 1,77
Outras doenças do aparelho circulatório	Deaths PM (%)	240 4,32	541 3,74	648 2,87	97 1,29	120 2,36	1646 2,98
Subtotal DAC	Deaths PM (%)	922 16,61	2124 14,68	2938 13,02	490 6,53	541 10,63	7015 12,71
Chambers and septa	Deaths PM (%)	670 12,07	1554 10,74	4260 18,88	1357 18,08	866 17,01	8707 15,78
Valves	Deaths PM (%)	172 3,10	428 2,96	1605 7,11	699 9,31	282 5,54	3186 5,77
Unspecified	Deaths PM (%)	2927 52,74	8283 57,25	9902 43,89	3834 51,08	2759 54,20	27705 50,21
Others	Deaths PM (%)	531 9,27	1199 8,29	1600 7,09	384 5,12	254 4,99	3968 7,19
Vessels	Deaths PM (%)	328 5,91	81 6,09	2255 9,99	742 9,88	388 7,62	4594 8,33
Subtotal MCS	Deaths PM (%)	4628 83,39	12345 85,32	19622 86,98	7016 93,47	4549 89,37	48160 87,29
Total CSD + MCS	Mortes MP (%)	5550 100,00	14469 100,00	22560 100,00	7506 100,00	5090 100,00	55175 100,00

PM: proportional mortality; CSD: circulatory system disease; MCS: malformations of the circulatory system; total CSD + MCS: total deaths due to circulatory system disorders.

The Northern and Northeastern regions had a higher percentage of diagnoses of deaths due to CSD in the first year of life, which can be explained by misdiagnoses of MCS and CSD, probably more frequent in those regions, because the differential diagnosis between those causes is more difficult when diagnostic resources are scarce or delayed.²¹

Of the CMs, MCSs had the highest mortality because they require an early diagnosis for therapy initiation, considering that among children born with some type of congenital heart disease, survival is below 14% during the first month of life and 30% during the first year in the absence of medical intervention.²² Surgical interventions in the first year of life are necessary for 50% of the patients with congenital heart disease, which results in high expenditures for treatment and complex technical and human resources.²³⁻²⁵ However, for adequate therapeutic support, a correct diagnosis of MCS is necessary, and, in Brazil, even in the Southern and Southeastern regions, unspecified MCSs are the most frequent CMs, which reflects

not only difficulties in access to care but also poor quality of diagnosis.

The number of echocardiography devices showed a weak relation with the diagnosis rate of MCSs by macroregion. The Northern region had the lowest ratio between the number of available devices and diagnostic rates, but the West-Central region, which had a number of devices close to that of the Southern region, had a diagnosis rate 3 times lower. The Southeast, with a lower ratio of echocardiography devices than the West-Central, had a diagnosis rate 3.1 times higher. This can be explained by the fact that not all devices used in Brazil are able to perform neonatal and pediatric examinations, in addition to depending on the availability of probes appropriate for children, specific software, echocardiographers trained in pediatrics, devices located near sites with greater patient demand, and patient accessibility.²⁶⁻²⁸

The number of cardiac surgeons, pediatricians, and centers performing pediatric cardiac surgery followed the

same relationship as the number of echocardiography devices, which demonstrates that it is not only the amount of technological and human resources per region that determines the diagnostic capacity, but also how and when these resources are made available to the population. Early diagnosis of CMs, including MCSs, should be established before birth to enable the patients to be referred to specialized treatment centers even before their birth.^{29,30}

This study has limitations, such as the use of official databases, whose information had been collected by the institutions that provide assistance to childbirth and death and that do not follow a common protocol or research planning. Another limitation was the analysis of data from sources with temporal differences. However, this problem did not affect our results because the data underwent little variation over the study period and the calculated means were similar to those of the following years. Another limitation was the heterogeneous quality of the information about causes of death and diagnosis of CM in the death and live birth certificates, which depends on the adherence to the ICD-10 rules and the proper completion of death and live birth certificates. However, death and live birth certificates are the only comprehensive sources on Brazilian death and birth data available that allow population analysis. Other possible limitation was the use of the diagnosis of MCS only at birth, considering that many CMs are diagnosed over the first days of life. In addition, the time elapsed from diagnosis to death from MCS could not be known because information on the time of diagnosis was not available.

Conclusion

Regional differences in the rates of diagnosis of MCS at birth and of death due to MCS in the first year of life in Brazil

are associated with unequal availability of technological and human resources for health care. The lower that availability, the more delayed the diagnoses or the lower their number. The underestimation of death rates from MCS in the Northern and Northeastern regions was due to competition with other causes, such as CSD, external and ill-defined causes, as well as deficiencies in diagnosis. Several actions are necessary to improve the diagnosis and therapy of MCS, such as measures to increase the health care resources, whose access should be made available to the entire population.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Salim TR, Andrade TM, Klein CH, Oliveira GMM

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. World Health Organization. (WHO) Birth defects. Sixty-third world health assembly A63/10. Geneva, 2010. Available from http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf?ua=1
2. Global Burden of Disease Collaborative Network. (Cited September 2018) Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017. Available from <http://ghdx.healthdata.org/gbd-results-tool>
3. Hoffman JIE, Kaplan S. The Incidence of Congenital Heart Disease. *Jam Coll Cardiol*. 2002;39(12):890-900
4. Brasil.Ministério da Saude. Secretariat of Health Surveillance, Secretariat of Health Care, Ministry of Health. Manual of surveillance of child and fetal death and the Committee for the Prevention of Child and Fetal Death. 2nd.Brasilia;2009.
5. Brasil. Ministério da Saúde. Ministry of Health. Datasus: health information, morbidity and epidemiological information. [Quoted on August 2018]. Available from :<http://www.datasus.gov.br>.
6. World Health Organization. (WHO). International statistical classification of diseases and health-related problems: International Classification of Diseases. (ICD). 10th review. Sao Paulo: EDUSP; 1995
7. Scheffer, M.(coord). Medical Demography in Brazil 2015. Department of Preventive Medicine, USP School of Medicine. Regional Council of Medicine of the State of São Paulo. Federal Council of Medicine. Sao Paulo: 2013.vol.3 ISBN: 978-85-89656-22-1
8. Scheffer, M.(coord). Medical Demography in Brazil 2011. Department of Preventive Medicine, USP School of Medicine. Regional Council of Medicine of the State of São Paulo. Federal Council of Medicine. Sao Paulo: 2011.vol.1
9. Scheffer, M.(coord). Medical Demography in Brazil 2013. Department of Preventive Medicine, USP School of Medicine. Regional Council of Medicine of the State of São Paulo. Federal Council of Medicine. Sao Paulo: 2013.vol.3
10. Brasil. Ministério da Saúde. TABNET, health information / Datasus. [Cited in 2019 Nov 12].Available from <http://www2.datasus.gov.br/DATASUS/index.php?area=0204&id=6906>
11. Atlas of Human Development in Brazil. [Cited in 2019 Nov 12].Available from <http://www.atlasbrasil.org.br/2013/pt/home/>
12. Statistics/Data Analysis. STATA Corporation: STATA, Version 14. Texas: University of Texas (USA); 2013.
13. Microsoft Corporation Microsoft Excel. Version 2016. Redmond: Washington, 2016.
14. Reller MD, Strickland JM, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of Congenital Heart Defects in Metropolitan Atlanta, 1998–2005. *Pediatr*. 2008 December; 153(6): 807–13. doi:10.1016/j.jpeds.2008.05.059.
15. Yu C, Moore BM, Kotchetkova I, Cordina RL, Celermajer DS. Causes of death in a contemporary adult congenital heart disease cohort. *Heart Journal*, 2018. DOI: 10.1136/heartjnl-2017-312777

16. Caneo LF, Jatene MB, Yatsuda N, Gome WJ. A reflection on the performance of pediatric cardiac surgery in the State of São Paulo. *Rev Bras Cir Cardiovasc*. 2012;27(3):457-62. DOI: 10.5935/1678-9741.20120076
17. Duncan P, Bertolozzi MR, Cowley S, Egry EY, Chiesa AM. "Health for All" in England and Brazil? In *J Health Serv*. 2015;45(3):545-63. DOI: 10.1177/0020731415584558
18. Stopa SR, Malta DC, Monteiro CN, Szwarcwald CL, Goldbaum M, Galvão Cesar CL. Use of and access to health services in Brazil, 2013 National Health Survey. *Rev Saude Publ*. 2017;51(Suppl 1):3s. DOI: 10.1590/s1518-8787.2017051000074
19. Brasil. Ministério da Saúde. Secretariat of Health Care Department of Strategic Programmatic Actions. Covenant to Reduce Maternal and Neonatal Mortality. Brasília;2004. [Cited in jun 15] Available from <http://portal.arquivos.saude.gov.br/images/pdf/2016/junho/20/2.a%20Pacto%20redução%20mortalidade.pdf>
20. Nunes ML, Carlini CR, Marinowic D, Neto FK, Fiori HH, Scotta MC and et al. Microcephaly and Zika virus: a clinical and epidemiological analysis of the current outbreak in Brazil. *J Pediatr (Rio J)*. 2016 May-Jun;92(3):230-40. doi: 10.1016/j.jped.2016.02.009.
21. Salim TR, Soares GP, Klein CH, Oliveira GMM. Mortality from Circulatory System Diseases and Malformations in Children in the State of Rio de Janeiro. *Arq Bras Cardiol*. 2016;106(6):464-73.
22. Brum CA, Stein AT, Pellanda LC. Infant mortality in Novo Hamburgo: associated factors and cardiovascular causes. *Arq Bras Cardiol*. 2015;104(4):257-65.
23. Pinto Jr VC, Rodrigues LC, Muniz CR. Reflexões sobre a formulação de política de atenção cardiovascular pediátrica no Brasil. *Rev Bras Cir Cardiovasc*. 2009;24(1):73-80.
24. Bhide P, Gund P, Kar A. Prevalence of Congenital Anomalies in an Indian Maternal Cohort: Healthcare, Prevention, and Surveillance Implications. *PLoS ONE*. 2016; 11(11): e0166408. doi:10.1371/journal.pone.0166408
25. Rossi AC, Prefumo F. correlation between fetal autopsy and prenatal diagnosis by ultrasound: a systematic review. *Eur J Obstet Gynecol*. [Cited in 2019 Nov 16] Available from: <http://dx.doi.org/10.1016/j.ejogrb.2016.12.024>
26. Li A, Peng Z, Zhang C. Comparison of Echocardiography and 64-Multislice Spiral Computed Tomography for the Diagnosis of Pediatric Congenital Heart Disease. *Med Sci Monit*. 2017 May 13;23:2258-66.
27. Pinheiro DO, Varisco BB, Silva MB, Duarte RS, Deliberali GD, Maia CR. Accuracy of Prenatal Diagnosis of Congenital Cardiac Malformations *Rev Bras Ginecol Obstet*. 2019;41:11-6. DOI <https://doi.org/10.1055/s-0038-1676058>.
28. Andreazzi MFS, Bravo MIS. Privatization of management and social organizations in health care. *Trab Educ Saúde*. 2014;12(3):499-518.
29. Kermorvant-Duchemin E, Yves Ville Y. Prenatal diagnosis of congenital malformations for the better and for the worse. *J Matern Fetal Outcomes in Critical Congenital Heart Disease*. *Pediatrics*. 2017;140(4):e20170999
30. Steurer MA, Baer RJ, Keller RL, Oltman S, Chambers CD, Norton ME. Gestational age and outcomes in critical congenital heart disease. *Pediatrics*. 2017;140(4):e20170999



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HDI, Technological and Human Resources for the Diagnosis and Treatment of Circulatory System Malformations in Brazil - Analysis of the Reality in Brazil

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Short Editorial related to the article: HDI, Technological and Human Resources in the Diagnosis and Treatment of Malformations of the Circulatory System in Brazil

In Brazil in 2019, circulatory system diseases (CSD) were the leading cause of death.¹ In children under one year of age, CSD is the ninth leading cause of death and, in the age group from 1 to 9 years old, the eighth.² In recent decades, there has been a reduction in the infant mortality rate to 11.9/1,000 live births (LB) in 2019.³ Despite the progressive reduction observed in recent years, this rate remains high when compared to that in developed countries. In Sweden, the infant mortality rate in the period of 2015/2020 was 2.0/1,000 LB. In Brazil, in children under five years of age, mortality was 14.0/1,000 LB, which occurred mainly in the first year of life.³ The main causes of neonatal mortality are perinatal asphyxia, extreme prematurity, and congenital malformations. Among the congenital malformations (CM), CSD have the greatest impact on mortality, as they are classified as preventable causes of death, which could be reduced through early interventions.⁴ High mortality rates due to malformations of the circulatory system (MCS) result from the lack of pre and postnatal diagnosis, resulting in inadequate treatment and a higher number of deaths.⁴⁻⁸

The study by Salim et al. aimed to verify the association of MCS diagnosis at birth and death from MCS in the first year of life with the human development index (HDI) and technological and human resources for the diagnosis and treatment of MCS by the macroregions of Brazil, using data obtained from DATASUS, in the period of 2000/2015.⁹

Between 2000/2015, the authors found a CM rate of 660.8/100,000 LB, being 18,444 due to MCS, and a diagnosis rate of 38.55/100,000 LB. Considering the five Brazilian macro-regions, the South and Southeast regions had the highest rates of diagnosis of MCS at birth and death from MCS, while the North and Northeast regions had the lowest rates of diagnosis of MCS at birth and death from MCS in the first year of life. The Midwest region, with resources similar to those of the South and Southeast regions, had a low rate of diagnosis

of MCS at birth and an improvement in the diagnosis of MCS after death. These data are a matter of concern, demonstrating the negative impact that social inequalities have on the population's health care, where the best results are described in the regions with the highest HDI values, technological and human resources. However, the national rates of CM and MCS diagnosis are even lower when compared to the global rates in the same period and for the same age group: 1.40 and 1.78, respectively.³ Differences remain when compared to developed countries, where there is greater investment in health care resources.^{3,10}

We still experience a significant gap in the number of pediatric cardiac surgeries performed annually in the country.¹¹ Considering a prevalence of congenital heart disease (CHD) of 9:1,000 LB, the estimate is of 28,846 new cases/year of CHD, of which approximately 50% will need cardiac surgery in the first year of life, corresponding to an average need for cardiac surgery in CHD of around 23,077 procedures/year.¹² Pinto Jr et al., when analyzing the situation of Brazilian cardiovascular surgery, regarding the number of procedures carried out in 2002, found a deficit of 65%, with the highest rates being found in the North and Northeast regions (93.5% and 77.4%, respectively) and the lowest ones in the South and Midwest regions (46.4% and 57.4%, respectively).¹¹

Caneo et al. compared the need and number of cardiac surgeries performed in the first year of life in 2010 between the state of São Paulo and Poland, which had similar HDI and population size at the time. In Poland, children under 1 year of age underwent 100% of the necessary surgeries, while in São Paulo, only 50% did. This demonstrates that even in one of the main cardiac surgical centers of the country, we still have a long way to go in terms of early diagnosis and intervention.¹³

It is worth highlighting some aspects in the study by Salim et al, such as a higher mortality rate from MCS in the North, Northeast, and Midwest regions, among cases of CM in the first year of life.^{7,9} This occurs due to several conditions: the CHD considered critical requires early pre and postnatal diagnosis, childbirth care, and guaranteed access to reference centers for the indicated cases, which requires specialized human and technological resources.^{7,8,11,14} According to the data found, there is a significant deficit of human resources with adequate training to carry out the diagnosis and care of children with heart disease, especially in the North, Northeast, and Midwest regions, related not only to pediatricians but also to pediatric cardiologists with training in echocardiography, cardiovascular surgeons and the availability of pediatric cardiac surgical centers by macroregion.

Keywords

Cardiovascular Disease; Heart Defects; Public Health Service; Infant Mortality; Perinatal Mortality.

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The reduction of infant mortality is still a major challenge in Brazil for governments, health professionals, and society as a whole. The improvement of public health strategies and greater attention to newborns, aiming at early diagnosis and treatment of congenital heart disease is necessary.¹⁴

According to Ottersen et al., the objective of the policy for equity in health is not to eliminate all differences in health so that everyone has the same quality of care, but to reduce or eliminate the ones that result from factors considered preventable and unfair.¹⁵

References

1. Instituto Brasileiro de Geografia e Estatística [Internet]. Brasília: IBGE; 2021 [cited 2021 Jun 8]. Available from: <http://www.ibge.gov.br/home>
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Secretaria de Atenção à Saúde. Manual de vigilância do óbito infantil e fetal e do Comitê de Prevenção do Óbito Infantil e Fetal. 2nd ed. Brasília: Ministério da Saúde; 2009.
3. Global Burden of Disease Study 2019 (GBD 2019) results. Global Health Data Exchange website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2019.
4. World Health Organization. International statistical classification of diseases and health-related problems: ICD-10. 10th ed. Malta: WHO; 2010.
5. Scheffer M, editor. Medical demography in Brazil 2011. São Paulo: Conselho Regional de Medicina; 2011.
6. Salim TR, Soares GP, Klein CH, Oliveira GM. Mortality from circulatory system diseases and malformations in children in the state of Rio de Janeiro. *Arq Bras Cardiol*. 2016;106(6):464-73. doi: 10.5935/abc.20160069.
7. Salim TR, Andrade TM, Klein CH, Oliveira GMM. Inequalities in mortality rates from malformations of circulatory system between Brazilian Macrorregions in individuals younger than 20 Years. *Arq Bras Cardiol*. 2020;115(6):1164-73. doi: 10.36660/abc.20190351.
8. Brum CA, Stein AT, Pellanda LC. Infant mortality in Novo Hamburgo: associated factors and cardiovascular causes. *Arq Bras Cardiol*. 2015;104(4):257-65. doi: 10.5935/abc.20140203.
9. Salim TR, Andrade TM, Klein CH, Oliveira GMM. HDI, Technological and Human Resources in the Diagnosis and Treatment of Malformations of the Circulatory System in Brazil. *Arq Bras Cardiol*. 2021; 117(1):63-71.
10. Duncan P, Bertolozzi MR, Cowley S, Egy EY, Chiesa AM, França FOS. "Health for All" in England and Brazil? *Int J Health Serv*. 2015;45(3):545-63. doi: 10.1177/0020731415584558.
11. Pinto VC Jr, Rodrigues LC, Muniz CR. Reflexions about formulation of politics for attention to cardiovascular pediatrics in Brazil. *Rev Bras Cir Cardiovasc*. 2009;24(1):73-80. doi: 10.1590/S0102-76382009000100014.
12. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-900. doi: 10.1016/s0735-1097(02)01886-7.
13. Caneo LF, Jatene MB, Yatsuda N, Gomes WJ. A reflection on the performance of pediatric cardiac surgery in the State of São Paulo. *Rev Bras Cir Cardiovasc*. 2012;27(3):457-62. English, Portuguese. doi: 10.5935/1678-9741.20120076.
14. Lopes SAVA, Guimarães ICB, Costa SFO, Acosta AX, Sandes KA, Mendes CMC. Mortality for critical congenital heart diseases and associated risk factors in newborns: a cohort study. *Arq Bras Cardiol*. 2018;111(5):666-73. doi: 10.5935/abc.20180175.
15. Ottersen OP, Dasgupta J, Blouin C, Buss P, Chongsuvivatwong V, Frenk J, et al. The political origins of health inequity: prospects for change. *Lancet*. 2014;383(9917):630-67. doi: 10.1016/S0140-6736(13)62407-1.



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Sensitivity and Specificity of Cutoff Points of Resting Heart Rate from 6,794 Brazilian Adolescents: A Cross-Sectional Study

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Abstract

Background: Resting heart rate (RHR) may be a useful screening tool for cardiovascular risk. However, RHR cutoff points, an interesting clinical approach, have never been described in young populations.

Objective: To establish RHR cutoff points in Brazilian adolescents and to analyze whether cutoff points are associated with cardiovascular risk factors.

Methods: The sample was composed of 6,794 adolescents (10 to 19 years old). Blood pressure and RHR were assessed by oscillometric device. Body mass index and waist circumference were also assessed. Receiver operating characteristic curve was adopted to analyze the sensitivity and specificity, and associations of high RHR with cardiovascular risk factors were analyzed by binary logistic regression. A p value < 0.05 was considered statistically significant for all the analyses.

Results: Mean RHR values were higher among participants ages 10 to 14 years than 15 to 19 years, for boys ($p < 0.001$) and girls (< 0.001). The proposed RHR cutoff points for cardiovascular risk factors detection were significant for boys ages 10 to 14 (> 92 bpm) and 15 to 19 years (> 82 bpm), as well as for girls ages 15 to 19 years (> 82 bpm) ($p < 0.05$ for all), whereas no cutoff point was identified for girls ages 10 to 14 years ($p > 0.05$). Proposed RHR cutoff points were associated with abdominal obesity, overweight, and high blood pressure in boys in girls. RHR cutoff points were associated with the cluster of cardiovascular risk factors in adolescents ages 15 to 19 years.

Conclusion: The proposed RHR cutoff points were associated with cardiovascular risk factors in adolescents.

Keywords: Heart Rate; Adolescent; Epidemiology; Adiposity; Blood Arterial; Risk Factors; Obesity; Cross-Sectional Studies.

Introduction

Resting heart rate (RHR) is an accessible measure that reflects the balance between the sympathetic and parasympathetic nervous systems.¹ Elevated RHR has been associated with adverse cardiovascular disease events and mortality in adults.^{2,3} It has also been associated with high blood pressure, abdominal obesity, and overweight,⁴⁻⁸ including in children and adolescents.⁸ Elevated RHR in childhood and adolescence seems to track long-term risk of cardiovascular disease to adulthood.⁹ Therefore, RHR

may be a useful screening tool for cardiovascular risk in young populations.

In children and adolescents, RHR decreases with age and is sex dependent.¹⁰⁻¹² Thus, RHR percentiles derived in the National Health and Nutrition Examination Survey (NHANES 1999-2008) in the United States,¹² an international study,¹³ and the German Health Interview and Examination Survey on Children and Adolescents (KiGGS) have presented RHR percentiles by age and sex, from the ages of 3 to 17 years.⁵

Despite the percentiles provided in previous studies, RHR cutoff points, which would be a more interesting clinical approach to improve the usefulness of this marker,¹⁴⁻¹⁶ have never been described. Likewise, as almost all of the studies were conducted in high-income countries,^{5,12,13} it is still unknown whether such results can be extrapolated for adolescents living in low- to middle-income countries (e.g., Brazil). Thus, the primary purpose of this study was to establish RHR cutoff points in 10 to 19 year olds. Secondary analysis aimed to explore whether these critical values were associated with cardiovascular risk factors.

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Methods

Study design and sample

This cross-sectional study was performed using the databases from three school-based studies in the following populations: 1) students ages 14 to 19 years from the public school system in the state of Pernambuco (Northeast Region of Brazil)⁴; 2) students ages 10 to 17 years from the public school system in the city of Londrina (state of Paraná, South Region of Brazil)¹⁷; and students ages 10 to 17 years from both public and private schools in the city of Presidente Prudente (state of São Paulo, Southeast Region of Brazil).¹⁸ Therefore, the target population in the current study was students ages 10 to 19 years old. The three studies were approved by the ethics committees of the University of Pernambuco, Londrina State University, and São Paulo State University, in compliance with the Brazilian National Research Ethics System Guidelines. The study procedures have been previously described.^{4,17}

Both studies had similar inclusion criteria, such as without known diabetes mellitus, cardiovascular disease, or neurological or mental disabilities. Due to cardiovascular measures (RHR and blood pressure), adolescents were excluded if they reported any of the following: alcohol use, use of any form of tobacco and/or illicit drugs, and participation in any physical exercise training on the day of measurement.

Behavioral variables such as physical activity level and unhealthy behavior were not considered in the present study due to methodological differences in the instruments used among studies. Therefore, only biological variables such as sex, age, blood pressure, RHR, and anthropometric measurements (weight, height, and waist circumference) with similar procedures were compiled in the current study.

Resting heart rate - Predictors

RHR measurements were obtained using the Omron HEM 742 blood pressure monitoring device (Omron, Shanghai, China), which has been previously validated¹⁹. After approximately 30 minutes at rest (approximate time to answer the questionnaire) and a period of at least five minutes in a seated position, all adolescents had their RHR measured three times, and the last two measurements were considered for analysis.

Outcomes

Blood pressure

Blood pressure was measured using the Omron HEM 742 blood pressure monitoring device (Omron, Shanghai, China).¹⁹ Each adolescent rested in a seated position for at least five minutes, with legs uncrossed. Blood pressure was measured in the right arm placed at the heart level, with an appropriate cuff size. For analysis, the means of the two last measurements were considered, and adolescents were classified as having high blood pressure if they had systolic and/or diastolic blood pressure equal to or greater than the reference sex-, age-, and height-specific 95th percentile.²⁰

Overweight and abdominal obesity

Height and weight were obtained from adolescents without shoes and coats using a stadiometer and an autonomic scale, respectively. Overweight was determined as proposed by Cole et al.²¹ Waist circumference was obtained in the standing position at the level of the umbilicus using a constant tension tape, and adolescents with waist circumference values above the 80th percentile considering sex and age were considered as having abdominal obesity.²²

Cluster of cardiovascular risk factors

The clustering of cardiovascular risk factors was determined by the sum of abdominal obesity, overweight, and high blood pressure. For analysis, only adolescents with all information were included and the cluster score ranged from 0 to 3.

Statistical analysis

The three databases were compiled by a single researcher in a data sheet using SPSS/PASW software (IBM Corp, New York, USA) and possible errors were checked by a second independent researcher. Normal distribution was analyzed by graphical analysis (histogram). Continuous variables were summarized as means, with standard deviation and percentiles, whereas categorical variables were summarized as relative frequency. Comparisons of age and RHR between sexes were performed using independent t test, whereas the chi-square test was used for comparing categorical variables (abdominal obesity, overweight, high blood pressure, and Cluster of cardiovascular risk factors).

The sensitivity and specificity of RHR in the detection of cardiovascular risk factors was performed using the receiver operating characteristic (ROC) curve. The association between the adolescents classified with high RHR and the cardiovascular risk factors separated or in the form of a cluster was enhanced by binary logistic regression. The confidence interval adopted was 95%, and the statistical significance was 5%. The statistical packages used were SPSS and Medcalc. A p value < 0.05 was considered statistically significant for all analyses.

Results

The number of adolescents available, evaluated, and excluded was described previously.^{4,17,18} Thus, a total of 6,794 adolescents (4,040 girls and 2,754 boys) with a mean age of 16.0 ± 1.8 years old were included in the study. Characteristics of adolescents are shown in Table 1. Girls showed higher RHR and abdominal obesity, whereas boys had a higher prevalence of high blood pressure.

Smoothed RHR percentiles from adolescents by age and sex are shown in Figure 1 and Table 2. Mean RHR for boys ages 10 to 14 was higher than in boys ages 15 to 19 (80.7 ± 13.0 bpm versus 73.0 ± 12.0 bpm, $p < 0.001$). Mean RHR for girls ages 10 to 14 was also higher than in girls ages 15 to 19 (83.8 ± 13.0 bpm versus 80.6 ± 12.0 bpm, $p < 0.001$).

The proposed cutoff points and ROC curve indicators of detection of elevated RHR in both sexes according to age are shown in Table 3. For girls ages 10 to 14, the area under the curve was not significant at the cutoff point found ($p > 0.05$), whereas, for boys (10 to 14 and 15 to 19 years old) and girls ages 15 to 19, the area under the curve was significant ($p < 0.05$).

Table 1 – General characteristics of Brazilian adolescents by sex, in 2011 (n = 6,794)

	Total	Boys (n=2,754)	Girls (n=4,040)	p
Age (years)	16.0 ± 1.8	16.0 ± 1.9	16.0 ± 1.7	0.427 ^a
Resting heart rate (bpm)	78.4 ± 12.8	74.4 ± 12.6	81.1 ± 12.2	<0.001 ^a
Abdominal obesity (%)	20.7	16.5	23.5	<0.001 ^b
Overweight (%)	17.9	18.0	17.8	0.842 ^b
High blood pressure (%)	16.6	24.0	11.6	<0.001 ^b
Risk factors (%)				<0.001^b
None	66.1	64.5	67.2	<0.001 ^b
One	17.6	19.0	16.6	
Two	11.3	9.9	12.3	
Three	5.0	6.6	3.9	

bpm: beats per minute; ^a: independent t test; ^b: Chi-square test.

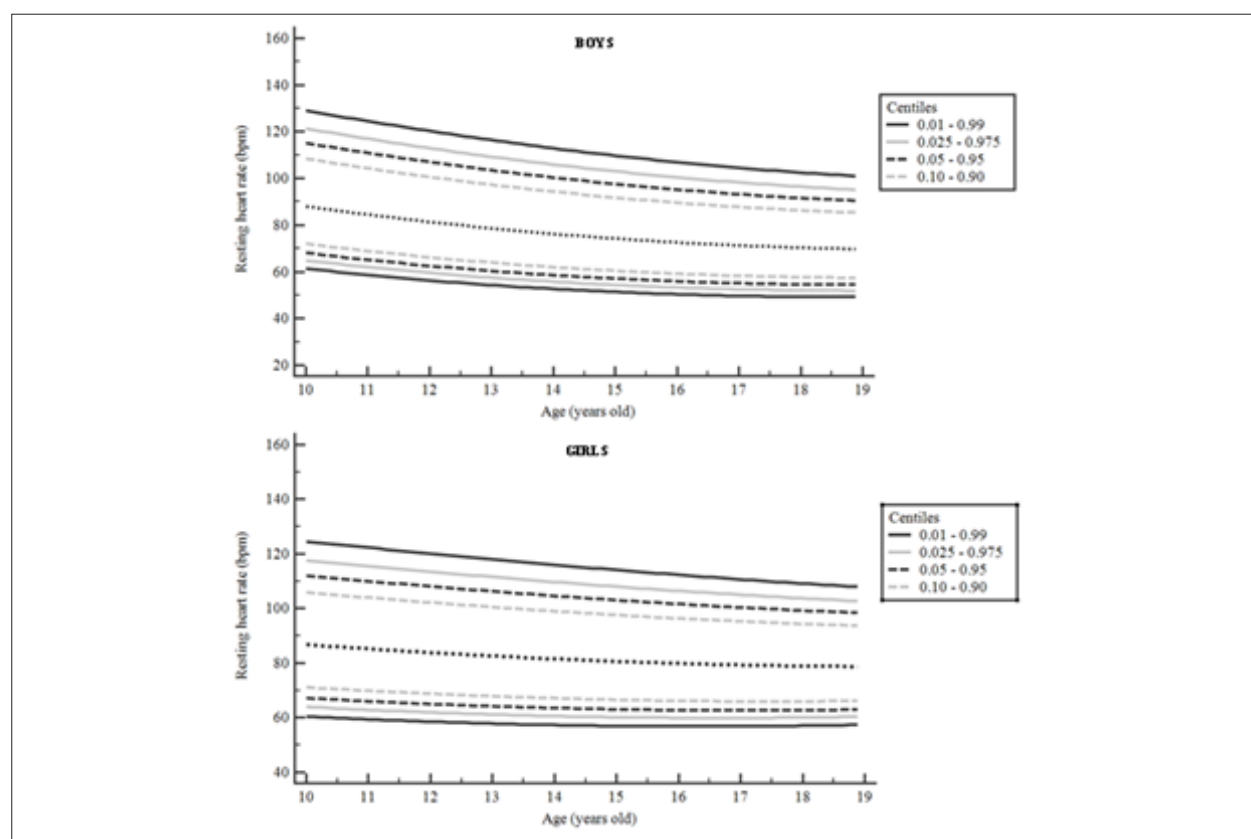


Figure 1 – Smoothed resting heart rate for Brazilian adolescent boys and girls (n = 6,794). bpm: beats per minute.

Table 4 shows the associations between RHR cutoff points and cardiovascular risk factors. In boys ages 10 to 14, there were associations between elevated RHR and abdominal obesity and overweight. In boys ages 15 to 19, there were associations between elevated RHR and abdominal obesity, overweight, and high blood pressure. In girls ages 15 to 19, as well, elevated RHR was associated with abdominal obesity, overweight, and high blood pressure. In addition, in boys and girls (ages 15 to 19), the RHR cutoff points

were independently associated with the cluster of cardiovascular risk factors (Table 5).

Discussion

The main findings of the current study were threefold: a) RHR cutoff points have high specificity in detecting the cardiovascular risk in boys ages 10 to 14 and 15 to 19; b) in

Table 2 – Mean $\pm$ standard deviation and percentile values for resting heart rate in adolescents ages 10 to 19 years

	Age (years)	Mean $\pm$ SD	Resting heart rate percentiles								
			1	2.5	5	10	50	90	95	97.5	99
Boys (n=2,754)	10	85.3 $\pm$ 14.6	61.4	64.9	68.1	72.1	83.0	108.4	115.2	121.4	129.1
	11	85.7 $\pm$ 12.6	58.7	62.1	65.2	69.0	87.5	104.4	110.9	117.0	124.5
	12	84.4 $\pm$ 13.6	56.3	59.6	62.6	66.3	83.5	100.7	107.1	113.0	120.3
	13	80.7 $\pm$ 11.3	54.3	57.5	60.4	64.0	79.0	97.3	103.5	109.3	116.4
	14	77.8 $\pm$ 12.3	52.7	55.8	58.6	62.1	77.8	94.4	100.4	106.0	112.9
	15	76.1 $\pm$ 11.6	51.4	54.4	57.1	60.5	75.0	91.8	97.7	103.1	109.8
	16	73.4 $\pm$ 12.5	50.4	53.3	56.0	59.2	73.4	89.6	95.3	100.5	107.0
	17	72.1 $\pm$ 12.0	49.7	52.5	55.1	58.3	71.0	87.8	93.3	98.3	104.6
	18	70.7 $\pm$ 11.5	49.3	52.1	56.6	57.7	70.0	86.4	91.6	96.5	102.5
	19	72.3 $\pm$ 10.9	49.8	54.6	56.0	60.0	70.0	86.0	90.0	99.4	111.6
Girls (n=4,040)	10	85.9 $\pm$ 11.5	61.3	64.5	67.6	71.3	86.0	106.2	112.7	118.8	126.5
	11	86.4 $\pm$ 12.4	60.2	63.4	66.4	70.0	84.0	104.2	110.7	116.7	124.1
	12	87.0 $\pm$ 13.6	59.3	62.5	65.4	68.9	85.5	102.4	108.7	114.6	121.9
	13	83.4 $\pm$ 14.8	58.6	61.7	64.6	68.0	81.0	100.8	106.9	112.6	119.7
	14	82.1 $\pm$ 12.0	58.1	61.1	63.9	67.3	81.0	99.2	105.2	110.7	117.6
	15	82.2 $\pm$ 12.9	57.7	60.7	63.4	66.8	81.0	97.8	103.6	109.0	115.6
	16	80.1 $\pm$ 11.4	57.5	60.4	63.1	66.4	79.0	96.6	102.2	107.3	113.8
	17	80.5 $\pm$ 12.1	57.5	60.4	63.0	66.2	79.0	95.5	100.9	105.8	112.0
	18	79.4 $\pm$ 11.5	57.7	60.5	63.0	66.2	78.0	94.5	99.7	104.5	110.4
	19	80.1 $\pm$ 11.5	54.0	59.3	63.6	67.0	79.0	95.9	102.5	107.0	112.7

SD: Standard deviation.

Table 3 – Proposed cutoff points and receiver operating characteristic curve indicators of detection of resting heart rate for cardiovascular risk factors in adolescents (n = 6,773)

	Cutoff	AUC	95% CI	p	Sensitivity	95% CI	Specificity	95% CI
Boys 10 – 14 yo	>92	0.632	0.588 – 0.675	0.021	44.44	25.5 – 64.7	81.00	77.1 – 84.5
Boys 15 – 19 yo	>82	0.633	0.612 – 0.653	<0.001	35.96	26.1 – 46.8	82.67	81.0 – 84.2
Girls 10 – 14 yo	>94	0.528	0.486 – 0.570	0.635	32.14	15.9 – 52.4	80.78	77.2 – 84.0
Girls 15 – 19 yo	>82	0.709	0.693 – 0.724	<0.001	75.86	65.5 – 84.4	58.43	56.7 – 60.1

AUC: area under curve; CI: confidence interval; RHR: resting heart rate; yo: years old.

girls ages 15 to 19, the RHR cutoff points have high sensibility in detecting cardiovascular risk, whereas, in girls ages 10 to 14, the cutoff point could not be established; c) RHR cutoff points identified were independently associated with the cluster of cardiovascular risk factors.

In this study, there was a decline in RHR with increasing age from infancy into adolescence, similarly to others studies.^{5,12} This may be explained by improvements in baroreflex sensitivity and neural function with sexual maturation.²³ In fact, during maturation there is a progressive increase in parasympathetic cardiac activity related to sympathetic activity,²³ which supports a lower RHR in late adolescence.²⁴

RHR differed between boys and girls ages 15 to 19 (boys: 73.0 $\pm$ 12.0 bpm versus girls: 80.6 $\pm$ 12.0 bpm), corroborating with previous studies.^{4,5} These differences may be caused by the higher adiposity in girls.²⁵ Previous studies have also shown that both cardiorespiratory fitness and physical activity levels are higher in boys than girls,²⁶ and these factors are directly related to cardiac autonomic control.²⁷⁻²⁹

Previous studies have investigated RHR reference values in children and adolescents from birth to age 18, including a systematic review involving 143,346 participants, which showed median values of 123 bpm in adolescents ages 12 to 18.¹³ Others studies analyzing large national populations,

Table 4 – Crude and adjusted analyses of the association among cutoff points for resting heart rate and cardiovascular risk factors in adolescents

Independent variables	Models	Elevated RHR ^a
		OR (95% CI)
Boys (10 to 14 years old)		
Abdominal obesity (no = reference)	Crude	2.46 (1.60 – 3.79)
	Adjusted	2.37 (1.53 – 3.68)
Overweight (no = reference)	Crude	2.06 (1.38 – 3.10)
	Adjusted	1.87 (1.23 – 2.83)
High blood pressure (no = reference)	Crude	1.45 (0.93 – 2.26)
	Adjusted	1.42 (0.90 – 2.23)
Boys (15 to 19 years old)		
Abdominal obesity (no = reference)	Crude	1.89 (1.27 – 2.82)
	Adjusted	1.85 (1.24 – 2.76)
Overweight (no = reference)	Crude	1.88 (1.27 – 2.78)
	Adjusted	1.89 (1.28 – 2.80)
High blood pressure (no = reference)	Crude	2.83 (2.01 – 3.98)
	Adjusted	3.00 (2.12 – 4.23)
Girls (15 to 19 years old)		
Abdominal obesity (no = reference)	Crude	1.22 (1.04 – 1.43)
	Adjusted	1.26 (1.07 - 1.47)
Overweight (no = reference)	Crude	1.26 (1.05 – 1.50)
	Adjusted	1.27 (1.06 – 1.51)
High blood pressure (no = reference)	Crude	2.86 (2.28 – 3.59)
	Adjusted	2.82 (2.25 – 3.54)

Adjusted for age, period of the day. CI: confidence interval; OR: odds ratio; RHR: resting heart rate. ^a Elevated RHR: boys 10 to 14 years old: > 83 bpm; boys 15 to 19 years old: > 92 bpm; girls 10 to 14 years old: unavailable; girls 15 to 19 years old: > 82 bpm.

such as the KiGGS⁵ and NHANES¹² surveys, observed RHR median values, throughout the age range, varying between 69 and 104 bpm for boys and 74 and 108 bpm for girls. In comparison with these studies, we observed a narrower RHR (median values 70 to 83 bpm for boys and 79 to 86 bpm for girls), which can be explained by the narrow age range.

The main novelty of this study was the identification of cutoff points for RHR in adolescents that were associated with important cardiovascular risk factors for adolescents, namely, abdominal obesity, overweight, and high blood pressure, all of which are independently associated with cardiac autonomic dysfunction,^{27,30} therefore explaining, at least in part, the association with RHR. Likewise, RHR cutoff points were also associated with the cluster of risk factors in a sex-dependent manner, indicating that the accumulation of risk factors leads to more alterations in autonomic function in a dose-dependent manner.

The major strengths of the current study are the relatively large sample size, the coverage of a wide age range, the use of an automated technique for RHR measurements to avoid observer bias, and the fact that data analysis was performed by a single researcher in a blinded fashion.

Adolescents with conditions or medication that influencing RHR were excluded. Despite these strengths, this study presents some limitations that need to be considered. First, we had only a single assessment of RHR. We could not determine the Tanner stage. Therefore, future studies should consider the sexual maturation of adolescents. The cross-sectional design of this study is a limitation, as no causality can be inferred, making longitudinal studies necessary to validate the cut points found. Although this is the first study with cutoff points in Brazilian adolescents, we have analyzed few regions in Brazil, making more multicenter studies necessary. Finally, as other potential confounders that may affect RHR (use of tobacco, alcohol consumption, and exercise prior to measurement) were not controlled, their influence cannot be disregarded. Despite that, prior studies have also adopted a similar strategy to the current one.^{5,12,13}

Conclusion

The current study identified > 92 bpm for boys ages 10 to 14, > 82 bpm for boys ages 15 to 19, and > 82 for girls ages 15 to 19 as cutoff points for RHR and demonstrated

Table 5 – Adjusted analyses of the association between cutoff points for resting heart rate and clustering of cardiovascular risk factors in adolescents

Risk factors	Elevated RHR ^a
	OR (95% CI)
Boys (10 to 14 years old)	
None	Reference
One	0.86 (0.50 – 1.49)
Two	2.48 (1.43 – 4.28)
Three	2.33 (1.20 – 4.52)
Boys (15 to 19 years old)	
None	Reference
One	3.14 (2.12 – 4.67)
Two	2.22 (1.26 – 3.90)
Three	3.72 (2.12 – 6.54)
Girls (15 to 19 years old)	
None	Reference
One	1.33 (1.11 – 1.60)
Two	1.24 (1.01 – 1.54)
Three	3.70 (2.47 – 5.53)

Adjusted for age, period of the day. CI: confidence interval; OR: odds ratio; RHR: resting heart rate. ^a Elevated RHR: boys 10 to 14 years old: > 83 bpm; boys 15 to 19 years old: > 92 bpm; girls 10 to 14 years old: unavailable; girls 15 to 19 years old: > 82 bpm.

the association between these cutoff points and the cluster of cardiovascular risk factors. These cutoff points may help physicians and other health professionals to interpret and stage cardiovascular risk, using a simple, easy and low-cost measure.

Author Contributions

Conception and design of the research: Farah BQ, Christofaro DGD, Barros MVG, Ritti-Dias RM; Acquisition of data: Farah BQ, Christofaro DGD, Tebar WR, Ritti-Dias RM; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Farah BQ, Christofaro DGD, Ritti-Dias RM; Obtaining financing: Christofaro DGD, Barros MVG; Critical revision of the manuscript for intellectual content: Farah BQ, Christofaro

DGD, Andrade-Lima A, Germano-Soares AH, Tebar WR, Barros MVG, Ritti-Dias RM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

References

- Valentini M, Parati G. Variables influencing heart rate. *Prog Cardiovasc Dis*. 2009;52(1):11-9.
- Aune D, Sen A, o'Hartaigh B, Janszky I, Romundstad PR, Tonstad S, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. *Nutr Metabol Cardiovasc Dis*. 2017;27(6):504-17.
- Fox K, Bousser MG, Amarenco P, Chamorro A, Fisher M, Ford I, et al. Heart rate is a prognostic risk factor for myocardial infarction: a post hoc analysis in the PERFORM (Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history of ischemic stroke or transient ischemic attack) study population. *Int J Cardiol*. 2013;168(4):3500-5.
- Farah BQ, Christofaro DG, Balagopal PB, Cavalcante BR, de Barros MV, Ritti-Dias RM. Association between resting heart rate and cardiovascular risk factors in adolescents. *Eur J Pediatr*. 2015;174(12):1621-8.
- Sarganas G, Schaffrath Rosario A, Neuhauser HK. Resting Heart Rate Percentiles and Associated Factors in Children and Adolescents. *J Pediatrics*. 2017;187:174-81 e3.
- Christofaro DGD, Casonatto J, Vanderlei LCM, Cucato GG, Dias RMR. Relationship between Resting Heart Rate, Blood Pressure and Pulse Pressure in Adolescents. *Arq Bras Cardiol*. 2017;108(5):405-10.
- Christofaro DGD, Andrade SM, Vanderlei LCM, Fernandes RA, Mota J. Sports practice is related to resting heart rate in adolescents regardless of confounding factors: Cross-sectional study. *Science & Sports*. 2018; 33(5): 319-322.

8. Fernandes RA, Freitas Junior IF, Codogno JS, Christofaro DG, Monteiro HL, Roberto Lopes DM. Resting heart rate is associated with blood pressure in male children and adolescents. *J Pediatr*. 2011;158(4):634-7.
9. Lindgren M, Robertson J, Adiels M, Schaufelberger M, Aberg M, Toren K, et al. Resting heart rate in late adolescence and long term risk of cardiovascular disease in Swedish men. *Int J Cardiol*. 2018;259:109-15.
10. Salameh A, Gebauer RA, Grollmuss O, Vit P, Reich O, Janousek J. Normal limits for heart rate as established using 24-hour ambulatory electrocardiography in children and adolescents. *Cardiol Young*. 2008;18(5):467-72.
11. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. *Eur Heart J*. 2001;22(8):702-11.
12. Ostchega Y, Porter KS, Hughes J, Dillon CF, Nwankwo T. Resting pulse rate reference data for children, adolescents, and adults: United States, 1999-2008. *Natl Health Stat Report*. 2011 (41):1-16.
13. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377(9770):1011-8.
14. Carter JV, Pan J, Rai SN, Galandiuk S. ROC-ing along: Evaluation and interpretation of receiver operating characteristic curves. *Surgery*. 2016;159(6):1638-45.
15. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993;39(4):561-77.
16. Farah BQ, Christofaro DGD, Cavalcante BR, Andrade-Lima A, Germano-Soares AH, Vanderlei LCM, et al. Cutoffs of Short-Term Heart Rate Variability Parameters in Brazilian Adolescents Male. *Pediatr Cardiol*. 2018;39(7):1397-403.
17. Christofaro DG, De Andrade SM, Mesas AE, Fernandes RA, Farias Junior JC. Higher screen time is associated with overweight, poor dietary habits and physical inactivity in Brazilian adolescents, mainly among girls. *Eur J Pediatr Sport Sci*. 2016; 16(4):498-506.
18. Zanuto EF, Ritti-Dias RM, Tebar WR, Scarabottolo CC, Delfino LD, Casonatto J, et al. Is physical activity associated with resting heart rate in boys and girls? A representative study controlled for confounders. *J Pediatr (Rio J)*. 2020;96(2):247-54.
19. Christofaro DG, Casonatto J, Polito MD, Cardoso JR, Fernandes R, Guariglia DA, et al. Evaluation of the Omron MX3 Plus monitor for blood pressure measurement in adolescents. *Eur J Pediatr*. 2009;168(11):1349-54.
20. Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? *Am J Physiol Regul Integr Comp Physiol*. 2004;286(5):R803-13.
21. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240.
22. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y. *Am J Clin Nutr*. 2000;72(2):490-5.
23. Chen SR, Chiu HW, Lee YJ, Sheen TC, Jeng C. Impact of pubertal development and physical activity on heart rate variability in overweight and obese children in Taiwan. *J Sch Nurs*. 2012;28(4):284-90.
24. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev*. 2010;90(2):513-57.
25. Abou El Ella SS, Barseem NF, Tawfik MA, Ahmed AF. BMI relationship to the onset of puberty: assessment of growth parameters and sexual maturity changes in Egyptian children and adolescents of both sexes. *J Pediatr Endocrinol Metab*. 2020;33(1):121-8.
26. Nelson MC, Neumark-Stzainer D, Hannan PJ, Sirard JR, Story M. Longitudinal and secular trends in physical activity and sedentary behavior during adolescence. *Pediatrics*. 2006;118(6):e1627-34.
27. Farah BQ, Andrade-Lima A, Germano-Soares AH, Christofaro DGD, de Barros MVG, do Prado WL, et al. Physical Activity and Heart Rate Variability in Adolescents with Abdominal Obesity. *Pediatr Cardiol*. 2018;39(3):466-72.
28. Farah BQ, Prado WL, Tenorio TR, Ritti-Dias RM. Heart rate variability and its relationship with central and general obesity in obese normotensive adolescents. *Einstein (Sao Paulo)*. 2013;11(3):285-90.
29. Palmeira AC, Farah BQ, Soares AHG, Cavalcante BR, Christofaro DGD, Barros MVG, et al. Association between Leisure Time and Commuting Physical Activities with Heart Rate Variability in Male Adolescents. *Ver Paul Pediatr*. 2017;35(3):302-8.
30. Farah BQ, Barros MV, Balagopal B, Ritti-Dias RM. Heart rate variability and cardiovascular risk factors in adolescent boys. *J Pediatr*. 2014;165(5):945-50.



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Analysis of Sensitivity and Specificity of Cutoff Points for Resting Heart Rate in 6,794 Brazilian Adolescents: A Cross-Sectional Study

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Short Editorial related to the article: Sensitivity and Specificity of Cutoff Points of Resting Heart Rate from 6,794 Brazilian Adolescents:

A CrossSectional Study

Resting heart rate (RHR) is an accessible measure that may reflect the balance between the sympathetic and parasympathetic nervous system.¹ Elevated RHR levels are associated with cardiovascular events in adults² and cardiovascular risk factors, such as overweight,³ abdominal obesity and high blood pressure have been associated with high RHR.⁴ Therefore, obtaining a cutoff point for the RHR in children and adolescents is essential for better screening and subsequent clinical follow-up.

Furthermore, the early identification and screening of cardiovascular changes and cardiac autonomic modulation can be reflected by simple measures such as the RHR, since sedentary adolescents with abdominal obesity have lower heart rate variability (HRV) and, consequently, greater sympathetic stimulation, maintaining the RHR high and increasing the risk of developing heart damage throughout life.⁵

One method of verifying autonomic modulation is through the HRV, which when decreased indicates autonomic imbalance and has been associated with mortality and various cardiovascular risk indicators (general and abdominal obesity, high blood pressure and sedentary lifestyle) in adolescents.⁶⁻⁸ A previous study by Farah et al.,⁹ carried out with male adolescents, demonstrated that cutoff points for HRV have moderate-to-high sensitivity for detecting cardiovascular risk factors.⁹ This reinforces the relevance of studies that propose establishing cutoff points for biological signal variables, such as the RHR and its different clinical analyses, aiming to diagnose possible cardiovascular alterations in children and adolescents.

This is what Farah et al.¹⁰ proposed in this study, by establishing cutoff points for RHR in Brazilian adolescents and analyzing associations between cutoff points and cardiovascular risk factors. A total of 6,794 adolescents (aged 10 to 19 years), of both genders, were evaluated and blood pressure and RHR were measured using an oscillometric device. Body mass index (BMI) and waist circumference were also evaluated. The ROC curve was

used to analyze sensitivity and specificity, and associations of high RHR with cardiovascular risk factors were analyzed by binary logistic regression.¹⁰

The main findings of this study, in addition to determining the RHR cutoff points, was to establish the association of these cutoff points with cardiovascular risk factors, such as abdominal obesity, overweight and high blood pressure in boys and girls.

A study by Christofaro et al.¹¹ found an association between heart rate and systolic and diastolic blood pressure in adolescents, and it was pointed out that, for boys, there was an influence of abdominal obesity and BMI in those with a higher heart rate, but this did not occur in girls; thus, the authors suggested that patterns of body fat distribution and hormonal variations may influence these findings.¹¹ In fact, the android body fat distribution pattern is more associated with cardiovascular risk factors and female hormones (estrogens) provide some cardiovascular protection in girls.¹²

Furthermore, as expected, there is a decline in RHR with increasing age, probably due to the improvement in the baroreflex sensitivity and neural function with sexual maturation. Indeed, there is a progressive increase in vagotonic cardiac activity in relation to sympathetic activity during maturation, resulting in lower RHR in late adolescence.¹³

This study also has two other important highlights: the number of participants was considerable (important for epidemiological purposes) and it was carried out in three different regions of the country (northeast, southeast and south), possibly with different ethnicities, although it was not reported, therefore being representative from the perspective of genetic variability. Despite these results, the study has limitations: it was not possible to establish a cutoff point for girls aged 10-14 years and the reason was not explained. External factors that influence heart rate (smoking, level of physical activity, consumption of alcoholic beverages and caffeine) could not be identified, and it is important to highlight these limitations for future studies.¹⁴

For epidemiological screening purposes, establishing cutoff points that allow the identification of increased cardiovascular risk is of utmost importance, since it can improve public health strategies for a population that is presumably at higher risk. Also, regarding the young population, these strategies can be implemented even in schools (encouraging the practice of sports and healthy eating) with the reinforcement of a physiological substrate, the RHR, to ratify the importance of these strategies. Therefore, since it is a simple and low-cost variable to measure, its use can improve and increase the clinical practicality for health professionals in determining diagnosis and prognosis of young Brazilians.

Keywords

Heart Rate/physiology; Adolescent; Obesity; Adiposity; Blood Pressure; Epidemiology; Cross-sectional studies/methods.

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References

1. Valentini M, Parati GJ. Variables influencing heart rate. *Prog Cardiovasc Dis*. 2009; 52(1): 11-9.
2. Aune D, Sen A, Ó'Hartaigh B, Janszky I, Romundstad PR, Tonstad S, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality—a systematic review and dose–response meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis*. 2017; 27(6): 504-17.
3. Jardim PCBV. Overweight, the cardiovascular risk of the century. *Arq Bras Cardiol*. 2019; 113(2): 185-7.
4. Fernandes RA, Freitas Jr I, Codogno JS, Christofaro DG, Monteiro HL, Lopes DM. Resting heart rate is associated with blood pressure in male children and adolescents. *J Pediatr*. 2011; 158(4): 634-7.
5. Farah BQ, Andrade-Lima A, Germano-Soares AH, Christofaro DG, Barros MV, Prado WL, et al. Physical activity and heart rate variability in adolescents with abdominal obesity. *Pediatr Cardiol*. 2018; 39(3): 466-72.
6. Farah BQ, Prado WLd, Tenório TR. Heart rate variability and its relationship with central and general obesity in obese normotensive adolescents. *Einstein (SP)*. 2013; 11(3): 285-90.
7. Vanderlei LCM, Pastre CM, Freitas Júnior IF, Freitas JI, Godoy MF. Geometric indexes of heart rate variability in obese and eutrophic children. *Arq Bras Cardiol*. 2010; 95(1): 35-40.
8. Farah BQ. Variabilidade da Frequência Cardíaca como Indicador de Risco Cardiovascular em Jovens. *Arq Bras Cardiol*. 2020; 115(1):59-60.
9. Farah BQ, Christofaro DGD, Cavalcante BR, Andrade Lima A, Germano Soares FN, Ritti RM. Cutoffs of short-term heart rate variability parameters in Brazilian adolescents male. *Pediatr Cardiol*. 2018; 39(7): 1397-403.
10. Farah B, Christofaro D, Andrade Lima A., Soares AG, Tebar W, et al. William & Barros, Sensitivity and specificity of cutoff points of resting heart rate from 6794 brazilian adolescents: a cross-sectional study. *Arq Bras Cardiol*. 2021; 117(1):74-81.
11. Christofaro DGD, Casonatto J, Vanderlei LCM, Cucato GG, Dias RMR. Relationship between Resting Heart Rate, Blood Pressure and Pulse Pressure in Adolescents. *Arq Bras Cardiol*. 2017;108(5):405-410. doi:10.5935/abc.20170050
12. O'Neil A, Scovelle AJ, Milner AJ, Kavanagh A. Gender/Sex as a Social Determinant of Cardiovascular Risk. *Circulation*. 2018; 137(8):854-64. doi:10.1161/CIRCULATIONAHA.117.028595
13. Chen S-R, Chiu H-W, Lee Y-J, Sheen TC, Jeng C. Impact of pubertal development and physical activity on heart rate variability in overweight and obese children in Taiwan. *J Sch Nurs*. 2012;28(4):284-90.
14. Doom JR, Mason SM, Suglia SF, Clark CJ. Pathways between childhood/ adolescent adversity, adolescent socioeconomic status, and long-term cardiovascular disease risk in young adulthood. *Soc Sci Med*. 2017;188:166-75. doi:10.1016/j.socscimed.2017.06.044



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Coronary Artery Fistula: Association between Pathway Patterns, Clinical Features and Congenital Heart Disease

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Abstract

Background: Coronary artery fistula (CAF) is a direct connection of one or more coronary arteries to cardiac chambers or a large vessel; it may be associated with congenital heart disease.

Objective: To establish CAF pathway patterns from echocardiographic data and to correlate them with clinical aspects and congenital heart disease.

Methods: A total of 7.183 medical records of children under the age of five years with cardiac disease submitted to color Doppler echocardiography and Spearman's Correlation test were used to associate signs and symptoms and cardiopathy to CAF with a significance level of 5%.

Results: Twenty six children (0.0036%) presented CAF: from the right coronary artery (RCA) to the right ventricle (RV) 26.92%, from the left coronary artery (LCA) to the RV 23.08%, from the anterior interventricular branch (AIVB) to RV 23.08%, RCA to right atrium (RA) 11.54%, LCA for pulmonary trunk (PT) 7.69% or AIVB for PT 7.69%. In 57.69% of the patients, there was a positively correlated symptomatology to CAF with $p=0.445$ related to dyspnea or cyanosis (53.84%); in 96.15%, congenital heart disease associated with CAF, mainly interventricular communication (IVC) or interatrial communication (IAC) in 34.62% positively correlated to CAF with $p=0.295$. CAF pathway was represented in three dimensions by software modeling, texturing and animation Cinema 4D R19.

Conclusion: CAF is an uncommon anatomical entity that presents a clinical picture compatible with dyspnea and cyanosis, and this is associated with congenital heart disease, mainly with IVC or IAC. According to echocardiographic analyzes, fistulas in RCA, LCA, or AIVB represent about one-third of the patients, with a priority pathway for right heart chambers.

Keywords: Coronary Artery Disease; Arterio-Arterial Fistula, Congenital Heart Diseases; Anatomy; Dyspnea; Cyanosis; Echocardiography/methods; Imaging Three-Dimensional/methods.

Introduction

Coronary artery fistula (CAF) is a direct connection of one or more coronary arteries to cardiac chambers or a large vessel. It is one of the most common coronary artery (CA) anomalies, although, it is considered rare in general population.^{1,2} It is present in 0.002% of the population, and it represents 0.4% of all cardiac malformations.^{3,4}

Doppler echocardiogram has been indicated for the evaluation of congenital heart defects due to its diagnostic versatility, availability, cost-effectiveness and the amount of morphofunctional information of the heart.⁵

Due to the rarity of CAF and the potential contribution of its topographic characterization, the present study aims at determining CAF pathway patterns from echocardiographic data as well as to correlate them with clinical aspects and congenital heart disease.^{6,7}

Method

After ethical approval, 7,183 electronic medical records of pediatric patients with or without congenital heart disease from the Cardiology and Pediatric Cardiovascular Surgery Service of Hospital de Base (HB) and the Children Hospital and Maternity Hospital (CHMH) of São José do Rio Preto – SP – Brazil were considered. Two-dimensional color echocardiographic examinations (Philips Healthcare® HD 11 and HD 15 model) were performed according to the guidelines of the American Society of Echocardiography.⁸ Children with congenital heart defects without CAF, and children over five years of age due to congenital heart defect under care during initial months up to the first years of life were excluded from the study. The sample size used in the study was defined by convenience.

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Statistical Analysis

The statistical analyzes were obtained using the SPSS Statistics software version 23.0⁹ and the Excel tool (version 2.016). Variables considered in the study are categorical and comprised signs and symptoms such as: asymptomatic, low O₂ saturation, cyanosis of the extremities, labial or generalized, hyperthermia and dyspnea; cardiopathy associated with: Pulmonary Atresia, Coarctation of the Aorta, IAC or IVC, Atrioventricular Septal Defect, Pulmonary Valve Stenosis, Persistence Ductus Arteriosus, Tetralogy of Fallot or no associated heart disease, and CAF topography from the description of echocardiographic reports for three-dimensional reconstruction by modeling, texturing and animation software Cinema 4D R19.¹⁰ The normality of the data was verified using the Shapiro-Wilk test, which showed nonparametric data. Afterwards, the Spearman's Correlation test was applied to associate congenital heart disease and signs and symptoms to the CAF, which observed p value <0.05.⁹

Results

In the present study, a descriptive analysis was presented (Table 1), and for categorical variables, inferential crossover was analyzed (Tables 2 and 3). Spearman's correlation test was used, and for each crossing a single p value was presented. From the 7,183 medical records considered, CAF was detected in 26 cases (0.0036%). Table 1 shows categorical variables of pathways for CAF detected according to the echocardiogram, and shows that fistulas in the right coronary artery (RCA), left coronary artery (LCA) or in the anterior interventricular branch (AIVB) represent about one third of the patients, with priority pathway for the right heart chambers.

Table 2 correlated categorical variables, signs and symptoms (asymptomatic, low O₂ saturation, cyanosis of the extremities, labial or generalized, hyperthermia and dyspnea) with types of CAF (RCA, RV, RA, LCA, PT and AIVB) and shows that in patients with CAF asymptomatology is present in 26.92% of the patients and symptomatology in 57.69%, expressed by dyspnea (26.92%), cyanosis (26.92%) and hyperthermia (3.86%). Low oxygen saturation detected by pulse oximeter; in 15.38% of the patients. From these data, the Spearman Correlation Test was performed, which observed p value = 0.445 and it is understood that there is no statistical evidence of dependence between the variables analyzed.

Table 3 shows that CAF and associated congenital heart disease in 96.15% of the cases; mainly with interventricular communication (IVC) or interatrial communication (IAC) in 34.62% of the cases, tetralogy of Fallot (23.08%) and coarctation of aorta (11.53%). The categorical variables Associated Heart Disease (Pulmonary Atresia, Coarctation of the Aorta, IAC or IVC, Atrioventricular Septal Defect, Pulmonary Valve Stenosis, no associated heart disease, Persistence Ductus Arteriosus, Tetralogy of Fallot) were correlated with the types of CAF (RCA, RV, RA, LCA, PT and AIVB) and from these data, the Spearman Correlation Test was performed, which observed p value = 0.295 and it is understood that there is no statistical evidence of dependence between the variables analyzed.

The Figure 1 shows the pathway patterns found for CAF and their respective percentages.¹⁰

Discussion

In this study, CAF prevalence was observed in 0.0036% of the cases. Although the real frequency of coronary artery anomalies in the general population could be unknown or extremely rare.¹¹ Estimated prevalence ranges from 0.002%¹² to 0.1% to 1 or from 1% to 2%^{13,14} and represents 14% of all coronary artery anomalies.¹⁵

Asymptomatology was present in almost a third of the patients; signs and symptoms were represented by dyspnea, cyanosis and hyperthermia in 57.69% of the patients (Table 2). Although the lack of symptoms could be even more prevalent, angina due to the phenomenon of "coronary steal" (decreased cardiac output), endocarditis, acute myocardial infarction or heart failure could be present.^{14,16} Children with CAF are often asymptomatic, therefore, it is estimated that about 80% of patients under 20 years of age are asymptomatic.¹⁷

Most of the children (96.15%) of the study had another congenital heart disease associated with CAF, mainly IVC or IAC in one third of the patients (Table 3). However, CAF as an isolated manifestation could be present in 55% to 80% of the cases, and it was associated with congenital heart disease (Tetralogy of Fallot, persistence of the ductus arteriosus, IVC or IAC) in 20% to 45%,¹⁷ or coronary artery disease in up to 35% of the occurrences.¹⁸ In addition, CAF has frequently congenital etiology, but could be secondary to injury, infection, iatrogenic or Kawasaki disease.¹²

According to echocardiographic analyzes, the results have stood out that fistulas in RCA, LCA or AIVB represent about one third of the patients, with priority pathway for right cardiac chambers (Table 1). Manoly et al. reported that CAF is more prevalent in RCA (52% of the cases evaluated), with drainage to the right side of the heart in more than 90% of the cases, which has been corroborated by other authors.¹⁶

Two-dimensional color Echocardiography has been recommended to evaluate CAF, although angiography,^{1,16}

Table 1 – Categorical variables of coronary artery fistula pathways detected by echocardiogram

Type of fistula	N	%
RCA for RV	7	26.92
RCA for RA	3	11.54
LCA for PT	2	7.69
LCA for RV	6	23.08
AIVB for PT	2	7.69
AIVB for RV	6	23.08
Total	26	100

AIVB: anterior interventricular branch, LCA: left coronary artery, N: absolute value, PT: pulmonary trunk, RA: right atrium, RCA: right coronary artery, RV: right ventricle.

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Table 2 – Correlation of the categorical variables of signs and symptoms with the types of coronary artery fistula

Signs and symptoms	Types of coronary artery fistula												TOTAL	
	RCA/RV		RCA/RA		LCA/PT		LCA/RV		AIVB/PT		AIVB/RV			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Asymptomatic	0	0	2	66.67	1	50	2	33.33	0	0	2	33.33	7	26.92
Low O ₂ saturation	2	28.57	0	0	0	0	2	33.33	0	0	0	0	4	15.38
Extremities, labial, or generalized cyanosis	3	42.86	0	0	0	0	0	0	1	50	3	50	7	26.92
Hyperthermia	0	0	0	0	0	0	0	0	0	0	1	16.67	1	3.86
Dyspnea	2	28.57	1	33.33	1	50	2	33.33	1	50	0	0	7	26.92
Total	7	100	3	100	2	100	6	100	2	100	6	100	26	100
Value (p)	0.445													

AIVB: anterior interventricular branch, LCA: left coronary artery, N: absolute value, PT: pulmonary trunk, RA: right atrium, RCA: right coronary artery, RV: right ventricle.

Table 3 – Correlation of categorical variables of associated heart disease with types of CAF

Associated heart disease	Types of coronary artery fistula												TOTAL	
	RCA/RV		RCA/RA		LCA/PT		LCA/RV		AIVB/PT		AIVB/RV			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Pulmonary atresia	1	14.29	0	0	0	0	0	0	0	0	0	0	1	3.85
Coarctation of the aorta	0	0	0	0	1	50	0	0	1	50	1	16.67	3	11.53
IAC or IVC	2	28.57	2	66.67	0	0	2	33.33	0	0	3	50	9	34.62
Atrioventricular septal defect	0	0	0	0	0	0	0	0	0	0	1	16.67	1	3.85
Pulmonary valve stenosis	1	14.29	0	0	0	0	0	0	0	0	1	16.67	2	7.69
No associated heart disease	0	0	1	33.33	1	50	1	16.67	0	0	0	0	3	11.53
Persistent ductus arteriosus	0	0	0	0	0	0	0	0	1	50	0	0	1	3.85
Tetralogy of Fallot	3	42.86	0	0	0	0	3	50	0	0	0	0	6	23.08
Total	7	100	3	100	2	100	6	100	2	100	6	100	26	100
Value (p)	0.295													

AIVB: anterior interventricular branch; IAC: interatrial communication; IVC: interventricular communication; LCA: left coronary artery; N: absolute value; PT: pulmonary trunk; RA: right atrium; RCA: right coronary artery; RV: right ventricle.

transthoracic echocardiogram or computerized angiotomography present effective results.^{2,19} A possible limitation of this study refers to a further higher CAF prevalence of RCA to RA, resulting from iatrogenic form after a surgical procedure to correct Tetralogy of Fallot.^{20,21}

Because of the low prevalence of CAF, reduced amount of related scientific publications on the subject are available. The contribution of the present study points out to the relatively high sample size (26 records) for a rare cardiac anomaly.^{1,4} Even though echocardiographic analyzes on electronic records present two-dimensional representation; the three-dimensional analysis performed in this study could be more effective.²² Efforts to improve CAF imaging, preferably in three dimensions, can improve clinical treatment, surgical planning or intraoperative intervention.²³

Conclusions

CAF is an unusual anatomical entity that presents a clinical picture compatible with dyspnea and cyanosis, and it is associated with congenital heart disease, mainly with IVC or IAC. According to echocardiographic analyzes, fistulas in RCA, LCA, or AIVB are present in about one-third of the patients, with a priority pathway to right heart chambers.

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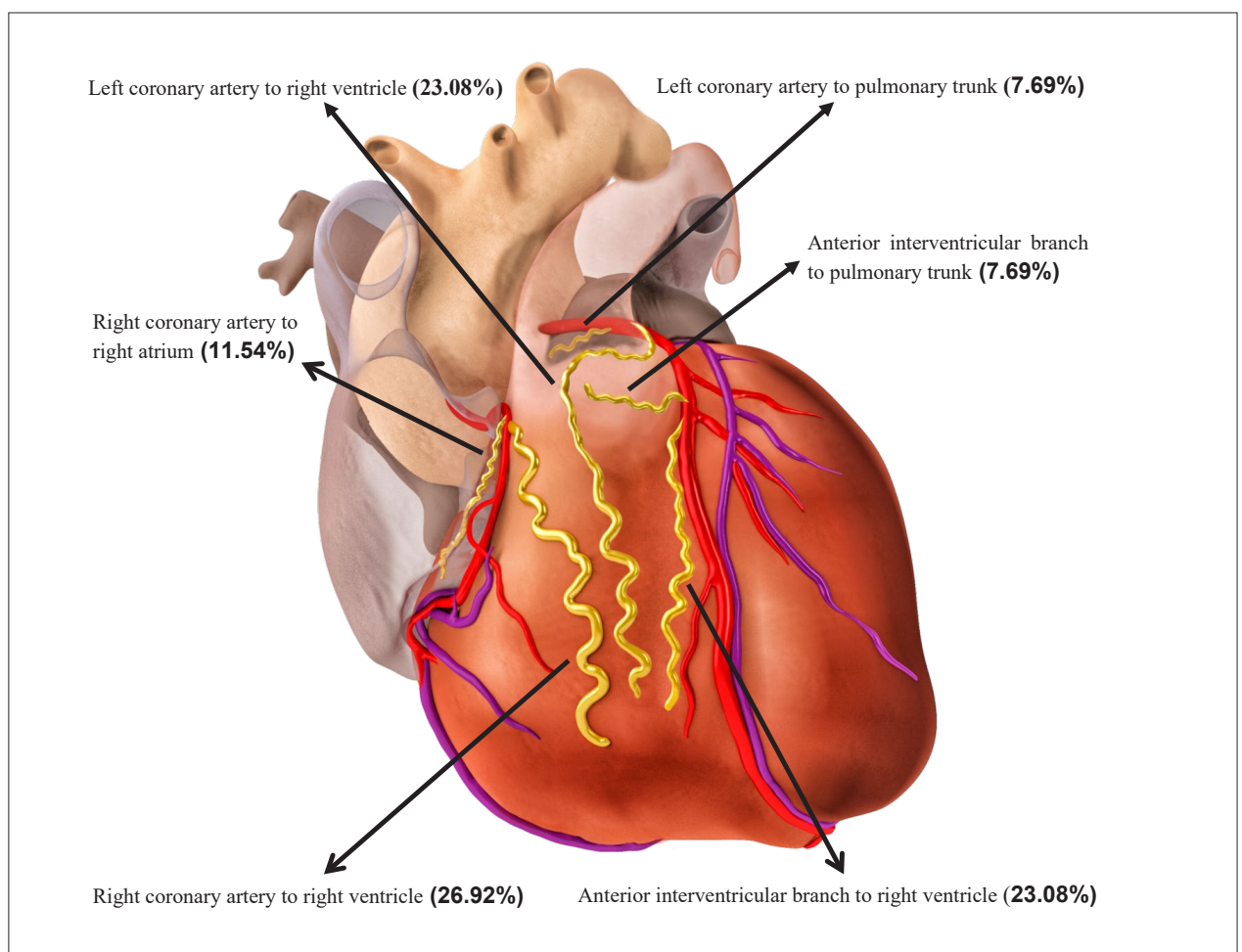


Figure 1 – Topographic representation of coronary artery fistula pathways and their respective percentages.

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Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Cobo DL, Batigalia F, Croti UA; Acquisition of data: Cobo DL, Batigalia F, Croti UA, Cobo RGF; Statistical analysis: Cobo DL, Batigalia F; Obtaining financing: Cobo DL; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Cobo DL, Batigalia F, Croti UA, Sciarra AMP, Foss MHD, Cobo RGF.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina de São José do Rio Preto-FAMERP-SP under the protocol number 81217417.7.0000.54. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Challoumas D, Pericleous A, Dimitrakaki IA, Danelatos C, Dimitrakakis G. Coronary Arteriovenous Fistulae: A Review. *Int J Angiol*. 2014 Mar;23(1):1-10.
2. Lee DY, Park SH, Bae MH, Lee JH, Yang DG, Park HS, et al. Multiple Fistula Emptying into the Left Ventricle Through the Entire Left Ventricular Wall. *J Cardiovasc Ultrasound*. 2012 Jun;20(2):108-11.
3. Loukas M, Germain AS, Gabriel A, John A, Tubbs RS, Spicer D. Coronary Artery Fistula: A Review. *Cardiovasc Pathol*. May-Jun 2015;24(3):141-8.
4. Xie M, Li L, Cheng TO, Sun Z, Wang X, Lv Q, et al. Coronary Artery Fistula: Comparison of Diagnostic Accuracy by Echocardiography versus Coronary Arteriography and Surgery in 63 Patients Studied between 2002 and 2012 in a Single Medical Center in China. *Int J Cardiol*. 2014 Sep 20;176(2):470-7.
5. Almeida I, Caetano F, Trigo J, Mota P, Marques AL. Transthoracic Echocardiography in the Diagnosis of Coronary Fistula. *Rev Port Cardiol*. 2014 Oct;33(10):655-6.
6. Delgado A, Moreira D, Rodrigues B, Correia E, Gama P, Cabral C, et al. Hypertrophic cardiomyopathy associated with left ventricular noncompaction cardiomyopathy and coronary fistulae: A case report. One genotype, three phenotypes?. *Rev Port Cardiol*. 2013 Nov;32(11):919-24.
7. Manoly I, Mahadevan VS, Hoschitzky JA. Hybrid Approach to Closure of an Acquired Coronary-Cameral Fistula. *Ann Thorac Surg*. 2014 Sep;98(3):e59-61.
8. Lang RM, Badano LP, Mor-avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Guidelines and Standards*. *J Am Soc Echocardiogr*. 2015 Jan;28(1):1-39.e14.
9. Marôco J. *Análise Estatística com o SPSS Statistics*. 7 ed. Portugal: Pêro Pinheiro – Portugal: Gráfica Manoel Barbosa & Filhos; 2018. p. 657-780.
10. Maxon a Nemetschek Company. Cinema 4D R19, versão 2018. [Cited in 2018 Jul 28]. Available from: <<https://www.maxon.net/en-gb/products/cinema-4d/overview>>
11. Haddad J, Novaes C, Schimidt A, Oliveira M, Figueiredo C, Marin Neto JA. Rare form of coronary fistula draining into the right ventricular apex. *Rev Bras Cardiol*. 2016; 24(1-4): 44-6.
12. Valera FJ, Doñate L, Hernández CE, Schuler M, Bel A, Montero JA. Surgical treatment of circumflex artery aneurysm with fistula to the coronary sinus and aortic regurgitation. *Cir Cardio*. 2014; 21(1):60-2.
13. Domínguez-Massa C, Bel-Mínguez AM, Pérez-Guillén M, Valera-Martínez FJ, Homero-Sos F. Coronary fistula from circumflex artery to superior caval vein. *Cir Cardio*. 2018; 25(3):170-2.
14. Ospina-Galeano AM, Navas-Gutiérrez SE, Ospina-Galeano DC, Bautista H, Velandia-Carrillo C. Anomalous Origin of the Right Coronary Artery With an Interarterial Course. *Rev Colomb. Cardiol*. 2017; 24(2):128.
15. Buccheri D, Chirco PR, Geraci S, Caramanno G, Cortese B. Coronary Artery Fistulae: Anatomy, Diagnosis and Management Strategies. *Heart Lung Circ*. 2018; 27(8):940-51.
16. Van Caenegem M, Vandekerckhove H. Coronary pulmonary fistula: A case series. *Int J Case Rep Imag*. 2016; 7(5):292-5.
17. Buccheri D, Luparelli M, Chirco PR, Piraino D, Andolina G, Assennato P. A call to action for an underestimated entity: Our algorithm for diagnosis and management of coronary artery fistula. *Int J Cardiol*. 2016 Oct 15; 221:1081-3.
18. Contreras-Gutiérrez VH, Téllez-Ramírez RA. Coronary arterio-venous fistula associated acute coronary syndrome: A case-report and review of literature. *Rev Med Hosp Gen Méx*. 2017;80(1):51-5.
19. Kline AD, Gupta D, Mastin ST, Chadran A. Coronary Cardiac Fistula: Evaluation by Cardiac CTA for Management. *World J Pediatr Congenit Heart Surg*. 2015 Jul;6(3):484-5.
20. Leardini P, Piotto VR, Silva MS, Tjeng R. Coronary Fistula. *Perspectivas Médicas: Red. de Revistas Científicas de América Latina y el Caribe, España y Portugal*. 2006; 17:26-8.
21. Mulinari LA, Navarro, FB, Pimentel GK, Miyazaki SM, Binotto CN, Pelissari EC, et al. The use and midium-term evaluation of decellularized allograft cusp in the surgical treatment of the tetralogy of Fallot. *Rev Bras Cir Cardiovas*. 2008; 23(2):197-203.
22. Joshi JK, Beache GM, Slaughter MS, Sobieski MA, Schneider W, Stoddard MF. Coronary Artery Fistula: 64-Slice Computed Tomographic Delineation and Correlation with Multiplane Transesophageal Echocardiography and Surgical Findings. *Echocardiography*. 2012; 29(3):69-71.
23. Attili A, Hensley AK, Jones FD, Grabham J, Dissesa TG. Echocardiography and Coronary CT Angiography Imaging of Variations in Coronary Anatomy and Coronary Abnormalities in Athletic Children: Detection of Coronary Abnormalities that Create a Risk for Sudden Death. *Echocardiography*. 2013; 30(2): 225-33.



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Coronary Artery Fistulae

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Short Editorial relates to the article: Coronary Artery Fistula: Association between Pathway Patterns, Clinical Features and Congenital Heart Disease

Abstract

Coronary artery fistula is a rare anatomic abnormality of the coronary arteries that affects 0.002% of the general population and represents 14% of all anomalies of coronary arteries. Its clinical relevance focuses mainly on the mechanism of the coronary steal phenomenon, causing myocardial functional ischemia, even in the absence of stenosis; therefore, angina and effort dyspnea are common symptoms. The suggested diagnostic approach is driven by patients' symptoms, and it consists of a number of instrumental examinations like ECG, treadmill test, echocardiography, computed tomography scan, cardiac magnetic resonance, and coronary angiography. If it is not an incidental finding, coronary angiography is required in view of optimal therapeutic planning. Small fistulae are usually asymptomatic, and prognosis is excellent if they are managed medically with clinical follow-up and echocardiography every 2 to 5 years. Large/giant, symptomatic fistulae, on the contrary, should undergo invasive closure, via either transcatheter approach or surgical ligation, whose results are equivalent at long-term follow-up. Antibiotic prophylaxis for prevention of bacterial endocarditis is recommended in all patients with coronary artery fistulae who undergo dental, gastrointestinal, or urological procedures. Life-long follow-up is always essential to ensure that the patient does not undergo progression of the disease or further cardiac complications.

Coronary artery fistula (CAF) is a connection between one or more coronary arteries and a cardiac chamber (coronary-cameral fistulae) or a major blood vessel (arteriovenous fistulae) when the myocardial capillary bed is bypassed. While they are generally isolated (80%), they may also be associated with other congenital cardiac malformations (20%) including tetralogy of Fallot, patent ductus arteriosus, atrial septal defects, and ventricular septal defects.^{1,2}

The exact incidence of CAF is still unknown, because the rate of undiagnosed cases remains high, but it is estimated that, whereas the incidence of coronary anomalies is 0.2% to 1.2% in the general population, CAF is present in 0.002%.^{3,4} CAF

represents about 0.2% to 0.4% of all cardiac malformations⁵ and 14% of all coronary anomalies.⁶ Several other studies indicate CAF in 0.3% of patients who presented with congenital heart disease, in 0.06% of children undergoing echocardiography, and in 0.13% to 0.22% of adults undergoing coronary angiography.⁷

About 75% of all CAF that are discovered incidentally are small and clinically silent.⁸

Although, in the past, the etiology of CAF was prominently of the congenital forms, over the years, the development and dissemination of interventional and surgical techniques have resulted in changes to its etiology, with a higher prevalence of the acquired forms,⁹ which may include those secondary to infective endocarditis, aortic dissection, previous surgery, endomyocardial biopsy, coronary angioplasty, bypass surgery, valve replacement, cardiac transplant, trauma, permanent pacemaker placement, closed-chest ablation of accessory pathways, neoplasms, and iatrogenic management of Kawasaki disease.¹⁰

The feeding artery of the fistula may drain from a coronary artery or one of its branches, and, usually after a dilated and tortuous course, it ends in one of the cardiac chambers or a vessel. CAF with a proximal origin is frequently large; on the contrary, if its origin is distal, it is usually tinier and more tortuous.¹¹

There may be multiple feeding arteries to a single CAF drainage point, or multiple drainage sites may exist. Multiple fistulae between the three major coronary arteries and the left ventricle have also been reported. In some cases, especially in adults, fistulae may originate from both coronary arteries, which drain into the pulmonary trunk. These fistulae can frequently cause angina and require closure.¹² CAFs arise more frequently from the right coronary artery (approximately 50% to 60%) and drain most often in the right heart (approximately 80%).

Fistulae with a large caliber could allow the well-known phenomenon of coronary steal in which the blood with a diastolic runoff is directed away from the normal coronary circulation and myocardial microcirculation. When the drainage site is located in the left atrium or pulmonary vein, there is an effective left-to-left shunt that determines a volume overload to the left heart only.

A presumptive diagnosis can occasionally be made upon hearing an atypical systolic, diastolic, or continuous murmur, although signs could be found on ECG, chest X-ray, or echocardiography.

Clarifying exams are multidetector computed tomography or magnetic resonance imaging. Computed tomography is superior to echocardiography in patients who are overweight, and they allow excellent anatomical delineation, in contrast to echocardiography. Coronary angiography remains the best diagnostic technique for CAF detection with cardiac structural involvement and for hemodynamic evaluation; furthermore, it makes it possible to program interventional closure with dedicated devices.¹³

Keywords

Myocardial Ischemia; Arterio-arterial fistula/diagnostic imaging; Arterio-arterial fistula/surgery; Coronary Angiography/methods; Closure Techniques/trends; Anti-Bacterial Agents/therapeutic use.

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CAF of small or moderate size should be closed only in the event that patients are symptomatic for myocardial ischemia, arrhythmias, ventricular dilation, or dysfunction of uncertain origin, or if there are complications due to endocarditis. Otherwise, patients with small, asymptomatic fistulae should not be subjected to closure, but they should undergo clinical follow-up with echocardiography every 2 to 5 years.

Patients with CAF who undergo percutaneous or surgical closure have good prognosis, which depends on the possible complications related to the techniques, the severity of the shunt, and the morphology of the fistula. Life expectancy is, however, normal, with recurrence rates ranging from 9% to 19% for transcatheter closure and 25% in surgical ligation.^{2,6,14}

Further details have just been made available thanks to recent interesting studies.¹⁵

References

1. Dodge-Khatami A, Mavroudis C, Backer CL. Congenital Heart Surgery Nomenclature and Database Project: anomalies of the coronary arteries. *Ann Thorac Surg* 2000;69(4 Suppl):S270-97.
2. Buccheri D, Chirco PR, Geraci S, Caramanno G, Cortese B. Coronary Artery Fistulae: Anatomy, Diagnosis and Management Strategies. *Heart Lung Circ*. 2018 Aug;27(8):940-51. doi: 10.1016/j.hlc.2017.07.014. Epub 2018 Feb 9.
3. Kardos A, Babai L, Rudas L, Gaál T, Horváth T, Tálosi L, et al. Epidemiology of congenital coronary artery anomalies: a coronary arteriography study on a central European population. *Cathet Cardiovasc Diagn*. 1997;42(3):270-5.
4. Vavuranakis M, Bush CA, Boudoulas H. Coronary artery fistulas in adults: Incidence, angiographic characteristics, natural history. *Cathet Cardiovasc Diagn*. 1995;35(2):116-20.
5. Chaloumas D, Pericleous A, Dimitrakaki IA, Danelatos C, Dimitrakakis G. Coronary arteriovenous fistulae: a review. *Int J Angiol*. 2014;23(1):1-10.
6. Qureshi SA. Coronary arterial fistulas. *Orphanet J Rare Dis* 2006 Dec 21;1:51.
7. Buccheri D, Luparelli M, Chirco PR, Piraino D, Andolina G, Assennato P. A call to action for an underestimated entity: Our algorithm for diagnosis and management of coronary artery fistula. *Int J Card* 2016 Oct 21;221:1081-3.
8. Mangukia CV. Coronary artery fistula. *Ann Thorac Surg*. 2012;93:2084-92.
9. Buccheri D, Dendramis G, Piraino D, Chirco PR, Carità P, Paleologo C, et al. Coronary artery fistulas as a cause of angina: How to manage these patients? *Cardiovasc Revasc Med* 2015;16(5):306-9.
10. Koenig PR, Kimball TR, Schwartz DC. Coronary artery fistula complicating the evaluation of Kawasaki disease. *Pediatr Cardiol* 1993;14(3):179-80.
11. Buccheri D, Pisano C, Piraino D, Cortese B, Chirco P, Dendramis G, et al. Coronary Artery Fistulas: Symptoms may not Correlate to Size. An Emblematic Case and Literature Review. *Internat Cardiovasc Forum J*. 2015;4,79-81.
12. Latson LA. Coronary artery fistulas: how to manage them. *Catheter Cardiovasc Interv* 2007; 70:110-6.
13. Said SA, Hofman MB, Beek AM, van der Werf T, van Rossum AC. Feasibility of cardiovascular magnetic resonance of angiographically diagnosed congenital solitary coronary artery fistulas in adults. *J Cardiovasc Magn Reson*. 2007;9(3):575-83.
14. Dimitrakakis G1, Von Oppell U, Luckraz H, Groves P. Surgical repair of triple coronary-pulmonary artery fistulae with associated atrial septal defect and aortic valve regurgitation. *Interact Cardiovasc Thorac Surg*. 2008;7(5):933-4.
15. Cobo DL, Batigalia F, Croti UA, Sciarra AMP, Foss MHD, Cobo RGF, et al. Fistula da Artéria Coronária: Associação entre Padrões de Trajetos, Características Clínicas e Cardiopatias Congênitas. *Arq Bras Cardiol*. 2021; 117(1):84-88.



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Relationship between Innate Immune Response Toll-Like Receptor 4 (TLR-4) and the Pathophysiological Process of Obesity Cardiomyopathy

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Abstract

Background: Obesity is a chronic low-grade inflammation condition related to cardiac disorders. However, the mechanism responsible for obesity-related cardiac inflammation is unclear. The toll-like receptor 4 (TLR-4) belongs to a receptor of the transmembrane family responsible for the immune response whose activation stimulates the production of proinflammatory cytokines.

Objective: To test whether the activation of the TLR-4 receptor participates in the obesity cardiomyopathy process, due to cytokine production through NF- κ B activation.

Methods: Male Wistar rats were randomized into two groups: the control group (C, n= 8 animals) that received standard diet/water and the obese group (OB, n= 8 animals) that were fed a high sugar-fat diet and water plus 25% of sucrose for 30 weeks. Nutritional analysis: body weight, adiposity index, food, water, and caloric intake. Obesity-related disorders analysis: plasma glucose, uric acid and triglycerides, HOMA-IR, systolic blood pressure, TNF- α in adipose tissue. Cardiac analysis included: TLR-4 and NF- κ B protein expression, TNF- α and IL-6 levels. Comparison by unpaired Student's t-test or Mann-Whitney test with a p-value < 0.05 as statistically significant.

Results: The OB group showed obesity, high glucose, triglycerides, uric acid, HOMA, systolic blood pressure, and TNF- α in adipose tissue. OB group presented cardiac remodeling and diastolic dysfunction. TLR-4 and NF- κ B expression and cytokine levels were higher in OB.

Conclusion: Our findings conclude that, in an obesogenic condition, the inflammation derived from cardiac TLR-4 activation can be a mechanism able to lead to remodeling and cardiac dysfunction.

Keywords: Cardiovascular Diseases/physiopathology; Obesity; Inflammation; Cytokines; Adipocytes; Fatty Acid synthases; Nutritional Assessment.

Introduction

Obesity, defined as an excessive body fat accumulation that may impair an individual's health,¹ is currently considered the most important nutritional disorder in both developed and underdeveloped countries.² Estimates show that in 2025 at least 18% of the adult population will be obese, a worrying condition since it can lead to several comorbidities, including cardiovascular diseases.^{3,4}

One of the main causes responsible for the obesity epidemic is the excessive consumption of hypercaloric diets, which are rich in saturated fat and refined sugars, associated with a sedentary health style.^{5,6} This modern lifestyle leads to adipose tissue hypertrophy that triggers, initially, a local inflammatory process, which may later affect and compromise the function of other organs, such as the heart.⁷ This inflammation of metabolic origin results in the synthesis of the proinflammatory cytokines led by different pathways, among them: adipose tissue lipolysis,⁸ adipocytes hypertrophy,⁹ fatty acids from the diet,¹⁰ and intestinal lipopolysaccharides (LPS) due to dysbiosis.¹¹ Within this context, free fatty acids and LPS are the main components involved in the inflammatory response, acting as Damage-Associated Molecular Patterns (DAMPs) and Pathogen-associated Molecular Patterns (PAMPs), respectively, which are recognized by some receptors, especially the Toll-Like Receptor 4 (TLR-4).¹²

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TLR-4 belongs to a family of receptors usually expressed in cells of the innate immune system, such as macrophages, neutrophils, and lymphocytes, and exerts an important role to detect and recognize pathogens leading to the innate¹³ and acquired¹⁴ immune response activation. This receptor is responsible for the activation of the nuclear factor kappa B (NF- κ B) with consequent synthesis of proinflammatory cytokines involved in the pathophysiology of several diseases, including heart diseases.¹⁵

However, the literature reports that the TLR-4 receptor is not expressed only in immune system cells. Cardiomyocytes also express this receptor and its activation, especially against infectious cardiac pathogens, contributes to the myocardial dysfunction process.^{16–18} Although the involvement of the immune system in the development of cardiac pathologic hypertrophy is well established,^{14,19,20} the TLR-4 pathway participation in the development and progression of obesity-related cardiac remodeling has not yet been clarified.²¹ Considering the lack of studies regarding this topic, the aim of this study was to test the hypothesis that the TLR-4 receptor activation participates in the obesity cardiomyopathy process, due to production of cytokine through the NF- κ B activation.

Material and Methods

Experimental Protocol

Male Wistar rats (n=16), 21 days of age, were obtained from *Universidade Estadual Paulista* (UNESP). Sample size was calculated by using SigmaStat for Windows, version 3.5 (Systat Software Inc., San Jose, CA, USA), considering the expected difference mean of 2.0, expected standard deviation of 1.0, test power of 90%, and α of 0.05. This calculation considered the adiposity index of previous studies published by our group.^{22–24} The animals were randomly divided into two experimental groups: the control group (C, n= 8 animals) that received standard diet/water and the obese group (OB, n= 8 animals) that received high sugar-fat (HSF) diet and water plus 25% of sucrose for 30 weeks. The diet model is a well-established model to induce obesity previously published by our research group.²⁵ The HSF diet contained soybean meal, sorghum, soybean peel, dextrin, sucrose, fructose, lard, vitamins, and minerals, plus 25% sucrose in drinking water. The control diet contained soybean meal, sorghum, soybean peel, dextrin, soy oil, vitamins, and minerals.

Food and water were offered *ad libitum* and the animals were kept in individual cages, in an environment with controlled temperature ($24 \pm 2^\circ\text{C}$), humidity ($55 \pm 5\%$), and light-dark cycle (12-12h). The study protocol (CEUA 1265/2018) was approved by the Ethics Committee on Animal Experimentation of the Botucatu School of Medicine, UNESP, São Paulo, Brazil, and followed the recommendations from the Guide for the Care and Use of Experimental Animals.²⁶ At the end of 30 weeks, the animals were fasted for 8h, then euthanized and the material was collected for analysis.

Nutritional Evaluation

Food and water consumption were evaluated daily. Caloric intake was determined by multiplying the energy value of

each diet (g $\times$ Kcal) by daily food intake. For the OB group, caloric intake also included water calories ($0.25 \times 4 \times \text{mL}$ consumed). The animals' body weight was measured weekly. After euthanasia, visceral fat (VAT), epididymal fat (EAT), and retroperitoneal fat (RAT) were collected and used to calculate the adiposity index (AI) by the formula: $[(\text{VAT} + \text{EAT} + \text{RAT}) / \text{ANIMAL WEIGHT}] \times 100$.

Obesity-related disorders analysis

Plasma glucose and triglycerides, (BioClin, Quibasa Química Básica Ltda., Belo Horizonte, Minas Gerais, Brazil) were measured by colorimetric-enzymatic method in an automatic enzymatic analyzer system (Chemistry Analyzer BS-200, MindrayMedical International Limited, Shenzhen, China). Insulin (EMD Millipore Corporation, Billerica, MA, USA) was analyzed in plasma by ELISA using a commercial kit. The reading was performed by Spectra Max 190 microplate spectrophotometer (Molecular Devices®, Sunnyvale, CA, USA).

The Homeostatic Model Assessment (HOMA-IR), which allows evaluating insulin resistance, was also calculated according to the following formula: $\text{fasting insulin } (\mu\text{UI} / \text{mL}) \times \text{fasting glucose } (\text{mmol} / \text{L}) / 22.5$.^{27,28}

The Systolic blood pressure (SBP) evaluation was assessed in conscious rats by the non-invasive tail-cuff method with a NarcoBioSystems® Electro-Sphygmomanometer (International Biomedical, Austin, TX, USA). The animals were warmed in a wooden box (50 x 40 cm) between 38–40°C with heat generated by two incandescent lamps for 4–5 minutes to stimulate arterial vasodilation. After this procedure, a cuff with a pneumatic pulse sensor was attached to the tail of each animal. The cuff was inflated to a pressure of 200 mmHg and subsequently deflated. Blood pressure values were recorded on a Gould RS 3200 polygraph (Gould Instrumental Valley View, Ohio, USA). The mean of three pressure readings was recorded for each animal.

Since obesity is associated with an inflammatory condition in adipose tissue, TNF- α and IL-6 levels were evaluated. Epididymal adipose tissue (400 mg) was triturated with 2 ml of phosphate buffer saline (PBS) (pH 7.4) and then centrifuged at 3,000 rpm and 4°C for 10 min. Using the supernatants, TNF- α and IL-6 were measured using commercial ELISA kits (R&D Systems) according to the manufacturer's instructions. The values were normalized by the protein amounts of each sample quantified by the Bradford method²⁹ and the results are expressed in picogram/g protein (pg/g protein). Epididymal adipose tissue was selected for presenting a similar inflammation pattern to that found in visceral fat.³⁰

Echocardiographic Analysis

The analysis was performed on live animals by transthoracic echocardiography, with a Vivid S6 system equipped with a multifrequency ultrasonic transducer of 5.0 to 11.5 MHz (General Electric Medical Systems, Tirat Carmel, Israel). The animals were lightly anesthetized by intraperitoneal injection with a mixture of ketamine (50 mg/kg) and xylazine (1 mg/kg) and placed in a left decubitus position. The structural measurements of cardiac images were obtained in the one-dimensional mode (M-mode) guided by the images

in the two-dimensional mode with the transducer in the parasternal position, minor axis. Left ventricular (LV) evaluation was performed with the M-mode cursor just below the mitral valve plane at the level of the papillary muscles. All examinations were performed by the same examiner and obtained according to the main method recommended by the American Society of Echocardiography. The aorta and left atrium images were obtained by positioning the M-mode cursor to plan the aortic valve level. The following cardiac structures were evaluated: left ventricular diastolic diameter (LVDD); left ventricular posterior wall thickness at end-systole (LVPWS); Left ventricular systolic interventricular septum thickness (LVSIS); aorta diameter (AD); left atrium (LA); and the relative wall thickness (RWT) of the LV. The LV systolic function was evaluated by cardiac output and also by heart rate (HR), since it is a cardiac systolic function modulator. The LV diastolic function was assessed by the transmitral flow early peak velocity (E); deceleration time of E wave (Dec. time). The study was supplemented by evaluation by early (E') and late (A') diastolic tissue Doppler of the mitral annulus (arithmetic mean travel speeds of lateral and septal walls), and the wave ratio (E/E' and E'/A').

Cardiac tissue analysis

Inflammation

One hundred milligrams (100mg) were homogenized in PBS and the supernatant was used. TNF- α and IL-6 quantification were performed by ELISA using a commercial kit (Linco Research Inc., R & D Systems, Millipore and B-Brigde International Inc.). The reading was performed by Spectra Max 190 microplate spectrophotometer (Molecular Devices®, Sunnyvale, CA, USA). The results were corrected by the total protein amount according to the Bradford method.

Real time PCR

The frozen left ventricular fragment was homogenized in TRIzol® for extraction of ribonucleic acid (RNA). Afterward, the RNA was subjected to reverse transcription, conversion of RNA to complementary deoxyribonucleic acid (cDNA), by the action of the enzyme reverse transcriptase, using the SuperScript II First-Strand Synthesis System for RT-PCR® Invitrogen, São Paulo, Brazil. The obtained cDNA was used in the polymerase chain reaction (PCR) using ready-made assays (Applied Biosystems, CA, USA) containing TaqMan MGB (FAM) primer and primer specific for TLR-4 (Rn00569848_m1).

Western Blot

The heart fragments were homogenized in lysis buffer and centrifuged. The supernatant was collected and the protein concentration was analyzed by the Bradford method.²⁹ After quantification, the cardiac protein extracts were diluted in a buffer solution containing 50 mM Tris-HCl (pH 6.8), 200 mM 2-Mercaptoethanol, 2% Sodium Dodecyl Sulfate (SDS), 0.1% bromophenol blue, and 10% glycerol. The dilutions (50ug) were heated and subjected to sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS-PAGE) in 10% polyacrylamide gels. After electrophoresis, the proteins

were electrotransferred to nitrocellulose membranes (Bio-Rad Biosciences; NJ, USA). Non-specific binding sites of the primary antibody to the membrane were blocked by incubation with 0.5% skimmed-milk powder solution, dissolved in TBS-T buffer pH 7.4. The membrane was then washed three times in basal solution and incubated overnight with TLR-4 specific primary antibody (sc293072), total NF- κ B (sc8008), phosphorylated NF- κ B (ser536) (sc33020). β -actin was used as an internal control (sc47778). After incubation, the membranes were washed and incubated with the respective secondary antibodies. Finally, immunodetection was performed by the chemiluminescence method, according to the manufacturer's instructions (ECL SuperSignal® West Pico Chemiluminescent Substrate – Thermo Scientific, Rockford, IL, USA, 34080), and analyzed by means of a densitometer (GS-710 calibrated imaging densitometer, Bio-Rad lab, CA, USA).

Statistical analysis

The data were submitted to Kolmogorov-Smirnov normality test. Parametric variables were compared by unpaired Student's *t*-test and the results are expressed as mean $\pm$ standard deviation. Non-parametric variables were compared by Mann-Whitney test and the results are expressed as median (interquartile range 25-75). Statistical analyses were performed using Sigma Stat for Windows, version 3.5 (Systat Software Inc., San Jose, CA, USA). A *p*-value < 0.05 was considered statistically significant.

Results

Table 1 shows the nutritional parameters. OB animals consumed less food, but more water compared to the control group, reflecting a similar caloric intake. The OB group also presented obesity characterized by increased body weight and adiposity index.

Regarding the obesity-related disorders, the OB group presented higher glucose, triglycerides, and uric acid, insulin resistance, increased systolic blood pressure, and adipose tissue inflammation, with elevated TNF- α and IL-6 levels compared to the control group (Table 2).

The echocardiographic analysis is presented in Table 3. At the end of 30 weeks, the OB group showed cardiac remodeling, characterized by reduced LVDD and increased LVPWS, LVSIS, LA, and AD. Moreover, OB animals presented diastolic dysfunction, represented by changes in the E wave, E wave deceleration time, and E'/A'.

Regarding the TLR-4 gene and protein expression in cardiac tissue, it is possible to verify that both were increased in the OB group (Figure 1).

NF- κ B phosphorylation in cardiac tissue was also higher in the OB group (Figure 2), resulting in increased cytokines, since this group showed higher TNF- α and IL-6 levels compared to the C group (Figure 3).

Discussion

This study hypothesized that the TLR-4 receptor activation participates in obesity-related cardiac disease by triggering cytokine production via NF- κ B. In order to induce obesity and

Table 1 – Nutritional parameters

Characteristics	Groups						p value
	Control (n=8)			OB (n=8)			
Final body weight (g)	493	±	50.8	583	±	75.9	0.001*
Adiposity index (%)	4.79	±	0.73	8.68	±	1.76	0.0004*
Food consumption (g/day)	23.92	±	2.37	13.0	±	2.20	0.0001*
Water consumption (ml/day)	34.6	±	5.08	41.6	±	3.47	0.001*
Caloric intake (Kcal/day)	85.9	±	8.52	98.3	±	8.35	0.07

OB: obese group. Data expressed as mean ± standard deviation. Comparison by unpaired Student's t-test. *indicates $p < 0.05$.

Table 2 – Obesity-related disorders

Characteristics	GROUPS						p-value
	Control (n=8)			OB (n=8)			
Glucose (mg/dL)	75.7	±	2.02	105	±	17.9	0.02*
Triglycerides (mg/dL)	63.5	±	18.6	104	±	25.4	0.003*
Uric acid (mg/dL)	0.44	±	0.09	0.62	±	0.20	0.04*
HOMA-IR	5.90	±	2.32	30.9	±	17.0	0.004*
Systolic Blood Pressure (mmHg)	121	±	5.77	128	±	6.48	0.03*
TNF-α Adipose tissue (pg/g protein)	52.7 (46.6 – 62.5)			152 (117 – 219)			0.001*
IL-6 Adipose tissue (pg/g protein)	13.0 ± 9.2			94.5 ± 33.3			< 0.001*

OB: obese group; HOMA-IR: Homeostatic Model Assessment. Data expressed as mean ± standard deviation or median (interquartile range). Comparison by unpaired Student's t-test or Mann-Whitney. * indicates $p < 0.05$.

disorders related to excessive body fat, the animals in the OB group were submitted to a HSF diet for 30 weeks. At the end of the experimental period, the results show that these animals presented higher adiposity index and several disorders, such as hyperglycemia, increased uric acid, insulin resistance, hypertriglyceridemia, elevated SBP, increased TNF-α and IL-6 levels in both heart and adipose tissue, confirming the efficacy of the diet model used.^{22–25}

The coexistence of obesity-related disorders — such as insulin resistance, diabetes, and dyslipidemia — associated with adipose tissue dysfunction, characterized by adipokine imbalance, promote maladaptive responses in the heart, such as myocyte hypertrophy, contractile dysfunction, and cardiac remodeling, which contribute to both the development and progression of chronic heart failure.^{31–33} This condition was confirmed in this study, since the echocardiogram evaluation showed cardiac remodeling and diastolic dysfunction in the OB group. It is important to emphasize that the concentric characteristics of cardiac remodeling observed in the OB group are the result of an increased functional overload and the maintenance of this condition, leading to cardiac diastolic dysfunction. Similar results have been related to the diet-induced obesity model in the literature.³⁴

The literature reports that cardiac remodeling can also be led by high concentrations of proinflammatory cytokines,

such as TNF-α and IL-6.^{35,36} TNF-α has been implicated in the development of left ventricular dysfunction, left ventricular remodeling, increased cardiac myocyte apoptosis and its direct action is exerted by TNF-α receptors, which are expressed by almost all nucleated cells. Increased IL-6 levels can also induce myocyte hypertrophy and myocardial dysfunction.³⁷ It is important to emphasize that these cytokines can be produced in response to TLR-4 pathway activation, and also L-6 seems to be released in direct response to TNF-α,³⁵ exacerbating the cardiac changes due to inflammatory condition. Therefore, our findings confirm the evidence regarding obesity cardiopathy and inflammation, since the cardiac levels of TNF-α and IL-6 were higher in the OB group.^{18,37}

The involvement between proinflammatory cytokines and obesity-related cardiac remodeling induced by diet can be attributed to several causes.^{18,38} Thus, the aim of this study was to evaluate cardiac TLR-4 activation as responsible for triggering the inflammatory process. It was observed that the OB group presented higher TLR-4 gene and protein expression together with increased NF-κB phosphorylation, confirming the activation of this pathway as a mediator of inflammation. The literature reports that this receptor can be activated by LPS of gram-negative bacteria, but also by fatty acids.³⁹ In obesity, the adipose tissue lipolysis represents an important source of free fatty acids, capable of activating the inflammatory pathway.^{40,41} This catabolic process can occur due to insulin

Table 3 – Echocardiographic analysis

Characteristics	GROUPS						p-value
	Control			OB			
LVDD (mm)	7.20	±	0.20	6.70	±	0.56	0.031*
LVDD/BW	14.7	±	1.6	11.9	±	1.3	0.002*
LVPWS (mm)	3.03	±	0.31	3.35	±	0.21	0.033*
LVSIS (mm)	3.35	±	0.21	3.57	±	0.19	0.045*
RWT	0.45	±	0.05	0.51	±	0.09	0.098
AD (mm)	3.73	±	0.12	3.99	±	0.13	0.001*
LA (mm)	4.75	±	0.12	5.17	±	0.38	0.011*
HR (bpm)	234	±	39	295	±	26	0.002*
Cardiac Output	0.91	±	0.01	0.88	±	0.06	0.142
Deceleration time (ms)	47.2	±	3.0	50.6	±	2.7	0.035*
E wave	68.3	±	5.2	73.1	±	3.3	0.046*
A wave	40.7	±	3.7	45.7	±	6.1	0.062
E/A ratio	1.68	±	0.08	1.61	±	0.016	0.327
E'/A' medium ratio	1.53	±	0.14	1.26	±	0.25	0.018*
E/ E' medium ratio	12	±	1.3	13.5	±	1.86	0.094

OB: obese group; LVDD: left ventricular diastolic dysfunction; BW: body weight; LVPWS: left ventricular posterior wall thickness at end-systole; LVSIS: left ventricular systolic interventricular septum thickness; RWT: relative wall thickness; AD: aorta diameter; LA: left atrium; HR: heart rate. Transmittal flow early peak velocity (E wave); deceleration time: deceleration time of the E wave. Doppler early (E') and late (A') diastolic of the mitral annulus (arithmetic average travel speeds of lateral and septal walls), and the ratio (E/E' and E'/A'). Data expressed as mean ± standard deviation. Comparison by unpaired Student's t-test. * indicates $p < 0.05$.

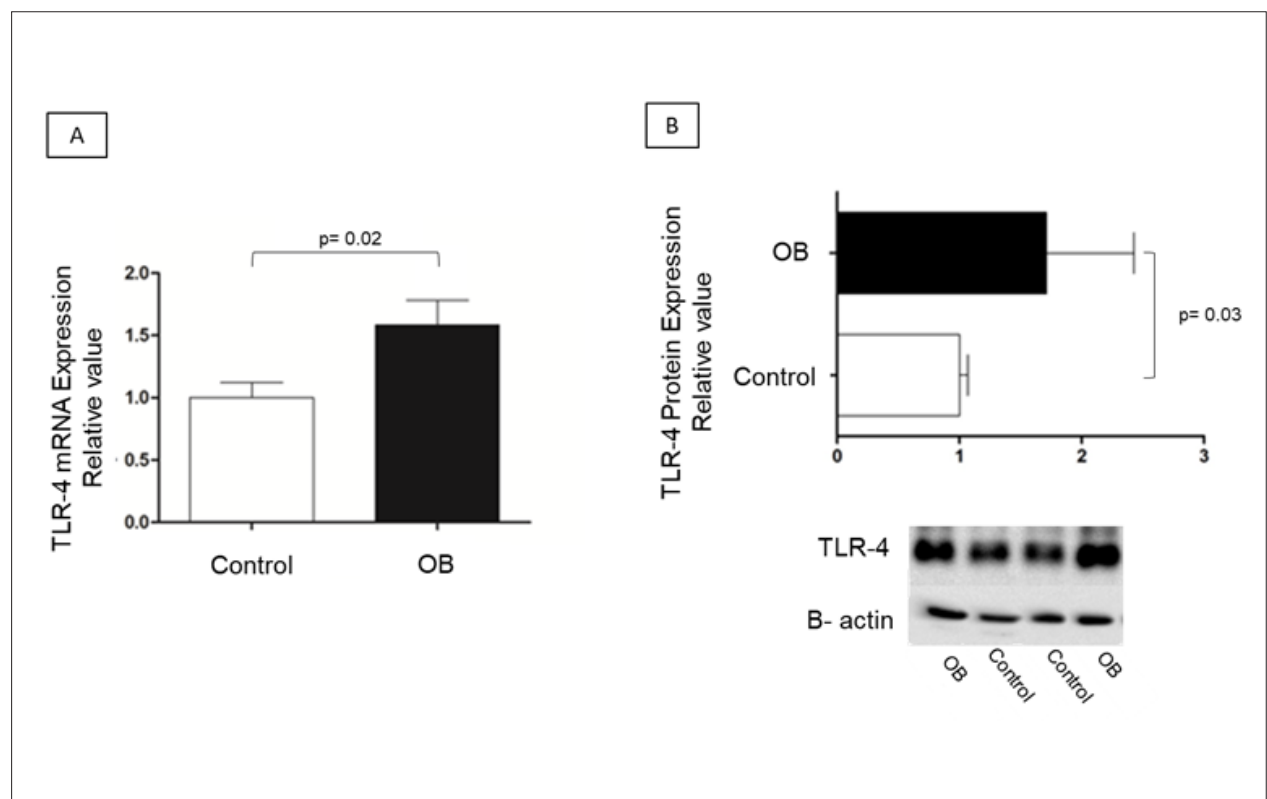


Figure 1 – TLR-4 expression in cardiac tissue. (A) Gene expression by real-time PCR; (B) Protein expression by Western Blot. Results expressed as mean ± standard deviation. Comparison by unpaired Student's t-test. * indicates $p < 0.05$; $n = 8$ animals/group.

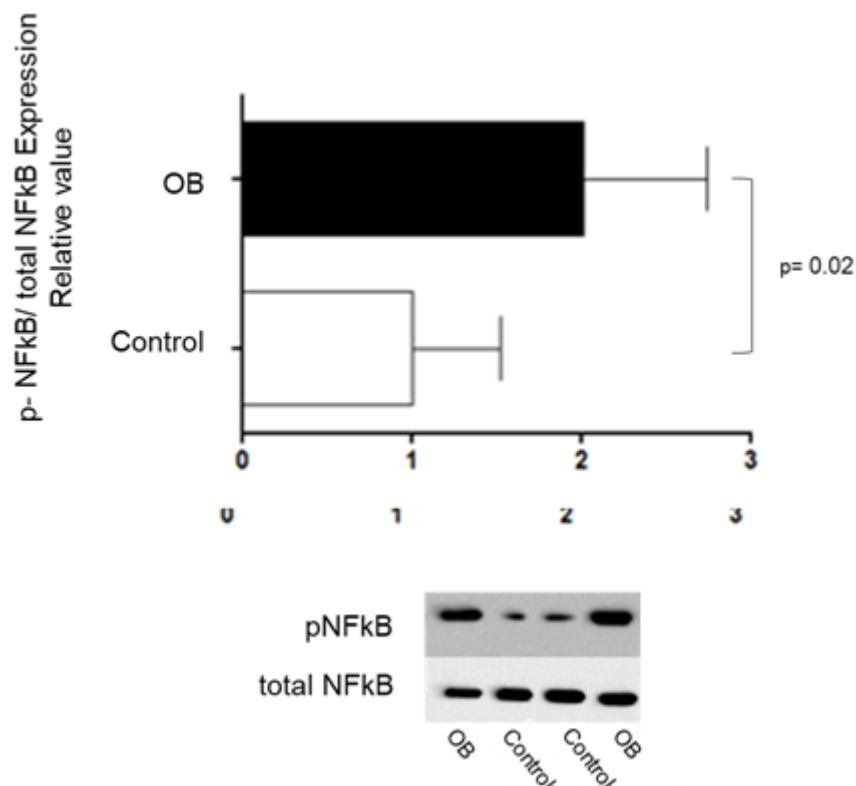


Figure 2 – Phospho and total NF-κB protein expression in cardiac tissue. Results expressed as mean $\pm$ standard deviation. Comparison by unpaired Student's *t*-test. *indicates $p < 0.05$; $n = 8$ animals/group.

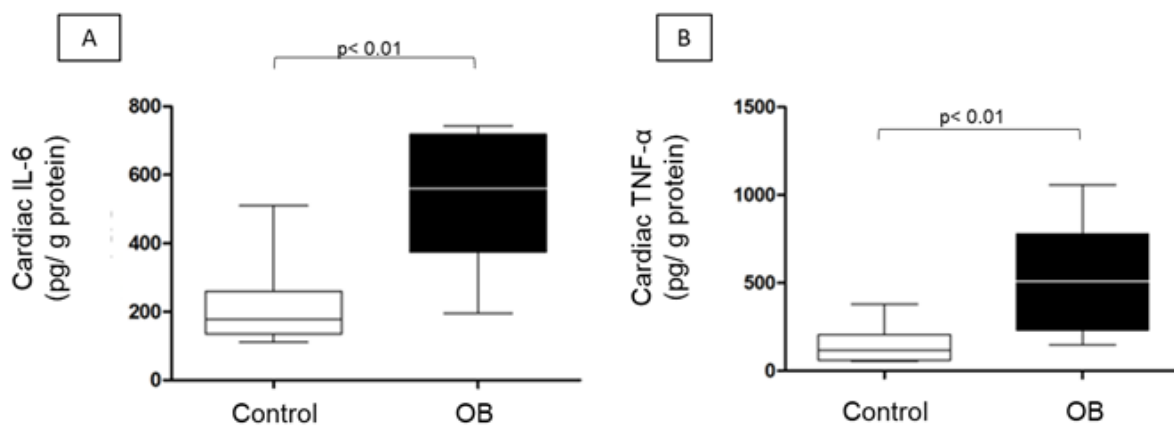


Figure 3 – Cardiac cytokines in cardiac tissue. (A) IL-6 (pg protein/g); (B) TNF-α. Results expressed as median and interquartile range. Comparison by Mann-Whitney test. * indicates $p < 0.05$; $n = 8$ animals/group.

resistance, once the adipose tissue becomes resistant to the hormone antilipolytic effect. Together with insulin resistance, increased TNF- α and IL-6 levels are also able to induce lipolysis in adipose tissue.^{42,43} These two lipolytic conditions were presented by the OB group. Moreover, associated with these mechanisms described above, some researchers report that the Western diet pattern is associated with changes in the intestinal microbiota, making this organ more permeable, allowing the translocation of pathogenic bacteria to the circulation.⁴² Bacterial LPS can be recognized by TLR-4, triggering the NF- κ B activation with consequent cytokine synthesis. Although this mechanism was not evaluated in this experiment, this relationship is already well established.^{43–45} In addition, the diet composition used in this study is also directly related to the TLR-4 receptor activation, since the saturated fatty acids offered in the diet have similar structures to bacterial LPS, being also able to be recognized, leading to an inflammatory process via TLR-4 pathway.^{46,47}

Conclusion

In summary, all these mechanisms may have been activated in a synergistic way, enhancing the production of cytokines that play a fundamental role in the development of cardiomyopathies. Thus, this study shows that the innate immune response through TLR-4 receptor activation is one of the mechanisms that can contribute to the onset of the myocardial inflammatory process in obesity. Therefore, since no studies were found in the literature showing an interaction between this inflammatory pathway, heart disease and obesity, our findings conclude that in an obesogenic condition, the inflammation derivative from cardiac TLR-4 activation is a new mechanism which can lead to remodeling and cardiac dysfunction.

References

1. World Health Organization. Obesity and overweight [Internet]. Geneva: WHO; 2011 [acesso 5 de maio de 2016]. Disponível em: <http://www.who.int/mediacentre/factsheets/fs311/en>. 2016
2. Francischi RPP, Pereira LO, Freitas CS, Klopfer M, Santos RC, Vieira P, et al. Obesidade: atualização sobre sua etiologia, morbidade e tratamento. *Rev Nutr*. 2000;13(1):17-28.
3. Bhat ZF, Morton JD, Mason S, Bekhit AEDA, Bhat HF. Obesity and neurological disorders: dietary perspective of a global menace. *Crit Rev Food Sci Nutr*. 2019;59(8):1294-310.
4. Mandviwala T, Khalid U, Deswal A. Obesity and cardiovascular disease : a risk factor or a risk marker ? *Curr Atheroscler Rep*. 2016;18(5):21.
5. Johnson AR, Wilkerson MD, Sampey BP, Troester MA, Hayes DN, Makowski L. Cafeteria diet-induced obesity causes oxidative damage in white adipose. *Biochem Biophys Res Commun*. 2016;473(2):545-50.
6. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr*. 2004;79(4):537-43.
7. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. *Metab Syndr Relat Disord*. 2015;13(10):423-44.
8. Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes*. 2009;117(6):241-50.
9. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab*. 2007;92(3):1023-33.
10. Kramer B, França LM, Zhang Y, Paes AM de A, Martin Gerdes A, Carrillo-Sepulveda MA. Western diet triggers toll-like receptor 4 signaling-induced endothelial dysfunction in female wistar rats. *Am J Physiol Heart Circ Physiol*. 2018;315(6):H1735-47.
11. Del Bas JM, Guirro M, Boqué N, Cereto A, Ras R, Crescenti A, et al. Alterations in gut microbiota associated with a cafeteria diet and the physiological consequences in the host. *Int J Obes*. 2018;42(4):746-54.
12. Huang S, Rutkowski JM, Snodgrass RG, Ono-Moore KD, Schneider DA, Newman JW, et al. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. *J Lipid Res*. 2012;53(9):2002-13.

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Study limitations

This study has few limitations. One of them is related to the absence of plasma fat-free acid evaluation.

Author Contributions

Conception and design of the research: Ferron AJT, Campos DHS, Cicogna AC, Francisqueti F, Corrêa C; Acquisition of data: Alves PHR, Costa MR, Hasimoto FK, Gregolin C, Garcia JL, Campos DHS, Mattei L, Moreto F, Bazan SGZ; Analysis and interpretation of the data: Alves PHR, Ferron AJT, Campos DHS, Bazan SGZ, Francisqueti F, Corrêa C; Statistical analysis: Ferron AJT; Obtaining financing: Corrêa C; Writing of the manuscript: Alves PHR, Ferron AJT, Francisqueti F, Corrêa C; Critical revision of the manuscript for intellectual content: Ferron AJT, Cicogna AC, Francisqueti F, Corrêa C.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

13. Ferraz EG, Silveira BBB, Sarmiento VA, Santos JN. Toll-Like Receptors : regulation of the immune responses. *Rev Gaúcha Odontol*. 2011;59(3):483-90.
14. Yuan X, Deng Y, Guo X, Shang J, Zhu D, Liu H. Atorvastatin attenuates myocardial remodeling induced by chronic intermittent hypoxia in rats: partly involvement of TLR-4/MYD88 pathway. *Biochem Biophys Res Commun*. 2014;446(1):292-7.
15. Frantz S, Kobzik L, Kim Y, Fukazawa R, Medzhitov R, Lee RT, et al. Toll4 (TLR4) expression in cardiac myocytes in normal and failing myocardium. 1999;104(3):271-80.
16. Liu T, Zhang M, Niu H, Liu J, Ruilian M, Wang Y, et al. Astragalus polysaccharide from Astragalus Melittin ameliorates inflammation via suppressing the activation of TLR-4/NF- κ B p65 signal pathway and protects mice from CVB3-induced virus myocarditis. *Int J Biol Macromol*. 2019 Apr 1;126:179-86.
17. Liu F, Wen Y, Kang J, Wei C, Wang M, Zheng Z, et al. Regulation of TLR4 expression mediates the attenuating effect of erythropoietin on inflammation and myocardial fibrosis in rat heart. *Int J Mol Med*. 2018;42(3):1436-44.
18. Zhang WB, Zhang HY, Zhang Q, Jiao FZ, Zhang H, Wang LW, et al. Glutamine ameliorates lipopolysaccharide-induced cardiac dysfunction by regulating the toll-like receptor 4/mitogen-activated protein kinase/nuclear factor- κ B signaling pathway. *Exp Ther Med*. 2017;14(6):5825-32.
19. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. *Circ Res*. 2016;118(11):1786-808.
20. Krejci J, Mlejnek D, Sochorova D, Nemec P. Inflammatory cardiomyopathy : a current view on the pathophysiology , diagnosis , and treatment. *Biomed Res Int*. 2016;2016(4087632).
21. Li F, Zhang H, Yang L, Yong H, Qin Q, Tan M, et al. NLRP3 deficiency accelerates pressure overload-induced cardiac remodeling via increased TLR4 expression. *J Mol Med*. 2018;96(11):1189-202.
22. Francisqueti FV, Ferron AJT, Hasimoto FK, Alves PHR, Garcia JL, Santos KC, et al. Gamma oryzanol treats obesity- induced kidney injuries by modulating the adiponectin receptor 2 / PPAR- α axis. *Oxid Med Cell Longev*. 2018 Sep 05;2:1-9.
23. Costa MR, Garcia JL, Silva CCV, Ferron AJT, Francisqueti-Ferron FV, Hasimoto FK, et al. Lycopene modulates pathophysiological processes of non-alcoholic fatty liver disease in obese rats. *Antioxidants*. 2019;8(8):276.
24. Ferron AJT, Aldini G, Francisqueti-Ferron FV, Silva CCVA, Bazan SGZ, Garcia JL, et al. Protective effect of tomato-oleoresin supplementation on oxidative injury recovers cardiac function by improving β -adrenergic response in a diet-obesity induced model. *Antioxidants*. 2019;8(9):368.
25. Francisqueti FV, Minatel IO, Ferron AJT, Bazan SGZ, Silva VS, Garcia JL, et al. Effect of gamma-oryzanol as therapeutic agent to prevent cardiorenal metabolic syndrome in animals submitted to high sugar-fat diet. *Nutrients*. 2017;9(12):1299.
26. Olfert ED, Cross BM, McWilliam AA. Guide to the care and use of experimental animals. Vol. 1. Ottawa: Canadian Council on Animal Care; 1993.
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-9.
28. Ferron A, Jacobsen BB, Sant'Ana P, Campos D, Tomasi L, Luzivotto R, et al. Cardiac dysfunction induced by obesity is not related to β -adrenergic system impairment at the receptor-signalling pathway. *PLoS One*. 2015;10(9):e0138605.
29. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem*. 1976;72(1-2):248-54.
30. Luvizotto RAM, Nascimento AF, Imaizumi E, Pierine DT, Conde SJ, Correa CR, et al. Lycopene supplementation modulates plasma concentrations and epididymal adipose tissue mRNA of leptin , resistin and IL-6 in diet-induced obese rats. *Br J Nutr*. 2013;110(10):1803-9.
31. Jacob PS, Fujii TMM, Yamada M, Borges MC, Pantaleão LC, Borelli P, et al. Isocaloric intake of a high-fat diet promotes insulin resistance and inflammation in Wistar rats. *Cell Biochem Funct*. 2013;31(3):244-53.
32. Lawler HM, Underkofler CM, Kern PA, Erickson C, Bredbeck B, Rasouli N. Adipose tissue hypoxia, inflammation and fibrosis in obese insulin sensitive and obese insulin resistant subjects. *J Clin Endocrinol Metab*. 2016;101(4):1422-8.
33. Moreno-Fernández S, Garcés-Rimón M, Vera G, Astier J, Landrier JF, Miguel M. High fat/high glucose diet induces metabolic syndrome in an experimental rat model. *Nutrients*. 2018;10(10):1502.
34. Ferron AJT, Francisqueti FV, Minatel IO, Silva CCVA, Bazan SGZ, Kitawara KAH, et al. Association between cardiac remodeling and metabolic alteration in an experimental model of obesity induced by Western Diet. *Nutrients*. 2018;10(11):1675.
35. Hedayat M, Mahmoudi MJ, Rose NR, Rezaei N. Proinflammatory cytokines in heart failure: double-edged swords. *Heart Fail Rev*. 2010;15(6):543-62.
36. Nishida K, Otsu K. Inflammation and metabolic cardiomyopathy. *Cardiovasc Res*. 2017;113(4):389-98.
37. Anker SD, Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart*. 2004;90(4):464-70.
38. Mocan M, Mocan Hognogi LD, Anton FP, Chiorescu RM, Goidescu CM, Stoia MA, et al. Biomarkers of inflammation in left ventricular diastolic dysfunction. *Dis Markers*. 2019 Jun 2;2019:7583690.
39. Sopasakis VR, Sandstedt J, Johansson M, Lundqvist A, Bergström G, Jeppsson A, et al. Toll-like receptor-mediated inflammation markers are strongly induced in heart tissue in patients with cardiac disease under both ischemic and non-ischemic conditions. *Int J Cardiol*. 2019 Oct 15;293:238-47.
40. Francisqueti FV, Nascimento AF, Minatel IO, Dias MC, Luvizotto RDAM, Berchieri-Ronchi C, et al. Metabolic syndrome and inflammation in adipose tissue occur at different times in animals submitted to a high-sugar/fat diet. *J Nutr Sci*. 2017 Aug 21;6:e41.
41. Ruiz-núñez B, Dijk-Brouwer DAJ, Muskiet FAJ. The relation of saturated fatty acids with low-grade inflammation and cardiovascular disease. *J Nutr Biochem*. 2016 Oct;36:1-20.
42. Langin D, Arner P. Importance of TNF α and neutral lipases in human adipose tissue lipolysis. *Trends Endocrinol Metab*. 2006;17(8):314-20.
43. Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, et al. Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab*. 2003;88(7):3005-10.
44. Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferrì F, Pulcini G, et al. Food components and dietary habits: keys for a healthy gut microbiota composition. *Nutrients*. 2019;11(10):2393.
45. Ubanako P, Xelwa N, Ntwasa M. LPS induces inflammatory chemokines via TLR-4 signalling and enhances the Warburg Effect in THP-1 cells. *PLoS One*. 2019;14(9):e1222614.
46. Li P, Wu YH, Zhu YT, Li MX, Pei HH. Requirement of Rab21 in LPS-induced TLR4 signaling and pro-inflammatory responses in macrophages and monocytes. *Biochem Biophys Res Commun*. 2019;508(1):169-76.
47. Fonceca AM, Zosky GR, Bozanich EM, Sutanto EN, Kicic A, McNamara PS, et al. Accumulation mode particles and LPS exposure induce TLR-4 dependent and independent inflammatory responses in the lung. *Respir Res*. 2018;19(15):1-10.



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Reconnection Sites in Redo Ablation after Cryoballoon Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation

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Abstract

Background: In paroxysmal atrial fibrillation (PAF), pulmonary vein isolation using cryoballoon (CB-PVI) has similar efficacy as radiofrequency ablation (RF-PVI) has. In redo ablation procedures following RF-PVI, PV reconnection is high, whereas in patients with redo following CB-PVI, information is scarce.

Objective: To determine the sites of PV reconnection in patients who underwent redo ablation after initial CB-PVI.

Methods: Patients who underwent an AF redo procedure, following an initial CB-PVI for PAF were included. LA electroanatomic mapping was used. A reconnection site was defined as the presence of a voltage of 0.3mV or greater in the PV and unidirectional or bidirectional conduction in the PV during sinus rhythm. Reconnections sites were identified using a clock-face view description and were ablated with radiofrequency afterwards.

Results: Out of the 165 patients who underwent initial PVI, 27 required redo ablations, of which 18 (66.6%) were males, with a mean age of 55±12.3 years. The time of recurrence was 8.9±6.4 months. PV reconnection was found in 21 (77.8%) patients. There was a total of 132 conduction gaps, six per patient, 3.6 per PV. A significant number of gaps were in the anterosuperior region of the left superior PV (LSPV), and in the septal and inferior regions of the right superior PV (RSPV).

Conclusions: The upper PVs had the most reconnection sites, mostly at the anterior region of the LSPV and the septal region of the RSPV. The reason behind this may be due to greater atrial wall thickness, and difficulty in achieving adequate cryoballoon contact.

Keywords: Arrhythmias, Cardiac; Atrial Fibrillation, Pulmonary Veins; Radio Waves; Electrocardiography/methods; Electrocardiography, Ambulatory; Tachycardia, Ectopic Atrial; Holter.

Introduction

Pulmonary vein isolation (PVI) is the cornerstone of ablative therapy in paroxysmal and persistent atrial fibrillation (AF). The most common techniques to achieve PVI are cryoballoon ablation and point-by-point radiofrequency ablation, both of which have shown similar results.^{1,2} AF recurrence following the initial PVI procedure is assumed to be mediated with pulmonary vein (PV) reconnection; since 80% of patients who undergo redo ablation show PV conduction recovery in at least one site.³⁻⁵ A study to determine the presence of PV reconnections in patients who underwent redo ablation after initial CB-PVI was conducted. In addition, the sites that were most likely to have PV conduction recovery were described.

Methods

Symptomatic patients with AF who experienced recurrence after an initial cryoablation PVI, and who underwent a redo procedure, were included. Patients who received initial cryoablation therapy were those with drug-resistant AF with preserved left ventricular ejection fraction (LVEF), a left atrial anteroposterior (AP) diameter of 55 mm or less, and no evidence of left atrial (LA) appendage thrombi in a transesophageal echocardiogram.

The procedure was performed under conscious sedation, and the femoral veins were used as venous access. A decapolar catheter (Webster® Decapolar Catheter Deflectable) was positioned in the coronary sinus and an ICE-guided atrial transseptal puncture was performed using an 8F sheath (Preface Braided Guiding Sheath) and a Brockenbrough needle (BRK Transseptal Needles). A 12F steerable sheath (FlexCath®sheath Medtronic, Minneapolis, MN, USA) and a circular mapping catheter (Achieve Medtronic) were then inserted in the LA. A 28-mm cryoablation balloon catheter (Arctic Front, Cryocath™, Medtronic, CA, USA or Arctic Front Advance, Minneapolis, MN) was used to deliver cryoablation therapy at the antrum of each pulmonary vein. Cryoablation therapy was delivered for 180 to 300 seconds until a

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minimum temperature of -40°C was reached and PVI was ensured. Therapy was considered successful if PV entrance and exit block were both achieved. During right PV isolation, the quadripolar catheter was positioned in the superior vena cava to continuous phrenic nerve stimulation at 1,800 ms cycle length and 20 mA output to avoid hemidiaphragm paralysis.

During follow-up, an electrocardiogram and 24-hour Holter monitor (or pacemaker monitoring) were prescribed three months after the procedure and six months thereafter. Antiarrhythmic medication was suspended after the first three months if no AF or atrial tachyarrhythmias were identified. A recurrence was defined as the presence of AF or another atrial tachycardia, in an electrocardiogram strip, or during at least 30 seconds in a Holter monitor after the first follow-up visit.

Redo procedure was performed under conscious sedation, using femoral vein access, and only one atrial transeptal puncture. Anticoagulant was not suspended to perform the ablation procedure. Carto 3® System (Biosense Webster, Diamond Bar, CA, USA) and a multipolar catheter (Pentaray Nav, Biosense Webster) were used to construct voltage maps of the LA and of each PV, using $<0.3\text{mV}$ as a cutoff value for scar tissue and $>1.0\text{mV}$ for normal tissue. PV isolation was defined as absence of electrical activity inside the PV during sinus rhythm or AF, and/or the presence of entrance and exit block if the patient was in sinus rhythm.

Sites with conduction gaps were identified using a clock-face view description, as such 12 different places were considered. Once the sites of PV reconnection were located, they were ablated with radiofrequency using an irrigated contact-force sensor catheter (ThermoCool SmartTouch, Biosense Webster). In addition, fragmented electrograms were actively searched and tagged, especially in the posterior wall and roof of the LA. If the patient was in sinus rhythm, atrial pacing at a CL of 170ms was used to induce AF in order to search for fragmented electrograms, which were subsequently ablated. Ablation of the anterior wall and ridge was done at 40 W, whereas 25W was used for the posterior wall with a temperature limit of 45°C . We used an infusion rate of 17 to 30 mL/min of normal saline, and a pressure force of 6-30g.

If the patient was in AF, ablation was considered successful if there was an impedance drop of 8-10 ohms, a decrease in amplitude, or elimination of atrial electrograms. If the patient was in sinus rhythm, ablation success was determined by loss of pacing capture at the ablation site. Lastly, ablation lines were made at the roof and mitral isthmus, and if typical atrial flutter was detected, ablation of the cavotricuspid isthmus was done as well.

Statistical Analysis

This is a descriptive observational study. Data distribution was tested with the Shapiro Wilk normality test. Categorical variables were expressed as total number and percentages, whereas normally distributed variables were expressed as mean and standard deviation. SPSS v.20 was used for data analysis. Statistical significance was considered if $p < 0.05$.

Results

Study population

From 2014 to 2018, 164 patients underwent PVI using the cryoablation balloon technique, of which 27 experienced AF recurrence and had to undergo redo procedure, after a follow up of 10.7 ± 7.2 months. Of these patients, 18 (66.6%) were men with a mean age of 55 ± 12.3 years, a mean CHA2DS2-VASc score of 1.9 ± 1.6 , and mean LVEF of $60.8 \pm 17.2\%$. Other patients' characteristics can be seen in Table 1. Informed and written consent was required prior to the redo AF ablation procedure.

Redo procedure and PV reconnection

The characteristics of redo procedures are described in Table 2. The time to AF recurrence was 8.8 ± 8.2 months. Of the 27 patients studied, AF recurrence was detected in 17 (62.9%), with Holter monitoring, seven (25.9%) with EKG, and three (11.1%) with pacemaker monitoring. Besides that, 18 (66.6%) were in sinus rhythm; the others were in AF. A reconnection site was defined as the presence of a voltage of 0.3mV or greater in the PV, and unidirectional or bidirectional conduction in the PV during sinus rhythm.

Three vein accesses were obtained in femoral veins. In all cases, only one transeptal puncture guided by intracardiac ultrasound was performed; first, the Pentaray catheter was introduced to perform a voltage and conduction map of the LA and PV. 109 PV were identified among the 27 patients who underwent redo ablation, of which 36 (33.0%) had at least one reconnection site. 22 patients (81.5%) had at least one PV with a conduction gap, with a mean of 1.6 ± 0.4 PV per patient. Nine patients had a reconnection site in one PV (40.9%), 11 patients (50%) in two different PV, one patient (4.5%) in three PV, and one patient (4.5%) in all four PV.

Location of PV conduction gaps

A total of 132 PV conduction gaps were observed, with a mean of 6.0 ± 0.5 conduction gaps per patient and 3.6 ± 0.3 gaps per PV; these reconnections were located at the following sites: 56 (42.4%) at the left superior PV, 35 (26.5%) at the right superior PV, 29 (21.9%) at the right inferior PV, and 12 (9.1%) at the left inferior PV (Figure 1). The site with the most reconnections was the junction between the LSPV and the left atrial appendage (endocardial ridge) followed by the posteroinferior region of the LSPV (71%); and, lastly, the posterior region of LSPV (29%). The LIPV had the least connection gaps, which were evenly distributed around the vein. The RSPV had the most reconnections out of the right pulmonary veins, mostly at the anterior-superior and inferior regions (94% of the total). RIPV gaps were evenly distributed around the vein, slightly favoring the inferior regions.

Fragmented electrogram locations and other arrhythmias

Fragmented atrial electrograms were identified in eight (29.6%) patients, mostly in the posterior wall. Typical atrial flutter was found in nine (33.3%) patients and underwent cavotricuspid-isthmus ablation until bidirectional block was achieved.

Original Article

Table 1 – Patients' characteristics

Men	18 (66.6)
Age (years)	55±12.3
Hypertension	15 (55.5)
Diabetes mellitus	8 (29.6)
Heart failure	1 (3.7)
History of infarction	1 (3.7)
History of stroke (%)	3 (11.1)
Pacemaker carrier(%)	3 (11.1)
Duration of AF (months)	13.2±13.5
CHA2DS-VASC	1.9±1.6
Number of antiarrhythmic drugs tested	1.2±0.6
LVEF	60.8±17.2
LA diameter (mm)	40.2±8.0
Time before recurrence (months)	8.9±6.4

Data are expressed in numbers (%) or mean ± standard deviation.
AF: atrial fibrillation; LA: Left atrium; LVEF: left ventricle ejection fraction. Data analysis was performed with SPSS v.20.

Table 2 – Characteristics of redo procedure

Patients with PV reconnection	21 (77.8)
Time before recurrence (months)	10.56.5
Number of veins per patient	1.6±0.4
Number of gaps per patient	6.0±0.5
Number of gaps per PV	3.6±0.3
Left superior pulmonary vein gaps	56 (42.4)
Left inferior pulmonary vein gaps	12 (9.1)
Right superior pulmonary vein gaps	35 (26.5)
Right inferior pulmonary vein gaps	29 (21.9)
Additional ablation performed	
Complex fractionated atrial electrograms	4 (14.8)
Cavotricuspid isthmus isolation	3 (11.1)
Total procedure time (minutes)	130±17
Fluoroscopy time (min)	8.5±1.7

Data are expressed in numbers (%) or mean ± standard deviation.
Data analysis was performed with SPSS v.20. VP: pulmonary vein.

The mean duration of the RF redo ablation procedures was 130±17 minutes, with a mean fluoroscopy time of 8.5±1.7 minutes. There were two procedure-related complications, an inguinal hematoma which underwent conservative treatment, and a pericardial effusion, which was promptly resolved following pericardial puncture.

Discussion

Point-by-point radiofrequency pulmonary vein isolation has shown to be an effective treatment for paroxysmal

AF, and as such is currently recommended in AF clinical guidelines.⁶ The cornerstone of paroxysmal AF ablation therapy is PVI, which has traditionally been performed with radiofrequency.⁷⁻⁹ Most recently, cryoablation therapy emerged as a viable alternative, with similar results.^{1,2} In the Fire and Ice Study; both approaches were equally effective, especially when comparing second-generation cryoballoon with contact-force catheter.¹⁰

In patients who undergo a redo procedure after an initial PVI, PV connection gaps can be found in more than 95% of the time. The left pulmonary veins seem to have the most reconnections, especially at the anterior and inferior areas.^{4,11,12} Katering et al.,¹³ published a case series of AF redo procedures which documented an average of 2.9 PV reconnections in comparison to our findings, 1.6. Recently, another study published showed a recurrence time after PVI with cryoablation and radiofrequency of 7.4±8.8 months and 9.8±14.5 months, respectively, which was similar to our findings, 8.9±6.4 months. In the cryoablation group of such study, 80.6% had at least one PV with conduction gaps, with an average of 2.9 gaps per PV, which were equally distributed among the four PV. In our study, 81.5% of patients had at least one PV conduction gap, with a mean of 6.0 gaps per patient and 3.6 gaps per PV. The vein with most conduction gaps was the LSPV, followed by the RSPV, the LIPV, and the RIPV. The reason behind our higher gap numbers may be explained by the way we measured them. We identified 12 different regions in the PV, as opposed to the eight used by other authors. In other two studies, PV reconnections were found in 54 and 71% of patients, and anterolateral region of the LSPV (where the endocardial ridge can be found) was the most frequent site of conduction gaps.^{14,15} Overall, the anterosuperior region of the superior veins was the site with the most gaps, in the aforementioned studies and in the present study. However, whereas the RIPV was the inferior PV with the most reconnections, our results showed the inferoanterior region as the main source of reconnections, which differs from the findings of Katering et al.,¹³ which saw a more homogenous distribution. Lastly, fractionated electrograms in the LA were found in 29.6% of patients, a much higher incidence than that reported by Galand et al.⁵

We believe that in places in which there are more reconnections, the cryoballoon does not have adequate contact and, therefore, cryotherapy does not reach a deeper ablation. This phenomenon occurs because PV antrum shape is not always circular, are oval in many, and the dimensions of each vein also varies, therefore the support of the cryoballoon is not homogeneous.¹⁴ In addition, an adequate cryoablation lesion must have sufficient depth. As such, sites of the PV antrum with a thicker wall, like junction of the LSPV and the ostium of the LA appendage (endocardial ridge) are prone to have non-transmural lesions. Kowalski et al. confirmed this assumption by showing in dissected human hearts, that PV conduction gaps occurred when the radiofrequency lesion was not transmural.¹⁶ Finally, an adequate technique is important to achieve pulmonary vein occlusion prior to delivering the cryoablation therapy. Several different strategies have been described. However, there will always be cases when complete isolation is impossible.¹⁷

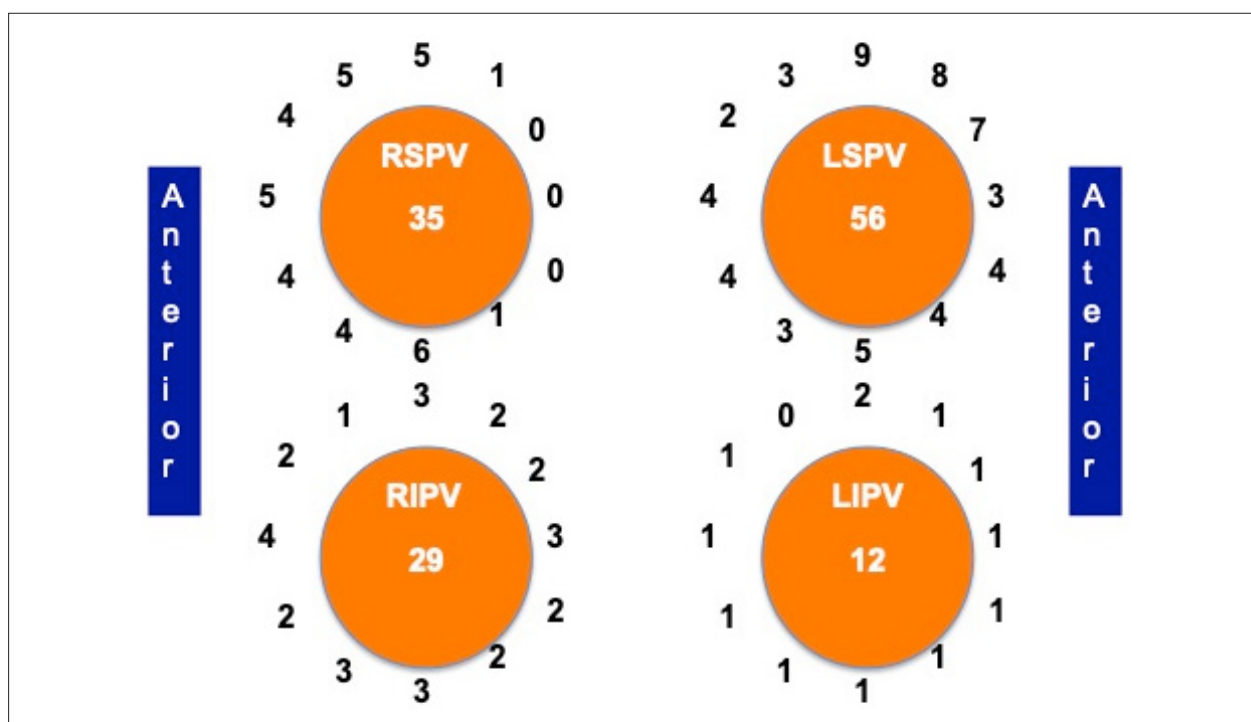


Figure 1 – Distribution of the reconnection gaps in the four PV (the number on the core of each circle). The LSPV is the most reconnected, 71% of the gaps are in the anterosuperior and anteroinferior regions. The RSPV had more reconnections in the anterosuperior and septal regions. LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

One limitation of the present study relies on its descriptive nature. A longitudinal prospective design would provide further clinically relevant results.

Conclusion

The incidence of PV conduction gaps in our study was similar to the findings of other studies. The superior pulmonary veins have the most conduction gaps and are in the anterosuperior region at the LA appendage and LSPV junction, and towards the part of the septum in the RSPV. Lack of adequate balloon contact due to anatomical variations in PV, inadequate technique and sites with thick wall in the PV antrum underlie reconnections after initial cryoballoon AF ablation procedure. Finally, in patients with AF recurrence following the initial CB-IVP, roughly 30% have triggers, which are in the body of the LA, mainly in the posterior wall.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Nolasco RR; Acquisition

of data: Bazzini-Carranza DE, Zavaleta E; Writing of the manuscript: Nolasco RR, Leon-Larios GD; Critical revision of the manuscript for intellectual content: Leon-Larios GD, Calixto-Vargas O.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, et al, for the FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;374(23):2235–45.
2. Buiatti A, von Olshausen G, Barthel P, Schneider S, Luik A, Kaess B, et al. Cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: an updated metaanalysis of randomized and observational studies. *Europace* 2017; 19(3):378–84.
3. Rajappan K, Kistler PM, Earley MJ, Thomas G, Izquierdo M, Sporton SC, et al. Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: a prospective characterization of anatomical sites. *Pacing Clin Electrophysiol*. 2008; 31(12):1598–605.
4. Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation*. 2005 Jan 18;111(2):127–35.
5. Galand V, Pavin D, Behar N, Auffret V, Fénéon D, Behaghel A et al. Localization of gaps during redo ablations of paroxysmal atrial fibrillation: Preferential patterns depending on the choice of cryoballoon ablation or radiofrequency ablation for the initial procedure. *Arch Cardiovasc Dis*. 2016;109(11):591–8.
6. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2017; 00: 1–160.
7. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation* 2000; 102(21):2619–2628.
8. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010;122(23):2368–2377.
9. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011;57(2):160–166.
10. Kuck K, Brugada J, Schluter M, Braegelmann KM, Kueffer FJ, Chun J, et al. The FIRE AND ICE Trial: What We Know, What We Can Still Learn, and What We Need to Address in the Future. *J Am Heart Assoc*. 2018;7:e010777.
11. Mainigi SK, Sauer WH, Cooper JM, Dixit S, Gerstenfeld EP, Callans DJ, et al. Incidence and predictors of very late recurrence of atrial fibrillation after ablation. *J Cardiovasc Electrophysiol* .2007;18(1):69–74.
12. Van der zee SA, D’avila A. Redo Procedures in Patients with Paroxysmal Atrial Fibrillation. *J Innov Cardiac Rhythm Manag*. 2010;1:44–52.
13. Kettering K, Gramley F. Radiofrequency catheter ablation for redo procedures after pulmonary vein isolation with the cryoballoon technique. Long-term outcome. *Herzschr Elektrophys* .2017;28(2):225–31.
14. Godin B, Savoure A, Gardey K, Anselme F. Lessons from radiofrequency redo procedure after cryoballoon pulmonary vein isolation for paroxysmal atrial fibrillation. *Circ J*.2013;77:2009–13. Doi:10.1253/circj-cj-13-0046.
15. Furnkranz A, Chun KR, Nuyens D, Metzner A, Koter I, Schmidt B, et al. Characterization of conduction recovery after pulmonary vein isolation using the “single big cryoballoon” technique. *Heart Rhythm* 2010;7(2):184–90.
16. Kowalski M, Grimes MM, Perez FJ, Kenigsberg DN, Koneru J, Kasirajan V, et al. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. *J Am Coll Cardiol*. 2012; 59(10):930–8.
17. Chun KR, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I, et al. The ‘single big cryoballoon’ technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. *Eur Heart J* 2009;30(6):699–709.



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Reconnection of Pulmonary Veins After Ablation. A Challenge to be Overcome

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Short Editorial related to the article: Reconnection Sites in Redo Ablation after Cryoballoon Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia in the population and its incidence significantly increases with age.¹ As life expectancy rises, it is estimated that AF prevalence will suffer a significant increase, and its adequate control will continue to be a major challenge.

Until the end of the 90s, the therapeutic options available and most used in the reversion and prevention of AF recurrences were antiarrhythmic drugs (AA) and electrical cardioversion; however, clinical treatment with AA drugs has been shown ineffective in maintaining sinus rhythm, with a recurrence rate above 50%.

The understanding of the mechanisms involved in the genesis of AF through atrial mapping technology, as well as the low effectiveness of AA drugs and the high prevalence of AF, have stimulated research in the search for new therapeutic options to control this arrhythmia.

The discovery that ectopic foci located inside the pulmonary veins (PV) could trigger and perpetuate AF, ushered a new era in the treatment of this arrhythmia.

Due to the various studies demonstrating the efficacy and safety of the ablation procedure in recent years, non-pharmacological treatment is being indicated earlier and more frequently.

Regardless of the type of energy or the technique used, complete isolation of the PV is recognized as a fundamental basis for the non-pharmacological treatment of AF and, therefore, has been recommended as an initial step in the ablation of AF in national and international guidelines.¹⁻³ Initially, this technique was indicated only in paroxysmal AF, until subsequent studies demonstrated its non-inferiority in relation to other more complex and comprehensive procedures, in patients with persistent AF.⁴

Currently, PV can be isolated using radiofrequency energy with focal point-to-point applications, or through freezing, using the cryoprobe.

Although widely used in Europe and North America, it was only this year that cryoablation technology was regulated by the ANS - the national health agency - for use in Brazil.

The “Fire and Ice” Study was the first large randomized multicenter study comparing the results of the use of cryoballoon and radiofrequency energy in the ablation of paroxysmal AF and it demonstrated that the technologies were similar, both in terms of effectiveness and safety. In a secondary analysis of this study, the cryo balloon showed a lower rate of rehospitalization and re-intervention.⁵ Subsequently, other trials compared the technologies and demonstrated similar results.

Recently, two studies using cryoenergy have demonstrated the superiority of ablation as the first line of treatment for the control of AF when compared to pharmacological treatment.^{6,7}

We recently published in the Brazilian Archives of Cardiology the first experience of a Brazilian center using the cryoballoon for pulmonary vein isolation (PVI) as an initial approach for the non-pharmacological treatment of AF, and we demonstrated results similar to those obtained in large international centers.⁸

Despite all the technological advances, approximately one-third of the patients present recurrence of atrial arrhythmias after a successful initial procedure. The reconnection of the PV and the occurrence of foci outside the veins are the two main factors that justify the recurrence. Currently, the rates of acute PVI are quite high, and the major challenge is to maintain this isolation in the long term.

Previous studies evaluating patients undergoing redo ablation after a successful initial radiofrequency procedure have shown that the reconnection of the PV is the dominant factor for recurrence, since, among patients referred for a second procedure, 80% demonstrated reconnection of some vein.⁹

In the present study, Nolasco et al.¹⁰ reported reconnection of PV in 77.8% of patients referred for a second ablation procedure after PVI with cryoballoon, and observed sites of reconnection in the anterosuperior region of the upper left PV, and in the septal and inferior regions of the right upper PV, and attributed the findings to a greater thickness of the atrial wall, hindering the proper contact of the cryo balloon. These findings differ from the study by Godin et al.,¹¹ who observed 64% of reconnection of the PV in patients with paroxysmal AF referred for the second procedure; and identified a predominance of connection gaps in the lower portion of the lower veins, 80% in the lower-left PV and 67% in the lower right PV - also differing from the results of Kettering et al.¹² which saw that the distribution of the reconnection sites was similar between the veins.

Keywords

Reconnection; Pulmonary Veins; Ablation; Cryoablation; Atrial Fibrillation.

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The knowledge of sites with a greater predisposition for reconnection could serve as a guide for the development of technologies that would help overcome this great challenge, however, the discrepant results in relation to the sites of

reconnection in the different studies do not allow us to define regions that are more prone to reconnection and lead us to believe that difficulty in achieving permanent PVI is due to individual anatomical variations.

References

- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612.
- Magalhães LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyoshi RR, Lorga Filho AM, et al. Executive Summary of the II Brazilian Guidelines for Atrial Fibrillation. *Arq Bras Cardiol*. 2016;107(6):501-508. doi: 10.5935/abc.20160190.
- Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JC, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10):e275-e444. doi: 10.1016/j.hrthm.2017.05.012.
- Fink T, Schlüter M, Heeger CH, Lemes C, Maurer T, Reissmann B, et al. Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation With Additional Substrate Modification as Index Ablation Procedures in Patients With Persistent and Long-Standing Persistent Atrial Fibrillation: The Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). *Circ Arrhythm Electrophysiol*. 2017;10(7):e005114. doi: 10.1161/CIRCEP.117.005114.
- Kuck KH, Brugada J, Fünkrantz A, Metzner A, Ouyang F, Chun KR, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med*. 2016;374(23):2235-45. doi: 10.1056/NEJMoa1602014.
- Andrade JC, Champagne J, Deyell MW, Essebag V, Lauck S, Morillo C, et al. A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) - methods and rationale. *Am Heart J*. 2018;206:94-104. doi: 10.1016/j.ahj.2018.05.020.
- Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med*. 2021;384(4):316-324. doi: 10.1056/NEJMoa2029554.
- Boghossian SHC, Barbosa EC, Boghossian E, Rangel L, Benchimol-Barbosa PR, Alcantara ML, et al. Experience in a Brazilian Center with Cryoablation for Electric Isolation of the Pulmonary Veins in Paroxysmal and Persistent Atrial Fibrillation - Preliminary Results in Brazil. *Arq Bras Cardiol*. 2020;115(3):528-535. doi: 10.36660/abc.20200320.
- Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation*. 2005;111(2):127-35. doi: 10.1161/01.CIR.0000151289.73085.36.
- Nolasco RR, Leon-Larios G, Bazzini-Carranza DE, Zavaleta E, Calixto-Vargas O. Reconnection Sites in Redo Ablation after Cryoballoon Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation. *Arq Bras Cardiol*. 2021; 117(1):100-105.
- Godin B, Savoure A, Gardey K, Anselme F. Lessons from radiofrequency redo-procedure after cryoballoon pulmonary vein isolation for paroxysmal atrial fibrillation. *Circ J*. 2013;77(8):2009-13. doi: 10.1253/circj.cj-13-0046.
- Kettering K, Gramley F. Radiofrequency catheter ablation for redo procedures after pulmonary vein isolation with the cryoballoon technique: Long-term outcome. *Herzschrittmacherther Elektrophysiol*. 2017;28(2):225-231. doi: 10.1007/s00399-017-0493-3.



Exercise Training Improves Functions of Endothelial Progenitor Cells in Patients with Metabolic Syndrome

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Abstract

Background: Endothelial progenitor cells (EPCs) play an important role in maintaining endothelial function. Metabolic syndrome (MetS) is associated with EPC dysfunction. Although physical exercise has a beneficial impact on EPC activity, its mechanism is not completely clear yet.

Objective: The purpose of this study is to investigate the effects of physical exercise on the functions of EPCs and the underlying mechanisms in patients with MetS.

Methods: Volunteers with MetS were divided into exercise group (n=15) and control group (n=15). Before and after 8 weeks exercise training, EPCs were isolated from peripheral blood. Colony forming unit (CFU) assay, tube-formation assay, the protein expression of endothelial nitric oxide synthase (eNOS), phosphatidylinositol-3-kinase (PI3-K) and protein kinase B (AKT) were determined. A probability value <0.05 was considered to indicate statistical significance.

Results: After 8 weeks, the number of CFUs was significantly increased in the exercise group compared to the control group (p<0.05). In addition, we observed a significant decrease of homeostasis model assessment for insulin resistance (HOMA-IR), endothelin-1, high-sensitive C-reactive protein, and homocysteine levels in the exercise group. Exercise intervention could also enhance tube-formation capacity of EPCs and increase phosphorylation level of eNOS, PI3-K and AKT.

Conclusion: Physical exercise enhanced the functions of EPCs. The mechanism may be related to exercise, activating the PI3-K/AKT/eNOS pathway.

Keywords: Endothelial Progenitor Cells/citology; Metabolic Syndrome; Exercise; Obesity; Physical Activity; Inflammation; Nitric Oxide; Insulin Resistance; Risk Factors; cardiovascular Diseases.

Introduction

Metabolic syndrome (MetS) comprises a cluster of abnormalities, including central obesity, insulin resistance, dyslipidemia and hypertension.¹ MetS is prevalent in the world. The International Diabetes Federation (IDF) estimates that one-quarter of the world's adult population has MetS.² Patients with MetS have been shown to have an increased risk for cardiovascular disease.³ Although the etiology of MetS related to vascular complications is not fully understood, endothelial dysfunction maybe one of the possible mechanisms.⁴

Endothelial progenitor cells (EPCs), originating in the bone marrow, have the capacity to circulate, proliferate, and differentiate into mature endothelial cells. EPCs contribute to both reendothelialization and neoangiogenesis, thereby

EPCs play a vital role in maintaining endothelial function.⁵ Previous studies demonstrated that metabolic syndrome did not only decrease the levels of circulating EPCs, but also impaired the functions of EPCs.^{6,7} Some studies^{8,9} reported that aerobic exercise training could improve the number of resting circulating EPCs in healthy people or obese adults, and reductions in physical activity reduce the number of circulating EPCs.¹⁰ Although these findings suggest that aerobic exercise may modulate EPC functions, the mechanism is poorly understood.

Nitric oxide (NO) is an important endothelium-dependent relaxant factor¹¹ Its production is commonly associated with expression and activity of endothelial nitric oxide synthase (eNOS). It was reported that MetS decreased expression of eNOS and production of NO.¹² The core of MetS is insulin resistance and hyperinsulinemia. Our previous study demonstrated that hyperinsulinemia impaired tube-formation ability of EPCs by depressing eNOS phosphorylation.¹³ We hypothesized that exercise training may activate the eNOS pathway of EPCs and restore impaired function of EPCs.

The purpose of this study is to investigate the effects of physical exercise on the EPC functions and the underlying mechanisms in patients with MetS.

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Materials and Methods

Study population

Volunteers were recruited from a medical examination center, the first hospital of Qinhuangdao. Inclusion criteria: 1. Aged 30–65. 2. Subjects with MetS. MetS was defined using the criteria¹⁴ of the National Cholesterol Education Program — Adult Treatment Panel-III (at least three criteria based on five components: waist circumference, blood pressure, blood glucose, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C)).³ Subjects had no regular exercise for six months. 4. Subjects had not consumed alcohol for two months prior to this study. Exclusion criteria: 1. Subjects with cardiovascular disease or cerebrovascular disease. 2. Smokers. 3. Patients with cancer. 4. On medications known to affect EPC function, such as statins, probucol, metformin, angiotensin receptor blockers. Recruited volunteers (n=30) were randomly divided into exercise group (n=15) or control group (n=15). Randomization was done with sealed envelopes containing a computer-generated randomization sequence. Sample size was based on *preliminary data*. Our power calculation assumed at least a 70% increase in EPC-CFUs with a standard deviation of 40%. For a required power of 0.9 (90%), using a two-sample t-test for comparisons, a sample size of at least 8 in each group was required. This study was approved by the ethics committee of the Qinhuangdao First Hospital.

Exercise training program

Volunteers from the exercise group performed a training program six days per week for 8 weeks. As an aerobic exercise, they ran on a treadmill for 30 minutes while maintaining 60% of the maximum heart rate. As an **anaerobic exercise**, they completed 30-minute training wet with perspiration including, squats, deadlifts and bench press.⁸ They could start exercise at any time of the day.

Laboratory measurements

Physical and anthropometric variables were measured at baseline and after 8 weeks in both groups. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the umbilicus level using a flexible plastic tape with the participants in the standing position. Blood pressure was measured after participants had rested for 10 minutes (auscultatory method). Venous blood samples were collected from all participants at baseline and at 8 weeks (when the exercise program finished, blood samples were collected 48 hours later). Total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), homocysteine (HCY), glucose, and insulin were measured. IR was evaluated using the Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR) and was calculated as $\text{HOMA-IR} = (\text{mmol/L} \times \mu\text{U/mL}) / 22.5$. Serum concentrations of NO, ET-1, high-sensitivity C-reactive protein (hsCRP) were analyzed using ELISA kits (Zhuocai

Biotech, Shanghai, China), following the manufacturer's instructions for each kit.

Endothelial progenitor cells culture

EPCs were isolated and cultured, following previously described protocols.¹³ Peripheral blood (15 mL) was withdrawn at baseline and after the exercise training program. Mononuclear cells (MNCs) were isolated and cultured on a fibronectin-coated six-well chamber in MCBDF12 medium with supplements (10% FBS, VEGF10 ng/ml, bFGF 10 ng/ml, IGF 10 ng/ml, EGF 10 ng/ml, heparin 10 U/ml, and antibiotics) (Gibco) at 37 °C in a 5% CO₂ incubator. After changing the medium on day 2, the medium was replaced every 3 days.

Colony-forming unit assay

Cobblestone-shaped cells emerged 5 to 7 days after start of the MNC culture.

After 12 days of culture, the colony-forming unit (CFU) was identified by visual inspection with an inverted microscope (Leica). A central cluster surrounded by emerging cells was recognized as a CFU. The CFU assay was performed in all subjects (exercise group, n=15 and control group, n=15).

Tube-formation assay

Tube-formation assay was performed to assess the angiogenic potential of EPCs *in vitro*.¹⁵ EPCs were collected and resuspended in MCBDF12 medium with 2% FBS. These cells were seeded (50,000 cells/well) in a 24-well tissue culture plate, which had been evenly coated with matrigel (BD Labware). Seeded cells were incubated at 37 °C in a 5% CO₂ incubator for 4 hours. Gels were examined using phase-contrast microscopy (Leica), and the Angiogenesis Analyzer ImageJ plugin was used to determine the total tube-like segment length, the total area of the tubular structure and the number of network junctions in 5 randomly selected fields.

Western blot analysis

The total protein of EPCs was extracted with radioimmunoprecipitation assay lysis buffer (Beyotime Biotech, Shanghai, China). Protein concentrations were determined by BCA assay kit (Beyotime Biotech). Equal protein samples (40 µg) were loaded into each well of Pierce Precise Protein gel (Thermo-Fisher, Waltham, MA) and were run in 1 × Tris/HEPES/SDS running buffer at 100 V for 1 h. Proteins were then transferred to polyvinylidene difluoride membranes and blocked with 5% BSA for 2 h at 25 °C. Membranes were then incubated with primary antibodies at 4 °C overnight (1:1000 in 1% BSA/TBS-T) and with secondary antibodies (1:2000 in 1% BSA/TBS-T) at room temperature for 2 h. Membranes were washed two times with TBS-T for 10 min before incubations and once after incubations. The bound complex was detected using the Odyssey Infrared Imaging System (Li-Cor; Lincoln, NE). The images were analyzed using Image Studio Lite version

5.2 (LI-COR) to obtain the integrated intensities. Primary antibodies including anti-phospho-Akt-Ser⁴⁷³ (1:1,000), anti-Akt (1:1,000), anti-phospho-eNOS-Ser¹¹⁷⁷ (1:1,000), anti-eNOS (1:1,000), anti- β -actin (1:5,000), anti-PI3-K (1:1,000), anti-phospho-PI3-K (1:1,000) and horseradish peroxidase-conjugated goat anti-rabbit IgG (1:5,000) were purchased from Cell Signaling Technology (Beverly, MA, USA).

Statistical Analysis

All statistical analyses were performed by SPSS 17 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation. Categorical variables were expressed as numbers. Categorical variables were compared with the Fisher's exact test. The Shapiro-Wilk test was used to test for normality of distribution. Comparisons between continuous variables were made by unpaired t test between different groups. And paired t test was used to analyze the significance of within-group comparisons. A probability value <0.05 was considered to indicate statistical significance.

Results

Physical characteristics of both groups

Baseline and 8-week physical characteristics are presented in Table 1. At baseline, the physical characteristics were not significantly different between the two groups. After 8 weeks of exercise training, waist circumference and BMI were decreased in the exercise group, although they had no statistical difference compared to the control group.

Exercise training decreased insulin resistance and inflammation marker

After 8 weeks, patients from the exercise group had lower levels of insulin and HOMA-IR than those in the control group. This result indicated that exercise training could decrease insulin resistance in patients with MetS. The results also show that inflammation markers, including CRP and ET-1, were decreased in the exercise group. HCY were decreased in the exercise group. However, there were no significant differences in glucose, NO, TG, TC, LDL-c and HDL-c between the two groups. For more details, see Table 2.

Exercise training increased EPC colony formation

Colonies of EPC emerged 5 to 7 days after start of MNC culture. The colony exhibited "cobblestone" morphology and monolayer growth pattern (Figure 1).

As shown in Figure 2, after 8 weeks exercise training, the number of EPC-CFUs was bigger in the exercise group than in the control group ($p < 0.05$).

Exercise training improved tube-formation ability of EPCs

As shown in Figure 3, EPCs formed tubular networks on matrigel. Total length of tubular network, total area of tubular network and number of junctions were measured by image analysis system. After 8 weeks exercise training, EPCs in the

exercise group demonstrated increased network formation, compared with the control group ($p < 0.05$) (see table 3).

Exercise training increased PI3-K/Akt /eNOS phosphorylation

There were no differences of phosphorylated protein expression of PI3-K, AKT and eNOS at baseline. After 8 weeks, as shown in figures 4–6, exercise training increased phosphorylation level of PI3-K, AKT and eNOS in EPCs compared with THE control group ($p < 0.05$).

Discussion

The present study demonstrated that eight weeks of exercise training could improve EPC functions in patients with MetS. The mechanism may be related to exercise activating the PI3-K/AKT/eNOS pathway.

EPCs are involved in neovasculogenesis and maintenance of vascular integrity. An altered status of circulating EPCs represents a marker of endothelial dysfunction.³ In fact, some studies indicated that the number of circulating EPCs is an independent indicator of overall cardiovascular health.^{16,17} Our previous study demonstrated that patients with MetS had significantly decreased levels of circulating EPCs compared with healthy controls.⁶ A study by Jialal et al. found that EPCs from MetS subjects presented significantly impaired clonogenic capacity, decreased colony-forming units, and impaired capacity to incorporate into tubular structures.⁷ Exercise training is an important physiological stimulus to mobilize EPCs in healthy individuals.¹⁸ As we know, EPCs are a heterogeneous group of cells.¹⁹ There are two types of EPCs in circulation: early EPCs and outgrowth endothelial cells (OEC). Early EPCs are spindle-shaped cells and have no colony-forming ability. OECs have colony-forming potential and cobblestone shape. OECs have higher adhesive capacity and tubular forming capacity, and are more important in angiogenesis than early EPCs.⁸ In the current study, we observed a colony of cobblestone-shape cells but not spindle-shape cells. Our findings indicated that exercise training increased CFUs of EPCs in patients with MetS.

The results of this study indicated that exercise training improved the tube-formation ability of EPCs. These findings are consistent with previous studies. Silva et al. reported that exercise training could preserve endothelial function in obese mice.¹¹ Choi et al.⁸ demonstrated that regular exercise increased EPC-CFUs in healthy individuals.⁸ A study by Landers-Ramos et al. showed that 10 days of aerobic exercise training was sufficient to increase CD34⁺/KDR⁺ and KDR⁺ cells number and improve flow-mediated dilation in previously sedentary older adults.²⁰ Although these studies have demonstrated the benefits of exercise training, its mechanism is not elucidated yet. The current study shows that exercise training elevated phosphorylation of eNOS of EPCs. As we know, nitric oxide bioavailability is an important regulator of vascular reactivity and endothelial function. It does not only promote vasorelaxation but also regulates angiogenesis in response to tissue ischemia.¹² Diabetes may impair EPC function by modifying nitric oxide-related mechanisms. Chen et al. found that eNOS phosphorylation and NO production in EPC culture media was reduced when cells were incubated

Table 1 – Participant characteristics

	Grupo exercício (n=15)	Grupo controle (n=15)	Valor de p
Age (years)	50.71±9.68	50.28±11.34	0.819
Gender (male/female)	12/3	11/4	0.664
Height (cm)	170.91±7.18	170.66±7.46	0.918
Baseline weight (Kg)	87.42±11.56	88.22±12.91	0.849
8 weeks	85.41± 10.97	87.51±11.18	0.592
Baseline BMI (kg/m ²)	29.86±2.97	30.04±1.99	0.837
8 weeks	29.32±2.59	29.97±1.91	0.415
Baseline waist circumference (cm)	96.13±9.72	97.27±10.24	0.746
8 weeks	94.46±9.06	96.94±9.69	0.456
Baseline SBP (mmHg)	140.53±5.66	135.66±6.36	0.380
8 weeks	138.56±5.91	134.72±5.54	0.111
Baseline DBP (mmHg)	81.73±8.95	79.22±9.38	0.441
8 weeks	84.86±6.17	82.11± 7.58	0.614

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. p value refers to comparison between exercise group and control group (unpaired t test or Fisher's exact test were used).

Table 2 – Comparison of laboratory parameters between groups

	Exercise group (n=15)	Control group (n=15)	p value
Baseline TC (mmol/L)	4.61±1.45	4.39±1.23	0.618
8 weeks	4.24±1.24	4.25±1.34	0.980
Baseline TG (mmol/L)	2.19±0.71	1.92±0.89	0.352
8 weeks	2.24±0.83	2.05±0.87	0.515
Baseline LDL-C (mmol/L)	2.58±1.02	2.51±0.89	0.623
8 weeks	2.47±0.91	2.61±0.95	0.753
Baseline HDL-C (mmol/L)	1.03±0.21	1.06±0.18	0.623
8 weeks	1.06±0.12	1.05±1.05	0.763
Baseline HCY (μmol/L)	14.84±6.99	15.13±4.68	0.774
8 weeks	11.31±3.07 [#]	14.91±2.96	0.020
Baseline Hs-CRP (mg/L)	3.44 ±2.72	4.98± 3.22	0.338
8 weeks	1.75±0.94 [#]	3.88±2.13	0.047
Baseline glucose (mmol/L)	7.05±1.39	7.14±2.95	0.536
8 weeks	6.51±3.95	6.59±2.02	0.374
Baseline insulin (UI/mL)	7.49±4.45	6.67±3.12	0.746
8 weeks	5.48±2.96 [#]	7.59±3.89	0.039
Baseline HOMA-IR	2.91± 1.91	2.76±0.61	0.645
8 weeks	2.08±1.25 [#]	2.81±0.76	0.037
Baseline NO (μmol/L)	137.41± 94.17	154.82±87.12	0.585
8 weeks	141.92±40.62	167.15±119.89	0.139
Baseline ET-1 (μmol/L)	2.71±1.18	2.61 ±1.28	0.998
8 weeks	1.62±0.66 [#]	2.51±1.17	0.041

HOMA-IR: homeostasis model assessment for insulin resistance; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitive C-reactive protein; HCY: homocysteine; NO: nitric oxide; ET-1: endothelin-1. p value refers to comparison between different groups (unpaired t test). [#]p<0.05 compared with baseline (paired t test).

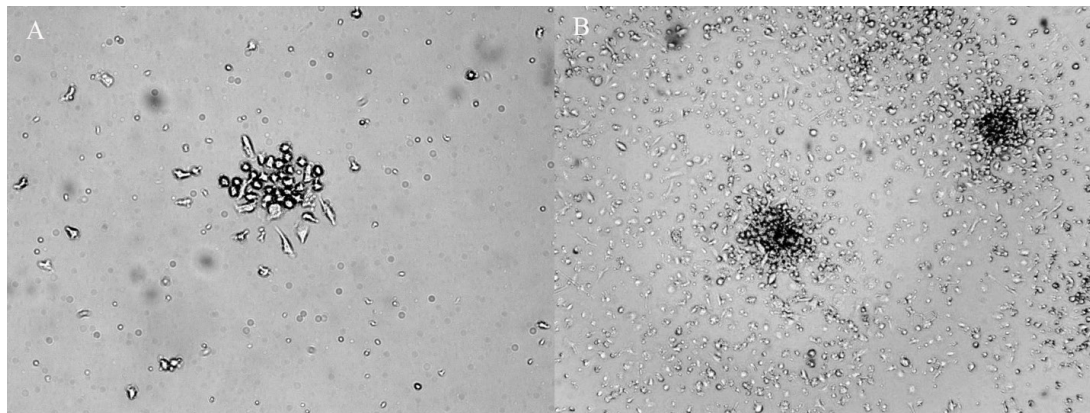


Figure 1 — Figure 1 — Colony of cultured EPCs. A) 6 days after culture, cobblestone-shaped EPCs appeared (100 × magnification). B) 12 days after culture, colony of EPCs (50 × magnification).

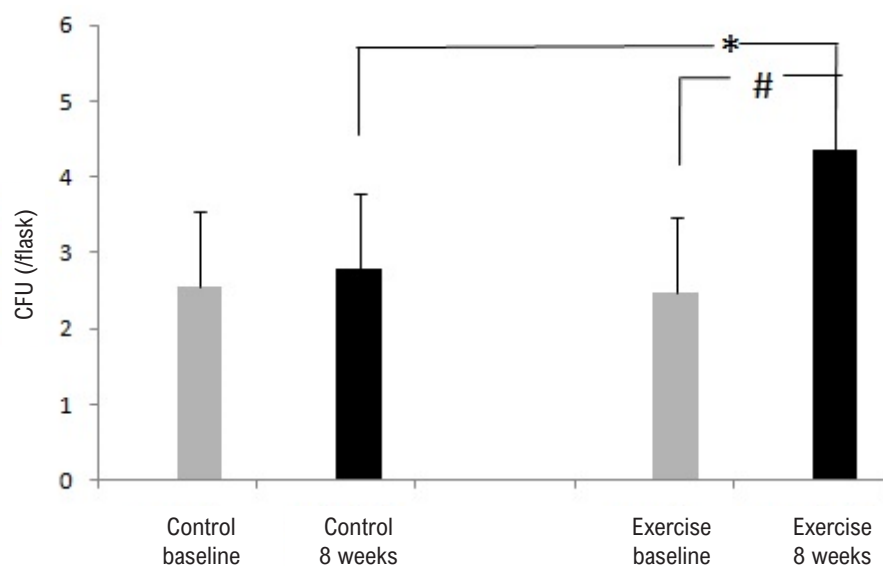


Figure 2 – Exercise training increased EPC-CFU. EPC-CFU was increased in the exercise group after 8 weeks. * $p < 0.05$ comparison between exercise group and control group; # $p < 0.05$ compared with baseline.

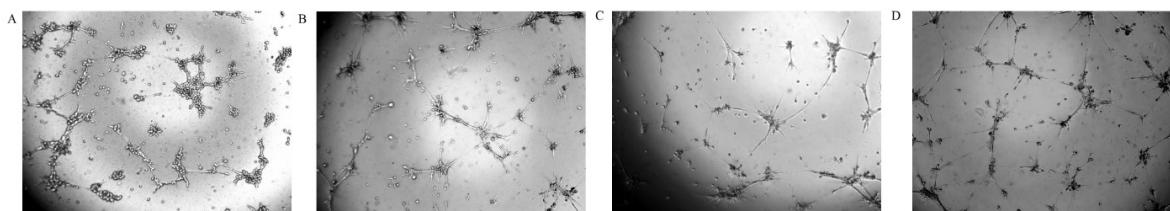


Figure 3 – Exercise training improved tube-formation ability of EPCs. A: control group at baseline; B: control group after 8 weeks; C: exercise group at baseline; D: exercise group after 8 weeks. The figure show that EPCs formed tubular networks on matrigel. After 8 weeks, exercise group EPCs had longer and better tubular networks.

Table 3 – Comparison of tube-formation ability between the exercise group and control group

	Exercise group (n =15)	Control group (n = 15)	p value
Baseline length (μm/field)	2913.20± 662.05	2512.01±829.46	0.154
8 weeks	3982.67 ±832.94 [#]	2713.33±705.57	0.000
Baseline area (μm ² /field)	278.60±93.34	274.86±95.57	0.915
8 weeks	440.66±100.74 [#]	276.01± 72.88	0.000
Baseline junction (/field)	8.93±3.59	9.06±2.84	0.911
8 weeks	12.60±2.74 [#]	8.93±2.08	0.001

p value refers to comparison between exercise group and control group (unpaired *t* test was used). [#]*p*<0.05 compared with baseline (paired *t* test was used).

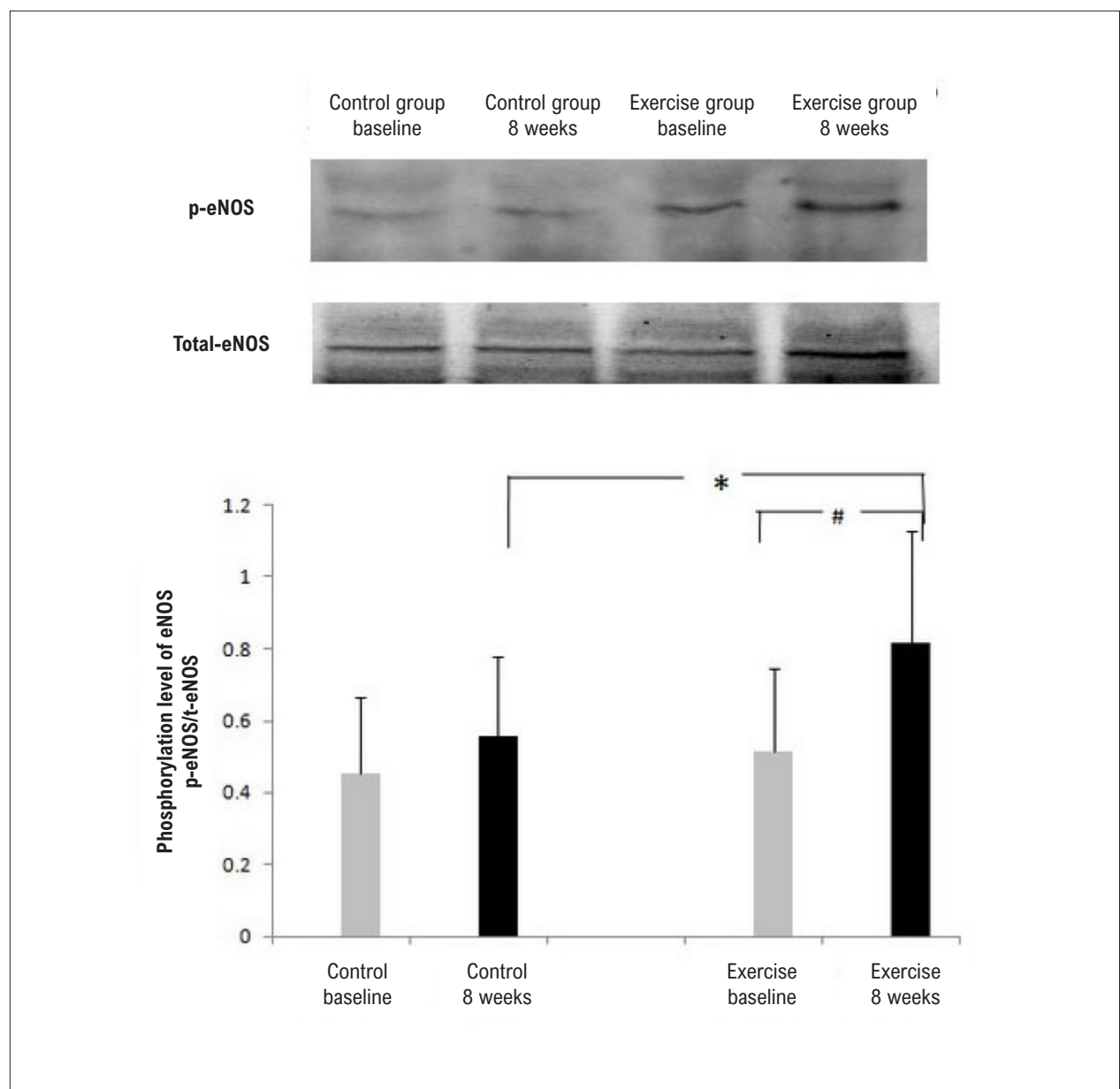


Figure 4 – Western blot of eNOS. Exercise training could increase eNOS phosphorylation level of EPCs. N=4, **p*<0.05 comparison between exercise group and control group; [#]*p*<0.05 compared with baseline.

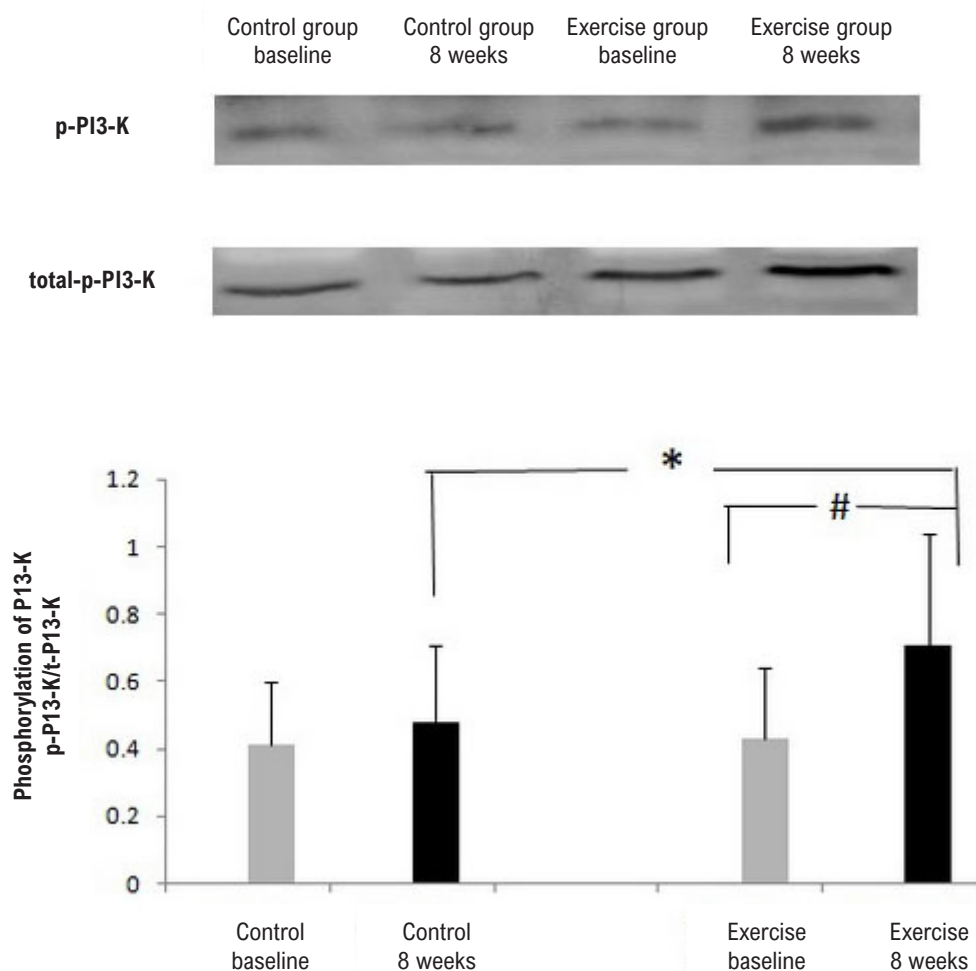


Figure 5 – Western blot da PI3-K. Os níveis de fosforilação de PI3-K aumentaram no grupo exercício após 8 semanas. N=4, * $p < 0,05$ comparação entre o grupo exercício e o grupo de controle; # $p < 0,05$ comparação com os valores basais.

in 25 mmol/L glucose compared with 5 mmol/L glucose.²¹ The PI3-K/Akt /eNOS pathway is a classical pathway to promote NO production and plays a vital role in regulating angiogenesis of EPCs. Our previous study testified that hyperinsulinemia depressed eNOS phosphorylation by depressing the PI3-K/Akt pathway, which was associated with the impaired tube-formation ability of EPCs.¹³ The current study indicated that exercise training could activate PI3-K/Akt /eNOS pathway in patients with MetS. As a result, exercise training restored impaired tube-formation ability of EPCs in patients with MetS.

Endothelial function depends on the delicate balance between vasodilators and vasoconstrictors.²² As a strong vasoconstrictor, high ET-1 plays a key role in the development of endothelial dysfunction. Our results demonstrated that exercise reduced circulating concentrations of ET-1 in MetS. This finding was consistent with a study by Dow et al.²³ Reduction of ET-1 may be an important mechanism underlying

the exercise-induced improvement in endothelium-dependent vasodilator function.

Limitations

Firstly, we did not explore paracrine secretion of EPCs. Although we detected cytokines including NO, CRP, HCY and ET-1 in circulation, we did not detect cytokines in the EPC culture medium. Secondly, we did not measure flow-mediated dilation (FMD) in patients with MetS. FMD is a kind of ubiquitous method to evaluate endothelial function. But we did not measure FMD because FMD has not enough sensibility in MetS. Thirdly, metabolic syndrome may induce EPC apoptosis. But in this study, we did not detect apoptosis of EPCs. Fourthly, exercise training-related mechanisms are very complex. Exercise may influence inflammation and oxidative stress. Results of this study show that exercise

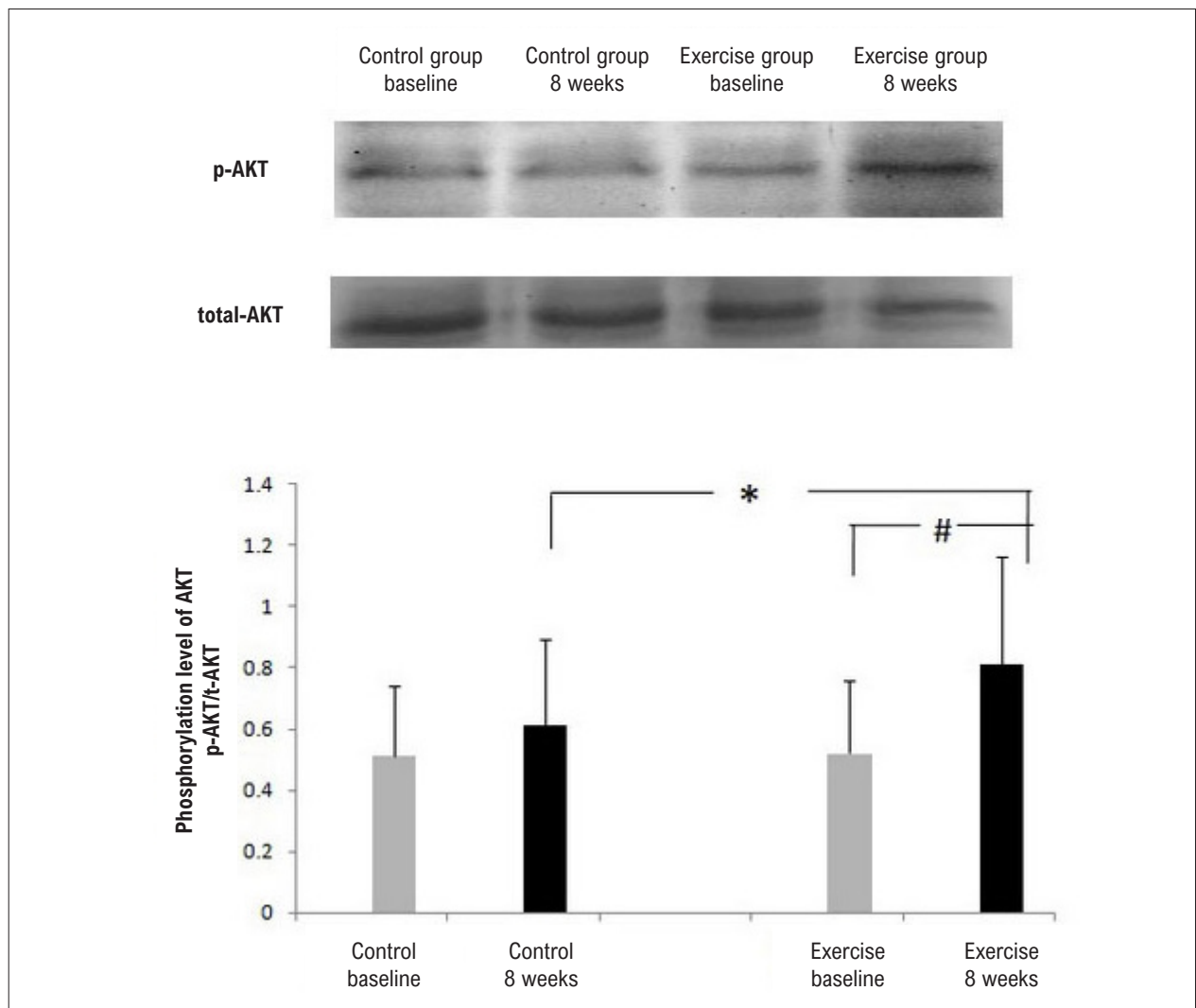


Figure 6 – Western blot of PI3-K. AKT phosphorylation levels were increased in the exercise group after 8 weeks. $N=4$, $*p<0.05$ comparison between exercise group and control group; $\#p<0.05$ compared with baseline.

training decreased circulating levels of CRP and HCY, which indicated that exercise training could depress inflammation and oxidative stress in patients with MetS. But we still did not know the correlation of inflammation and EPC dysfunction.

Conclusions

In conclusion, this study demonstrated that eight weeks of exercise training improved EPC functions in patients with MetS. The mechanism may be related to exercise activating the PI3-K/AKT/eNOS pathway. This study also revealed that exercise depressed inflammation and oxidative stress in patients with MetS. But we did not know the correlation of inflammation and EPC dysfunction.

Author Contributions

Conception and design of the research, Obtaining financing and Writing of the manuscript: Tan Q; Acquisition of data,

Analysis and interpretation of the data and Statistical analysis: Tan Q, Li Y, Guo Y; Critical revision of the manuscript for intellectual content: Li Y.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

References

- Francisqueti FV, Chavierini L C, Santos K C, Minatel I O, Ronchi C B, Ferron A J, et al. The role of oxidative stress on the pathophysiology of metabolic syndrome. *Rev Assoc Med Bras*. 2017; 63(1):85-91.
- Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract*. 2014; 2014:943162.
- Devaraj S and Jialal I I. Dysfunctional Endothelial Progenitor Cells in Metabolic Syndrome. *Experimental diabetic research*. 2012; 2012:585018.
- Hamburg N M, Larson M, Vita J A, Vasan R S, Keyes M J, Widlansky M, et al.
- Metabolic syndrome, insulin resistance, and brachial artery vasodilator function in framingham offspring participants without clinical evidence of cardiovascular disease. *Am J Cardiol*. 2008; 101(1) 82–8.
- Lee P S and Poh K K. Endothelial progenitor cells in cardiovascular diseases. *World J Stem Cells*. 2014; 6(3): 355-66.
- Jialal I, Devaraj S, Singh U, and Huet B A. Decreased Number and Impaired Functionality of Endothelial Progenitor Cells in Subjects with Metabolic Syndrome: Implications for Increased Cardiovascular Risk. *Atherosclerosis*. 2010; 211(1): 297–302.
- Tan Q, Zhang SY, Li Y. Circulating Endothelial Progenitor Cells were Decreased in Patients with Metabolic Syndrome. *Clin Lab*. 2018; 64(10):1679-83.
- Choi J K, Moon K M, Jung S Y, Kim J Y, Choi S H, Kim D Y, et al. Regular Exercise Training Increases the Number of Endothelial Progenitor Cells and Decreases Homocysteine Levels in Healthy Peripheral Blood. *Korean J Physiol Pharmacol*. 2014; 18(2):163-8.
- Huang J, Wang S, Xu F P, Wang D, Yin H, Lai Q, et al. Exercise training with dietary restriction enhances circulating irisin level associated with increasing endothelial progenitor cell number in obese adults: an intervention study. *Peer J*. 2017; 5:e3669.
- Guo Y, Ledesma R A, Peng R, Liu Q, Xu D. The Beneficial Effects of Cardiac Rehabilitation on the Function and Levels of Endothelial Progenitor Cells. *Heart, Lung and Circulation*. 2017; 26(1):10–7.
- Silva J F, Correa I C, Diniz T F, Lima P M, Santos R L, Cortes S F, et al. Obesity, Inflammation, and Exercise Training: Relative Contribution of iNOS and eNOS in the Modulation of Vascular Function in the Mouse Aorta. *Frontiers in physiology*. 2016; 7(7):386. Cubbon R M, Rajwani A, Wheatcroft S B. The impact of insulin resistance on endothelial function, progenitor cells and repair. *Diabetes Vasc Dis Res* 2007; 4(2):103–11.
- Tan Q, Li Y, Li X, Zhang SY. Hyperinsulinemia impairs functions of circulating endothelial progenitor cells. *Acta Diabetol*. 2019; 56(7):785-95.
- Grundys SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Cardiol Rev*. 2005; 13(6):322-7.
- Sheng Z L, Ju C W, Li B, Chen Z, Pan X, Yan G, et al. TWEAK promotes endothelial progenitor cell vasculogenesis to alleviate acute myocardial infarction via the Fn14-NF- κ B signaling pathway. *Experimental and therapeutic medicine*. 2018; 16(5): 4019-29.
- Schmidt-Lucke C, Rossig L, Fichtlscherer S, Vasa M, Britten M, Kämper U, et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation*. 2005; 111(22):2981-7.
- Werner N, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, et al. Circulating endothelial progenitor cells and cardiovascular outcomes. *N Engl J Med*. 2005; 353(10):999–1007.
- Sandri M, Adams V, Gielen S, Linke A, Lenk K, Kränkel N, et al. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation*. 2005; 111(25):3391–9.
- Tan Q, Qiu L G, Li G P, Li C, Zheng C, Meng H. Transplantation of healthy but not diabetic outgrowth endothelial cells could rescue ischemic myocardium in diabetic rabbits. *Scand J Clin Lab Invest*. 2010; 70(5):313-21.
- Landers-Ramos R Q, Corrigan K J, Guth L M, Altom C N, Spangenburg E E, Prior S J, et al. Short-term exercise training improves flow-mediated dilation and circulating angiogenic cell number in older sedentary adults. *Appl Physiol Nutr Metab*. 2016; 41(8): 832–41.
- Chen Y H, Lin S J, Lin F Y, Wu T C, Tsao C R, Huang P, et al. High glucose impairs early and late endothelial progenitor cells by modifying nitric oxide-related but not oxidative stress-mediated mechanisms. *Diabetes*. 2007; 56(6):159-68.
- Mahmoud A M, Szczurek M R, Blackburn B K, Mey J T, Chen Z L, Robinson A T, et al. Hyperinsulinemia augments endothelin-1 protein expression and impairs vasodilation of human skeletal muscle arterioles. *Physiol Rep*. 2016; 4(16): e12895.
- Dow C A, Stauffer B L, Brunjes D L, Greiner J J, DeSouza C. Regular Aerobic Exercise Reduces endothelin-1-mediated Vasoconstrictor Tone in Overweight and Obese Adults. *Exp Physiol*. 2017; 102(9):1133-42.



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Endothelial Progenitor Cells and Exercise: Working Together to Target Endothelial Dysfunction in Metabolic Syndrome

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Short Editorial related to the article: Exercise Training Improves Functions of Endothelial Progenitor Cells in Patients with Metabolic Syndrome

Our understanding of the crucial role played by the endothelium in cardiovascular biology has evolved over the past couple of decades, with the recognition that it is a dynamically-regulated organ, essential in maintaining vascular homeostasis. A healthy endothelium is able to adequately respond to physical and chemical signals and, through the release of a wide range of mediators, regulate, among others, vascular tone and growth, cellular adhesion, thrombogenicity, and inflammation.¹

Furthermore, it has been acknowledged that when the endothelium loses its physiological properties due to an imbalance between its injury and its appropriate recovery, a tendency towards vasoconstriction, pro-thrombotic, and pro-inflammatory states are shown. This condition, termed endothelial dysfunction, has been shown to precede the development of pro-atherosclerotic changes, leading to atherosclerotic plaque formation and its later clinical complications.²

Endothelial progenitor cells (EPCs) are a subtype of bone marrow-derived cells that express both endothelial and progenitor markers and that are mobilized or released into systemic circulation in response to specific stimuli, contributing to vessel formation and endothelial repair.³ A growing body of evidence has shown an inverse correlation between the functional activity of EPCs and cardiovascular (CV) risk factors, and, therefore, not only EPCs have been considered an independent indicator of overall CV health, but also a potential target for therapeutics in high CV risk conditions.⁴

Metabolic syndrome (MS), an important precursor of CV disease, has been implied as a major contributor to a weak functionality of EPCs.⁵ Insulin resistance, hyperglycemia, obesity, dyslipidemia and hypertension act through a

number of different pathways that ultimately impairs EPCs' mobilization, proliferation, and survival.⁶

Conversely, physical exercise has been consistently shown to improve EPC function, contributing to the promotion and maintenance of a healthy endothelium, and to a reduction in CV events.^{7,8} Therefore, current guidelines on CV prevention have acknowledged and underscored the engagement in regular physical exercise as a key management strategy for MS.⁹ However, although there is a growing interest in exploring the exercise-induced benefits on EPCs in this high risk population, its molecular mechanisms are far from being fully understood.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Tan et al.¹⁰ compared the functionality of EPCs in 30 physically inactive individuals with MS who were randomly assigned to an exercise group (n=15) or to a control group (n=15). After eight weeks of participation in regular exercise sessions that included both moderate-intensity aerobic and non-aerobic exercises, individuals from the exercise group showed enhanced EPC function expressed by an increased capacity to generate endothelial cell-colony forming units and enhanced tube formation. Moreover, the authors were able to identify a higher activation of the PI3K-Akt-eNOS signaling axis in the exercise group, which might contribute, at least in part, to the maintenance of cardiovascular homeostasis and vessel integrity.¹¹

It is important to note that, even though there is a limited number of studies comparing clinical outcomes according to different exercise interventions in the setting of MS, moderate vs. high-intensity training and aerobic vs. resistance exercise, either performed in combination or alone, seem to have different benefits on the MS components.¹² As such, it is reasonable to speculate that the positive findings in EPC function reported by Tan et al.¹⁰ might not be generalizable to other exercise training programs.

Therefore, the study of Tan et al.¹⁰ provides novel evidence that support the concept that physical exercise exerts a beneficial effect on endothelial repair capacity of EPCs in MS. Yet, future studies are needed to evaluate if different modalities of physical exercise have different effects on EPCs in order to allow efficient exercise prescription for individuals with this highly prevalent and complex cluster of metabolic disturbances.

Keywords

Physical Activity; Endothelial Function; Nitric Oxide; Cardiovascular Disease; Metabolic Syndrome.

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References

1. Alexander Y, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, et al. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovasc Res.* 2021;117(1):29-42.
2. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation.* 2005;111(3):363-8.
3. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997;275(5302):964-7.
4. Shantsila E, Watson T, Lip GY. Endothelial progenitor cells in cardiovascular disorders. *J Am Coll Cardiol.* 2007;49(7):741-52.
5. Punthakee Z, Goldenberg R, Katz P, Committee DCCPGE. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can J Diabetes.* 2018;42 Suppl 1:S10-S5.
6. Tran V, De Silva TM, Sobey CG, Lim K, Drummond GR, Vinh A, et al. The Vascular Consequences of Metabolic Syndrome: Rodent Models, Endothelial Dysfunction, and Current Therapies. *Front Pharmacol.* 2020;11:148.
7. Martinez JE, Taipeiro EF, Chies AB. Effects of Continuous and Accumulated Exercise on Endothelial Function in Rat Aorta. *Arq Bras Cardiol.* 2017;108(4):315-22.
8. Cavalcante SL, Lopes S, Bohn L, Cavero-Redondo I, Álvarez-Bueno C, Viamonte S, et al. Effects of exercise on endothelial progenitor cells in patients with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. *Rev Port Cardiol.* 2019;38(11):817-27.
9. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology - 2019. *Arq Bras Cardiol.* 2019;113(4):787-891.
10. Tan Q, Li Y, Yao Guo. Exercise Training Improves Functions of Endothelial Progenitor Cells in Patients with Metabolic Syndrome. *Arq Bras Cardiol.* 2021; 117(1):108-117.
11. Shiojima I, Walsh K. Role of Akt signaling in vascular homeostasis and angiogenesis. *Circ Res.* 2002;90(12):1243-50.
12. Ostman C, Smart NA, Morcos D, Duller A, Ridley W, Jewiss D. The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2017;16(1):110.



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Influence of Geographical Location on Access to Reperfusion Therapies and Mortality of Patients with STEMI in Sergipe: VICTIM Register

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Abstract

Background: The concentration of high-complexity services in Aracaju, Sergipe can impose certain disparity in the quality of care for the patients with ST-segment elevation acute myocardial infarction (STEMI) (STEMI) who receive care from Brazil's Unified Health System (SUS, acronym in Portuguese) and whose symptoms started in other health regions of the state.

Objective: To evaluate disparities in access to reperfusion therapies and 30-day mortality, among patients with STEMI, who were users of SUS, in each of the 7 health regions of Sergipe.

Methods: A total of 844 patients with STEMI in the period from 2014 to 2018, assisted by the only hospital with the capacity to offer primary percutaneous coronary intervention (PPCI) to SUS users in the state of Sergipe, were evaluated. The patients were divided into 7 groups according to the location at the onset of symptoms, following the existing division of health regions in the state. For comparison between groups, a significant difference was considered when $p < 0.05$.

Results: Of the total of 844 patients suffering from STEMI who were transferred to the hospital with PPCI that serves SUS patients, 386 patients (45.8%) underwent primary angioplasty. The mean rate of fibrinolytic use was 2.6%, with no differences between the regions. The mean total time of arrival to the hospital with PPCI was 21 hours and 55 minutes, with a median of 10 hours and 22 minutes (6 hours and 30 minutes to 22 hours and 52 minutes). Total 30-day mortality was 12.8%, but without differences between the regions, even when adjusted for age and sex.

Conclusions: This study reveals that fibrinolytics are underused throughout the state and that there is a significant delay in access to the hospital with PPCI, in all health regions of Sergipe.

Keywords: Cardiovascular Diseases; Myocardial Infarction; Myocardial Reperfusion; Mortality; Epidemiology; Cross-Sectional Studies

Introduction

Cardiovascular diseases (CVDs) represent the main cause of death in Brazil and worldwide. Within this group, ST-segment elevation acute myocardial infarction (STEMI) is responsible for the highest mortality

in the ischemic heart disease class, due to its severity in clinical prognosis.¹

In this context, early access and immediate coronary reperfusion is the main objective in the treatment of STEMI, because they reduce adverse outcomes and mortality.^{2,3} Among the reperfusion therapies, primary percutaneous coronary intervention (PPCI) and the use of fibrinolytics are the main therapeutic strategies. However, PPCI is considered the gold standard in treatment, if performed within fewer than 12 hours after the onset of symptoms, and it has been shown to be superior to fibrinolytics in reducing mortality, reinfarction and stroke.⁴

A previous study developed by Oliveira et al.⁵ showed that, in Sergipe, the time from the onset of symptoms to arrival at the hospital with PPCI (24.4 h $\pm$ 36.5 h) is twice as long as

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recommended in patients using Brazil's Unified Health System (SUS, acronym in Portuguese). While the rates of fibrinolytic use are low in both public and private services, they are even lower in SUS patients, and 30-day mortality was also higher in the SUS (11.9%) when compared to patients in the private service (5.9%). These data can be even worse when comparing the health regions of Sergipe.⁵

In addition, based on the SUS organizational principles, the state is divided into 7 health regions; however, despite the division, all the hospitals with a hemodynamics service are located in a single health region. Moreover, to make matters worse, only one of these hospitals is a cardiology reference for SUS users, and it is not open-doors.

In this context, this study aims to assess the possible differences regarding access to reperfusion therapies and mortality in patients with STEMI who are treated exclusively by the SUS, between the different health regions of Sergipe.

Material and methods

This is a cross-sectional study with a quantitative approach, conducted with data obtained between December 2014 and March 2018, using the database of the VICTIM Register (Via Crucis for the Treatment of Myocardial Infarction). This study was approved by the Ethics and Research Committee of the Federal University of Sergipe, under opinion number 483,749. The data were collected at the only hospital in the state where primary PPCI is made available by the SUS. This hospital, in turn, does not have an open-door system, that is, patients must be referred from other health services with confirmed diagnosis of STEMI.

Collection was carried out by the researchers using their own research instrument, the case report form (CRF), composed of sociodemographic variables, clinical conditions at hospitalization, data referring to the time and path traveled from the onset of symptoms to the care provided in a specialized hospital, angiography procedure, and evolution of the patients during hospitalization after the acute myocardial infarction. The information was collected through interviews with patients or companions and data from medical records.

Patients of both sexes, over 18 years old, with onset of symptoms within the territory of Sergipe, and with diagnosis of STEMI confirmed by the electrocardiogram, according to the defining criteria proposed by the V Guidelines of the Brazilian Society of Cardiology⁶ were included, provided that they received care exclusively from the SUS and signed the Free and Informed Consent Form.

The following exclusion criteria were applied: died before the interview; refused to participate in the research; presented onset of symptoms outside the territory of Sergipe; received care in a private network; did not characterize the Via Crucis, that is, those patients who did not travel the path from the onset of the symptoms to the arrival at the hospital with the capacity to perform PPCI because they had already presented STEMI within the hospital; those whose acute STEMI event was characterized as reinfarction (occurring within 28 days of the incident infarction); had a change in diagnosis during hospitalization; and assisted by agreement in a philanthropic hospital.

Once the study inclusion criteria were met, the patients were allocated consecutively. For analysis, patients with STEMI were divided into 7 groups, from the health region where onset of symptoms occurred, namely: 1. Aracaju, 2. Itabaiana, 3. Estância, 4. Lagarto, 5. Nossa Senhora do Socorro (Socorro), 6. Nossa Senhora da Glória (Glória), and 7. Propriá. These health regions were defined according to Deliberation No. 065/2012, of April 18th, 2012, which ratifies the division of the state territory of Sergipe into 7 health regions, determining the municipalities that make up each region (Figure 1). Based on the last census conducted by the Brazilian Institute of Geography and Statistics, the state of Sergipe and its 75 municipalities have an estimated population of just over 2 million inhabitants,⁷ who are divided, in the perspective of the SUS, into these 7 health regions.²

Statistical analysis

The categorical variables were described using absolute and relative frequency. The associations were tested using the chi-square test with Monte-Carlo simulations. The multiple comparisons for the proportions were tested using the Z test with Bonferroni correction. The continuous variables were described as median and interquartile range due to their non-adherence to the normal distribution assessed by the Shapiro-Wilk test. The differences in the measures of central tendency were tested using the Kruskal-Wallis test. The multiple comparisons for the measures of central tendency were tested by the Kruskal-Wallis test with Bonferroni correction. The gross and adjusted odds ratios were estimated for overall 30-day mortality through logistic regression. The significance level adopted was 5%, and the software used was R Core Team 2019.

Results

Sociodemographic Profile

A total of 844 patients were analyzed, 294 (34.8%) of whom were from the Aracaju health region, 102 (12.1%) from the Itabaiana region, 119 (14.1%) from the Estancia region, 122 (14.5%) from the Lagarto region, 119 (14.1%) from the Socorro region, 41 (4.85%) from the Glória region, and 47 (5.6%) from the Propriá region.

The total median age was 61 years old; among the regions, Estância had a significantly higher median age and the Glória region had the lowest. In all regions, there was prevalence of male patients and non-white ethnicity (70%), with a difference between the Socorro region when compared to Lagarto or Glória ($p = 0.02$) (Table 1).

Clinical features

Among the risk factors, diabetes mellitus was the only one that presented significant variability, ranging from 17.1% in Glória to 42.6% in Propriá ($p = 0.026$). The other risk factors showed similar prevalence values between the groups (Table 2).

Regarding the values of systemic blood pressure upon admission to the hospital with PPCI (Table 2), systolic blood

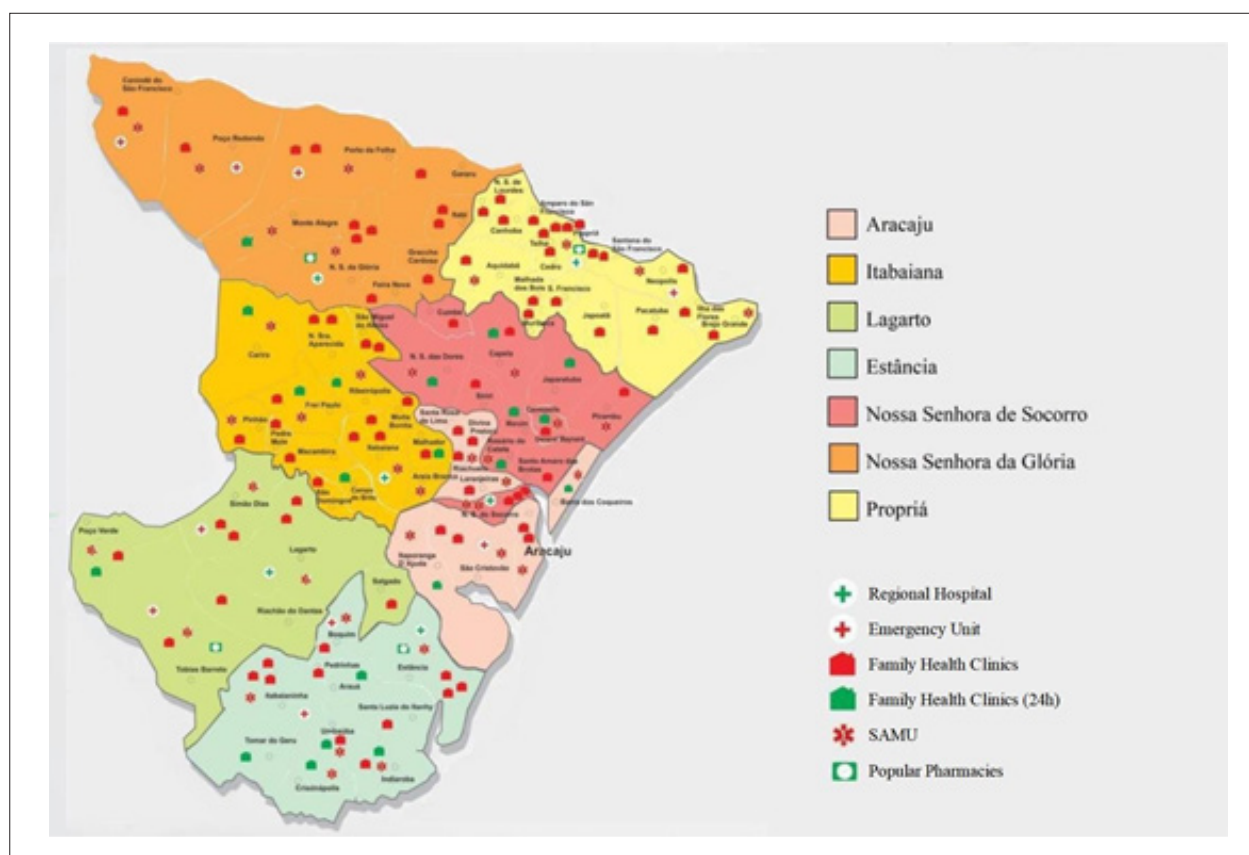


Figure 1 – Map of Sergipe and its health regions. Source: state health secretariat (2016)

pressure had a total median of 140 mmHg, presenting the highest value in the Aracaju region and the lowest in Nossa Senhora da Glória, with differences when compared to each other ($p = 0.016$). Diastolic blood pressure, on the other hand, reached a total median of 83 mmHg, with the highest median in Aracaju, Nossa Senhora do Socorro, and Itabaiana, and the lowest median in Nossa Senhora da Glória, Estância, Lagarto, and Propriá ($p = 0.007$).

The Lagarto region showed the highest rate of patients considered to be at high risk of mortality by the GRACE score (64.4%) (Table 2), while Aracaju had the lowest (41.9%), and it possible to observe a difference when comparing the Aracaju and Nossa Senhora da Glória regions in relation to Lagarto ($p = 0.001$). Of the total number of patients, 85.3% had Killip I, and 62.5% of the STEMI were of the anterior wall; this behavior pattern was repeated across the regions.

Coronary reperfusion

The total primary PPCI rate was 45.8%, with the Aracaju region having the highest (51.9%) and Glória the lowest (17.1%), with a difference when compared to Aracaju or Itabaiana ($p = 0.03$). Of the total, 25.1% of the study patients did not undergo PPCI, and the total rate of fibrinolytic use was 2.6% (Table 3).

The mean time between the onset of symptoms and arrival at the hospital with PPCI was 21 hours and 55 minutes with a median of 10 hours and 22 minutes (6 hours and 30 minutes to 22 hours and 52 minutes), with Glória showing the longest delay, and Aracaju the shortest. A statistical difference was recorded when the Glória and Socorro regions were compared in relation to Aracaju ($p = 0.001$). Of the periods that make up this entire time interval, the time elapsed between arrival at a hospital without PPCI and arrival at a hospital with PPCI was the most impactful, recording a median time of 7 hours and 37 minutes. In this regard, the region with the longest delay was Glória, and the one with the lowest was Aracaju; it was possible to observe differences when comparing the Lagarto and Glória regions with Aracaju (Table 4).

Regarding the number of institutions visited before the hospital with PPCI, the vast majority of the patients (81.2%) went through at least one institution before the hospital with PPCI. Nearly 2.4% of the patients went to at least three institutions before the hospital with PPCI, while only 1.7% had direct access to this hospital (Table 4).

Mortality

When assessing 30-day mortality (Table 5), it was observed that the Estância region had the highest rate (18.6%), and Nossa Senhora da Glória had the lowest (7.5%) ($p = 0.03$).

Table 1 – Sociodemographic characteristics of patients with STEMI by health region*

Demography	All (n=844)	Aracaju (n=294)	Itabaiana (n=102)	Estância (n=119)	Lagarto (n=122)	Socorro (n=119)	Glória (n=41)	Propriá (n=47)	p value
Age - years old*	61 (52-70)	59 (50-68)	63,5 (50.75-71)	66 (55-74)§//	65 (57-73)§//	60 (51-67)	58 (51,5-69,5)	60 (54-67)	<0.001
Sex n (%)									
Male	561 (66.5)	199 (67.7)	77 (75.5)	69 (58.0)	83 (68.0)	72 (60.5)	28 (68.3)	33 (70.2)	0.118
Female	283 (33.5)	95 (32.3)	25 (24.5)	50 (42.0)	39 (32.0)	47 (39.5)	13 (31.7)	14 (29.8)	
Social class† n (%)									
A	3 (0.4)	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.025
B	17 (2.2)	12 (4.3)	1 (1.1)	1 (0.9)	2 (1.8)	0 (0)	1 (2.9)	0 (0)	
C	74 (9.4)	35 (12.5)	9 (9.8)	7 (6.3)	7 (6.2)	11 (9.9)	1 (2.9)	4 (8.9)	
D	240 (30.5)	97 (34.6)	26 (28.3)	30 (27)	26 (23)	39 (35.1)	12 (34.3)	10 (22.2)	
E	453 (57.6)	133 (47.5)	56 (60.9)	73 (65.8)§	78 (69)§	61 (55)	21 (60)	31 (68.9)	
Ethnicity n (%)									
White	248 (30)	85 (29.4)	36 (35.3)	31 (27.7)	45 (36.9)//	21 (18.3)	17 (42.5)//	13 (28.3)	0.020
Non-white	578 (70)	204 (70.6)	66 (64.7)	81 (72.3)	77 (63.1)//	94 (81.7)	23 (57.5)//	33 (71.7)	
Schooling n (%)									
Never studied	225 (26.7)	49 (16.7)	38 (37.3)§	41 (34.5)§	50 (41)§¶	28 (23.5)	12 (29.3)	7 (14.9) ‡	<0.001
Elementary school	457 (54.1)	153 (52)	48 (47.1)	70 (58.8)	61 (50)	67 (56.3)	24 (58.5)	34 (72.3)	
High school	121 (14.3)	69 (23.5)	11 (10.8)	7 (5.9)§	8 (6.6)§	19 (16)	4 (9.8)	3 (6.4)	
Higher education	32 (3.8)	20 (6.8)	3 (2.9)	1 (0.8)	3 (2.5)	3 (2.5)	0 (0)	2 (4.3)	
Graduate degree	9 (1.1)	3 (1)	2 (2)	0 (0)	0 (0)	2 (1.7)	1 (2.4)	1 (2.1)	
Marital Status n (%)									
Single	115 (13.6)	45 (15.3)	10 (9.8)	15 (12.6)	18 (14.8)	18 (15.1)	4 (9.8)	5 (10.6)	0.050
Married	415 (49.2)	139 (47.3)	52 (51)	51 (42.9)	72 (59)	53 (44.5)	23 (56.1)	25 (53.2)	
Lives with a partner	130 (15.4)	42 (14.3)	13 (12.7)	26 (21.8)	15 (12.3)	20 (16.8)	9 (22)	5 (10.6)	
Divorced	73 (8.6)	33 (11.2)	10 (9.8)	4 (3.4)	7 (5.7)	8 (6.7)	4 (9.8)	7 (14.9)	
Widowed	111 (13.2)	35 (11.9)	17 (16.7)	23 (19.3)	10 (8.2)	20 (16.8)	1 (2.4)	5 (10.6)	

* The values are median and interquartile range. Social class (Brazilian Institute of Geography and Statistics) – A: > 20 times minimum wage, B: 10 to 20 times minimum wage, C: 4 to 10 times minimum wage, D: 2 to 4 times minimum wage, E: ≤ 2 times minimum wage. ‡ p < 0.05 when compared to Aracaju. § p < 0.05 when compared to Lagarto. ¶ p < 0.05 when compared to Propriá.

Table 2 – Clinical characteristics of the patients with STEMI by health regions*

Clinical characteristics	All (n=844)	Aracaju (n=294)	Itabaiana (n=102)	Estância (n=119)	Lagarto (n=122)	Socorro (n=119)	Glória (n=41)	Propriá (n=47)	p value
Cardiovascular risk n (%)									
Hypertension	530	176 (59.9)	61 (59.8)	72 (60.5)	76 (62.3)	86 (72.3)	26 (63.4)	33 (70.2)	0.282
Diabetes	275	104 (35.4)	24 (23.5)	46 (38.7)	35 (28.7)	39 (32.8)	7 (17.1)	20 (42.6)	0.026
Dyslipidemia	314	116 (39.5)	33 (32.4)	46 (38.7)	45 (36.9)	39 (32.8)	15 (36.6)	20 (42.6)	0.762
Smoking	282	102 (34.7)	37 (36.3)	32 (26.9)	32 (26.2)	45 (37.8)	20 (48.8)	14 (29.8)	0.078
Number of risk factors n (%)									
0	100	38 (12.9)	14 (13.7)	15 (12.6)	20 (16.4)	6 (5)	3 (7.3)	4 (8.5)	0.255
1	279	90 (30.6)	36 (35.3)	39 (32.8)	44 (36.1)	42 (35.3)	15 (36.6)	13 (27.7)	
2	297	100 (34)	38 (37.3)	40 (33.6)	35 (28.7)	50 (42)	18 (43.9)	16 (34)	
≥ 3	168	66 (22.4)	14 (13.7)	25 (21)	23 (18.9)	21 (17.6)	5 (12.2)	14 (29.8)	
Systemic blood pressure									
Systolic blood pressure	140 (123-160)	145 (130-160.75)	140 (123.7-157.5)	135 (120-160)	140 (120.75-157)	140 (120.75-160)	130 (120-147)¶	140 (120-160)¶	0.016
Diastolic blood pressure	83 (75-96)	87,5 (78-99.25)	87 (76.75-93)	80 (70-99)	80 (71.75-90)	87 (77-98.5)	80(70-87.5)	80 (71-90)	0.007
Killip†									
I	716	245 (83.9)	92 (92)	101 (84.9)	102 (84.3)	104 (87.4)	35 (85.4)	37 (78.7)	0.557
II	92 (11)	35 (12)	7 (7)	14 (11.8)	14 (11.6)	10 (8.4)	5 (12.2)	7 (14.9)	
III	18	7 (2.4)	1 (1)	3 (2.5)	2 (1.7)	1 (0.8)	1 (2.4)	3 (6.4)	
IV	13	5 (1.7)	0 (0)	1 (0.8)	3 (2.5)	4 (3.4)	0 (0)	0 (0)	
GRACE score§									
< 140 (low risk)	392	154 (58.1)#	41 (45.1)	51 (45.1)	42 (35.6)	63 (56.3)#	23 (56.1)	18 (43.9)	0.001
> 140 (high risk)	389	111 (41.9)#	50 (54.9)	62 (54.9)	76 (64.4)	49 (43.8)#	18 (43.9)	23 (56.1)	
Electrocardiogram 									
Previous	527	198 (67.3)	63 (61.8)	71 (59.7)	74 (60.7)	68 (57.6)	22 (53.7)	31 (66)	0.384
Non-previous	316	96 (32.7)	39 (38.2)	48 (40.3)	48 (39.3)	50 (42.4)	19 (46.3)	16 (34)	

* The values are median and interquartile range. † Value of the first record (in millimeters of mercury) documented in the medical record after hospital admission. Upon admission - Class I: absence of rales on the pulmonary fields and absence of a third sound, Class II: rales in more than 50% of the areas of the lung or presence of a third sound, Class III: rales in more than 50% of the lung fields, Class IV: Shock. Ranging from 0 to 263 calculated using the data on age, heart rate, systolic blood pressure, creatinine and Killip recorded at hospital admission. || Previous: on V1-V4 referrals, non-previous: on any of the V1-V4 referrals ¶ p < 0.05 when compared to Aracaju. # p < 0.05 when compared to Lagarto.

Table 3 – Procedures performed on patients with STEMI by health regions*

Procedures†	All (n=844)						p value
	Aracaju (n=294)	Itabaiana (n=102)	Estância (n=119)	Lagarto (n=122)	Socorro (n=119)	Glória (n=41)	
Fibrinolytic n (%)	22 (2.6)	3 (1)	3 (2.9)	5 (4.2)	4 (3.4)	1 (2.4)	0.477
Primary PCI n (%)	386 (45.8)	151 (51.4)†	51 (50)†	55 (46.6)†	51 (42.9)	7 (17.1)	0.003
Non-primary PCI n (%)	275 (32.6)	84 (28.6)	31 (30.4)	44 (37)	43 (36.1)	21 (51.2)	0.092
Did not perform PCI n (%)	212 (25.1)	67 (22.8)	23 (22.5)	29 (24.6)	29 (24.4)	13 (31.7)	0.595
Myocardial revascularization surgery	24 (2.8)	7 (2.4)	5 (4.9)	3 (2.5)	2 (1.7)	3 (7.3)	0.383

† PCI: percutaneous coronary intervention. ‡ p < 0.05 when compared to Glória.

Table 4 – Time and geographical course between onset of symptoms and arrival at the hospital with PPCI by health region*

	All (n=844)						p value
	Aracaju (n=294)	Itabaiana (n=102)	Estância (n=119)	Lagarto (n=122)	Socorro (n=119)	Glória (n=41)	
Timeline *†							
Time A	30' (10'-2h)	30' (10'-2h37')	30' (15'-2h)	30' (15'-2h)	30' (10'-2h)	30' (17'-4h)	1h (10'-2h)
Time B	30' (20'-1h)	30' (15'-48')	30' (20'-1h)	30' (15'-50')	30' (18'-1h)	30' (20'-1h)	30' (20'-1h)
Time C	7h37' (4h51'-18h)	6h30' (3h30'-15h40')	7h30' (4h53'-13h)	8h34' (5h28'-21h25') ‡	8h17' (4h40'-28h15')	12h40' (6h45'-26h56')‡	8h57' (6h35'-14h30')
Time D	10h22' (6h30'-22h52')	9h (5h7'-21h32')	10h (6h9'-15h47')	11h31' (7h3'-25h20')	12h40' (6h30'-32h)‡	16h (8h30'-32h01')‡	12h27' (7h50'-18h08')
No. of units visited							
0	14 (1.7)	9 (3.1)	1 (1)	2 (1.6)	1 (0.8)	0 (0)	0.483
1	685 (81.2)	248 (84.4)	85 (83.3)	100 (82)	93 (78.2)	31 (75.6)	37 (78.7)
2	125 (14.8)	32 (10.9)	14 (13.7)	17 (13.9)	20 (16.8)	9 (22)	9 (19.1)
≥ 3	20 (2.4)	5 (1.7)	2 (2)	3 (2.5)	5 (4.2)	1 (2.4)	1 (2.1)

* The values are median and interquartile range. Time A: from onset of symptoms to decision to call for help, Time B: decision to call for help to the hospital without PPCI, Time C: time to go from the hospital without PPCI to the hospital with PPCI, Time D: onset of symptoms at the hospital with PPCI. p < 0.05 when compared to Aracaju.

Table 5 – Odds ratio for 30-day mortality in patients with STEMI by health regions, adjusted for age and sex

Health regions	Mortality N (%)	Non-adjusted mortality OR (95%CI)	Adjusted mortality OR (95%CI)	p value
Aracaju*	27 (9.4) 27 (9.4)	1	1	
Itabaiana	9 (9.2)	0.98 (0.44-2.16)	0.93 (0.32-2.70)	0.900
Estância	22 (18.6)	2.22 (1.20-4.08)	1.70 (0.74-3.92)	0.214
Lagarto	22 (18.5)	2.19 (1.19-4.03)	2.07 (0.93-4.61)	0.074
Socorro	15 (12.7)	1.41 (0.72-2.75)	2.04 (0.86-4.87)	0.106
Glória	3 (7.5)	0.78 (0.23-4.68)	0.66 (0.13-3.48)	0.625
Propriá	8 (17)	1.98 (0.84-4.68)	1.93 (0.61-6.11)	0.263

*Represents the control group.

When adjusted for age and sex, adopting the Aracaju region as a control group, no statistical differences were observed.

Discussion

Three main findings expressively marked the results of this study. The first points to major delays in the arrival of patients with STEMI at the hospital with PPCI, regardless of the onset of symptoms. The second testifies to disparities in the use of reperfusion therapies between patients in the different health regions. The third shows the regional influence on mortality. These findings demonstrate that there is an urgent need to improve quality of care for patients with STEMI throughout the state of Sergipe.

Despite greater knowledge about the therapeutic goals in the management of STEMI, the reproducibility of these targets is still a difficult task, especially in the field of public health in Brazil.^{8,9} Patients with onset of STEMI in the state of Sergipe have a 30-day mortality rate far from what is considered desirable. A report by the European Society of Cardiology, including several countries, showed in-hospital mortality ranging from 3.1% to 6.1%.¹⁰ A French trial, carried out between 1995 and 2010, found a reduction in 30-day mortality from 13.7% to 4.4%. This decrease is due to multiple factors within care for patients with STEMI, such as the increase in the number of mobile intensive care units, an increase in the number of public information campaigns on the symptoms related to the disease, and lesser delays in both arrival at a qualified hospital and in the decision to seek help.¹¹

Concomitantly, both regions with the worst rates presented the highest mean age groups. Despite the reduction in mortality due to acute coronary syndromes at all ages, it is known that older patients have worse prognosis compared to younger ones, due both to the fact that they have a higher number of comorbidities and to the lesser use of reperfusion and medication therapies.^{3,12,13}

Before arriving at the hospital with the capacity to perform PPCI, some patients had to go through at least one health unit lacking this service until they were transferred to the specialized hospital. These data were also analyzed in this study and the result obtained was that most of the patients went to a hospital before arriving at the hospital with the capacity to perform PPCI, a fact that was already expected,

since the only public hospital with capacity for performing PPCI does not offer open-door service. Some patients who have direct access to the hospital with PPCI were regulated and referred by the Mobile Emergency Care Service.

The period between the onset of symptoms and access to a hemodynamics service plays a decisive role in the patients' prognosis.¹⁴ In Sergipe, in this period the mean time spent was 21 hours and 55 minutes with a median of 10 hours and 22 minutes (6 hours and 30 minutes to 22 hours and 52 minutes), bordering twice the 12-hour window established by the national and international guidelines. Evaluating from a regional perspective, this mean interval reached values of 26 hours and 24 minutes and 26 hours and 10 minutes in the Socorro and Glória regions, respectively, and they were shorter in Estância, with 16 hours and 22 minutes. However, despite this discrepancy, it was only possible to observe statistical differences when comparing Socorro and Glória to Aracaju. It is worth highlighting that the municipality farthest from the capital is nearly 3 hours away.

In the state of Sergipe, the time interval experienced by patients with STEMI from the onset of symptoms to access to a qualified hospital suffers a huge impact from the hospital interim period, constituting approximately 87% of the entire process. From this perspective, these results do not correspond to the geographic reality of Sergipe, which is considered the smallest state in Brazil, where it takes around 4 hours to go from one end of the state to the other by car. In addition to that, the Socorro region, despite its relative proximity to the Aracaju region compared to the others, paradoxically presents the largest of these delays, with 23 hours and 15 minutes.

Several elements can be linked to the prolongation of this interval, ranging from delays in disease diagnosis to inefficiency in the transportation means between the assisting institutions.^{1,15} A piece of data that deserves to be highlighted is the impossibility of referring patients directly to the qualified hospital. In Sergipe, the only hospital capable of offering definitive treatment to SUS patients with STEMI only receives patients through referrals made by another institution, as long as they are already diagnosed.

A study carried out in the state of North Carolina, in the period between 2008 and 2010, evaluated 1,288 patients diagnosed with STEMI, dividing them into two groups, those who were transferred directly to hospitals with PPCI

regardless of the distance and those who were transported to the nearest hospital without PPCI. In this comparison, 46.5% of the patients directly transferred to a center with a hemodynamics service arrived within 90 minutes after the first medical contact, while, in the other group, only 21.5% of the patients arrived at a hemodynamics center within 120 minutes after the first medical contact.¹⁶

Considering the major difficulty of access in the only hospital with the capacity to perform PPCI, less than half of the patients arrive within the 12-hour window from the onset of symptoms; the expressive underuse of fibrinolytics in the state of Sergipe can be considered an indicator of a very deficient care practice contributing to the high mortality observed in our records. The mean rate of fibrinolytic use of 2.6% differs greatly from other national and international records,^{17,18} and, in the scenario of difficult access to the only hospital capable of performing PPCI, it unequivocally exposes the important weakness and inefficiency of STEMI care in our state.⁴ Our findings could be even more critical, if the population studied was composed of all patients with STEMI in the state, that is, those who stayed in primary and secondary hospitals, without access to the tertiary hospital. Incorporating the network of regional hospitals with the capacity to perform thrombolysis in the scenario may increase the total rate of patients who are reperfused and reduce mortality in this setting.

Although primary angioplasty is the treatment of choice for these patients, in this study, only 45.8% of the patients underwent this therapy, reaching more striking values from the perspective of the Glória region, with 17.1%. These rates are below those found in other studies.¹⁹⁻²² Despite the variability across the regions, it was only possible to observe a statistical difference when comparing the Lagarto region to Aracaju.

The discrepancies found both in the PPCI rate and in the time to access this method are justified by the same failures in the health care network. A study conducted in the United Kingdom showed that, in the second half of 2011, 94% of the patients with STEMI were treated by PPCI, a significant increase when compared to the rate of 46% in 2008. Among the elements responsible for this progression are the following: direct transportation of patients to centers with PPCI, professional training for pre-hospital diagnosis, data collection regarding quality of care, and, finally, creation of national policies in order to facilitate access to the health care network.²³

Another study carried out in the United Kingdom using data from England and Wales, with a total of 228 hospitals and a sample of 34,722 patients with STEMI, showed that the use of aspirin at admission and thrombolysis outside the hospital are the strongest predictors of in-hospital survival. In addition to that, factors such as heart rate and systolic blood pressure at admission also impact 30-day mortality due to STEMI.³

Limitations

In view of the precariousness of well-documented records in some of the regions, data acquisition was supplemented through interviews, and part of these were self-reported, which can lead to inaccuracies in the time measures. It is also worth

noting that many SUS users are unaware of their previous health status, making it difficult to accurately measure the prevalence of comorbidities; this fact hinders adjustment of the risk across the different populations of the regions under study. Finally, this study restricted data collection to the hospital with PPCI, as it is the only reference in the treatment of STEMI in the state. This fact limits the results to the patients who had access to the reference center. However, we emphasize that, by limiting the population to the reference center, the observed scenario represents the best quality of care provided by the SUS in the state of Sergipe.

Conclusion

The VICTIM Register identified a glaring lack of sufficient access to PPCI in the state, recording a primary time window of access almost double that which is considered borderline, which was even worse in some sub-regions. In addition, there is marked underuse of fibrinolytics, as an alternative reperfusion therapy for STEMI, in all regions. High mortality rates persist, despite the therapeutic advances in cardiovascular science in the era of myocardial reperfusion. Together, our data demonstrate great inefficiency of the SUS in terms of assistance to patients with STEMI in the state of Sergipe. Our results should be investigated in other states and regions of the country to assess whether the precarious indicators herein observed are peculiar to Sergipe and the inserted region, or whether they represent “standard” care in the Brazilian public health system.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Oliveira JC, Ferreira GJS, Oliveira JC, Lima TCRM, Barreto IDC, Oliveira LCS, Arcelino LAM, Sousa AC, Barreto-Filho JAS; Acquisition of data: Oliveira JC, Ferreira GJS, Oliveira JC, Lima TCRM, Barreto IDC, Oliveira LCS, Arcelino LAM; Analysis and interpretation of the data: Oliveira JC, Ferreira GJS, Oliveira JC, Lima TCRM, Barreto IDC, Arcelino LAM, Sousa AC, Barreto-Filho JAS; Statistical analysis: Oliveira JC, Barreto IDC; Obtaining financing: Oliveira JC, Oliveira JC, Lima TCRM, Oliveira LCS, Barreto-Filho JAS; Writing of the manuscript: Oliveira JC, Ferreira GJS, Barreto-Filho JAS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

- Farshid A, Allada C, Chandrasekhar J, Marley P, McGill D, O'Connor S, et al. Shorter ischaemic time and improved survival with pre-hospital STEMI diagnosis and direct transfer for primary PCI. *Heart Lung Circ*. 2015;24(3):234-40.
- França AVC. Atenção Hospitalar no Estado de Sergipe: Saberes e tecnologias para implantação de uma política. In: França AVC. Atenção Hospitalar no Estado de Sergipe. Sergipe: Sergipe: Fundação Estadual de Saúde; 2021. p.1-188.
- Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003–2010. *Eur Heart J*. 2011; 33(5):630-9.
- Gershlick AH, Banning AP, Myat A, Verheugt WA, Gersh BJ. Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention?. *Lancet*. 2013; 382(9892):624-32.
- Oliveira JC, Santos MA, Oliveira JC, Oliveira LC, Barreto ID, Lima TC, et al. Disparities in Access and Mortality of Patients With ST-Segment elevation Myocardial Infarction Using the Brazilian Public Healthcare System: VICTIM Register. *J Am Heart Assoc*. 2019;8(20):e013057.
- Piegas LS, Timerman A, Feitosa GS, Nicolau JC, Mattos LA, Andrade MD, et al. V Diretriz da Sociedade Brasileira de Cardiologia sobre Tratamento do Infarto Agudo do Miocárdio com Supradesnível do Segmento ST. *Arq Bras Cardiol*. 2015;105(2):1-105.
- Instituto Brasileiro de Geografia e Estatística (IBGE). Estimativa populacional 2018. Disponível em: <<https://www.ibge.gov.br/estatisticas-ovoportal/sociais/populacao/9103-estimativas-de-populacao.html?=&t=downloads>>. Acesso em: 06 de fevereiro de 2018.
- Carvalho G, Rassi S, Guerios N, Curado FA, Bastos AT. Striving to meet targets for ideal treatment of acute myocardial infarction in Brazil: Data from the Midwest region. *J Interv Cardiol*. 2018;31(4):450-4.
- Piegas LS e Haddad N. Intervenção coronariana percutânea no Brasil: resultados do Sistema Único de Saúde. *Arq Bras Cardiol*. 2011;96(4):317-24.
- Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Mario C, et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J*. 2014;35(29):1957-70.
- Puymirat E, Simon T, Steg PG, Schiele F, Gueret P, Blanchard D, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308(10):998-1006.
- Halon DA, Adawi S, Dobrecky-Mery I, Lewis BS. Importance of increasing age on the presentation and outcome of acute coronary syndromes in elderly patients. *J Am Coll Cardiol*. 2004;43(3):346-52.
- Tran CT, Laupacis A, Mamdani MM, Tu JV. Effect of age on the use of evidence-based therapies for acute myocardial infarction. *Am Heart J*. 2004;148(5):834-41.
- Blankenship JC, Skelding KA, Scott TD, Berger PB, Parise H, Brodie BR, et al. Predictors of reperfusion delay in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention from the HORIZONS-AMI trial. *Am J Cardiol*. 2010;106(11):1527-33.
- Postma S, Dambrink JH, Boer MJ, Gosselink AT, Ottervanger JP, Koopmans PC, et al. The influence of residential distance on time to treatment in ST-elevation myocardial infarction patients. *Neth Heart J*. 2014;22(11):513-19.
- Fosbol EL, Granger CB, Jollis JC, Monk L, Lin L, Lytle BL, et al. The impact of a statewide pre-hospital STEMI strategy to bypass hospitals without percutaneous coronary intervention capability on treatment times. *Circulation*. 2013;127(5):604-12.
- Rosselló X, Huo Y, Pocock S, Werf FV, Chin CT, Danchin N, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. *Int J Cardiol*. 2017;(245):27-34.
- Vora AN, Holmes DN, Rokos I, Roe MT, Granger CB, French WJ, et al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. *JAMA*. 2015;175(2):207-15.
- Aguirre FV, Varghese JJ, Kelley MP, Lam W, Lucore CL, Gill JB, et al. Rural interhospital transfer of ST-elevation myocardial infarction patients for percutaneous coronary revascularization: the Stat Heart Program. *Circulation*. 2008;117(9):1145-52.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39(2):119-77.
- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):362-425.
- Santos J, Meira KC, Camacho AR, Salvador PT, Guimaraes RM, Pierin AM, et al. Mortalidade por infarto agudo do miocárdio no Brasil e suas regiões geográficas: análise do efeito da idade-período-coorte. *Cien Saud Colet*. 2018;(23):1621-34.
- Mclenachan JM, Gray HH, Belder MA, Ludman PF, Cunningham D, Birkhead J. Developing primary PCI as a national reperfusion strategy for patients with ST-elevation myocardial infarction: the UK experience. *EuroIntervention*. 2012;(8):99-107.



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Coronary Reperfusion in Acute Myocardial Infarction: Trying the Optimal. Executing the Possible

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Short editorial related to the article: Influence of Geographical Location on Access to Reperfusion Therapies and Mortality of Patients with STEMI in Sergipe: VICTIM Register

The infarction-related artery reperfusion strategy began in the 1970s with the intracoronary administration of fibrinolytics.^{1,2} This was followed by intravenous administration³ and mechanical thrombolysis of the “culprit” artery, initially with simple angioplasty and, later, with stenting.⁴ All of these procedures had a common goal: to reduce the ischemic/necrotic area, preserve muscle, improve ventricular function and, consequently, survival.

The success of the procedure depends on the time from the onset of symptoms to the moment of the chosen intervention, whether chemical or percutaneous. According to different guidelines, this interval is about 12 hours. The earlier the diagnosis and intervention, the better the clinical outcomes will be.⁵

Studies comparing mechanical x chemical thrombolysis have reported the superiority of the former in reducing mortality and severe hemorrhagic complications, which led the general decision to be the main strategy to treat patients.⁶ However, not all hospitals have a cath lab and, among them, a smaller number has the structure to keep it open 24 hours, 7 days a week. Studies conducted abroad have demonstrated the feasibility of transferring patients to hospitals with the possibility of performing percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI)⁷ within the time interval recommended by the best evidence. When this time interval cannot be fulfilled, fibrinolysis within 30 minutes of arrival at the first health institution or pre-hospital fibrinolysis is recommended.⁸⁻¹¹

In this study, which is of great importance for public health and cardiology management, the authors point out that in Sergipe the distribution of services that perform PCI is not regionalized and among those that do it, only one, located in Aracaju, serves patients referred from the public health system, through regulation from other health units, and emphasize the importance of time from the hospital without PCI to the hospital with PCI as having the greatest impact on the total time.¹² These are delays that occur even in Aracaju, whose

times, theoretically, should be much shorter than the observed median of 9 h from the onset of symptoms to arrival at the hospital with PCI.

As pointed out by the authors, the fact that this hospital does not have “open doors” justifies the proposition for health managers to reassess the flow of care for infarcted patients in the state, by increasing the percentages of chemical thrombolysis due to the impossibility of transferring them to centers with PCI within the recommended time, thus making it possible to reduce the high mortality rates observed. These data have an even greater impact if we consider that nearly 15% of patients went through two hospital units before reaching their final destination.¹² A detailed analysis of the subgroup of patients (1.7%) that had direct access to the hospital with PCI can provide data that are more consistent with the need to change this flow of care.

The Glória health region is one of the most distant from the capital, which may explain the longer times from the hospital without PCI to the hospital with PCI and from the onset of symptoms to arrival at that hospital. These data justify the lowest percentage of primary PCI (17.1%) among the regions of the state. Despite this, the study shows the lowest mortality rate (7.5%) in this region. It is important to highlight the lowest percentage of diabetics, the lowest average age and the highest rate of non-primary PCI in this region. On the other hand, the region of Estância, the mortality rate of which was the highest (18.6%), is close to the region of Aracaju, which justifies a time almost 5 hours shorter from the hospital without PCI to the hospital with PCI, and from onset of symptoms to arrival at the hospital with PCI 5 h and 30 min shorter, which explains a higher percentage of primary PCI (46.6%). However, this region has the highest average age and the second highest rate of diabetes. The global assessment of these data allows us to hypothesize that the time to care for the acute condition may have been compensated by the heterogeneous risk profile of the study population, which justifies the non-difference in mortality rates in the adjusted data.

Care of infarcted patients remains a challenge for cardiologists and health managers, especially in remote locations with scarce resources. It is possible that in recent months the COVID-19 pandemic has accentuated these inequalities, but while, guided by science, we seek the optimal, we must persist in the fight for the implementation of possible measures: identification of the causes of the greatest delays in care, geographically equal and symmetrical distribution of cardiology care centers, establishment of guidelines for expanding the use of chemical thrombolysis, including pre-hospital thrombolysis, which will contribute to reducing mortality rates from Propriá to Estância and from Glória to Aracaju.¹²

Keywords

Cardiovascular Diseases; Myocardial Infarction; Myocardial Reperfusion; Percutaneous Coronary Intervention; Fibrinolytic Agents.

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References

1. Chazov El, Matveeva LS, Mazaev AV, Sargin KE, Sadovskaia GV, Ruda MI. Intracoronary administration of fibrinolysin in acute myocardial infarct. *Ter Arkh.* 1976; 48: 8-19.
2. Rentrop KP, Blanke H, Wiegand V, Kosterling H, Oster H, Leitz K. Acute myocardial infarction. Intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol.* 1979; 2: 354-63.
3. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Grupo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). *Lancet.* 1986;1(8478): 397-402.
4. Nordmann AJ, Hengstler P, Harr T, Young J, Bucher HC. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Med.* 2004; 116(4): 253-62.
5. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018; 39(2):119-77.
6. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003; 361 (9351):13-20.
7. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizsko M, Aschermann M, et al. PRAGUE Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial – PRAGUE 2. *Eur Heart J.* 2003; 24(1):94-104.
8. Sociedade Brasileira de Cardiologia. V Diretriz da Sociedade Brasileira de Cardiologia sobre tratamento do infarto agudo do miocárdio com supradesnível do segmento ST. *Arq Bras Cardiol.* 2015; 105(2):1-105.
9. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta analysis. *JAMA.* 2000;283(20):2686-92.
10. McNamara RL, Herrin J, Wang Y, Curtis JP, Bradley EH, Magid DJ, et al. Impact of delay in door-to-needle time on mortality in patients with ST-segment elevation myocardial infarction. *Am J Cardiol.* 2007;100(8):1227-32.
11. Balk M, Gomes HB, Quadros AS, Saffi MAL, Leiria TLL. Análise comparativa entre pacientes com IAMCSST transferidos e pacientes de demanda espontânea submetidos à angioplastia primária. *Arq. Bras Cardiol.* 2019; 112 (4): 402-407.
12. Oliveira JC, Ferreira GJS, Oliveira JC, Lima TCR, Barreto IDC, Oliveira LCS, et al. Influence of Geographical Location on Access to Reperfusion Therapies and Mortality of Patients with STEMI in Sergipe: VICTIM Register. *Arq Bras Cardiol.* 2021; 117(1):120-129.



Physical Exercise Training and Chagas Disease: Potential Role of MicroRNAs

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Abstract

Chagas disease (CD) is caused by *Trypanosoma Cruzi*. This parasite can infect several organs of the human body, mainly the heart, causing inflammation, fibrosis, arrhythmias, and cardiac remodeling, promoting long-term Chronic Chagas Cardiomyopathy (CCC). However, little scientific evidence has elucidated the molecular mechanisms that govern the pathophysiological processes in this disease. MicroRNAs (miRNAs) are regulators of post-transcriptional gene expression that modulate signaling pathways, participating in pathophysiological mechanisms in CD, but the understanding of miRNAs in this disease is limited. On the other hand, a wide range of scientific evidence shows that physical exercise training (PET) modulates the expression of miRNAs by modifying different signaling pathways in healthy individuals. Some studies also show that PET is beneficial for individuals with CD; however, these did not evaluate the miRNA expressions. Thus, there is no evidence showing the role of PET in the expression of miRNAs in CD. Therefore, this review aimed to identify miRNAs expressed in CD that could potentially be modified by PET.

Introduction

Chagas Disease (CD) is a complex disease caused by *Trypanosoma Cruzi* (*T. cruzi*), a flagellated protozoan parasite, infection at the intracellular level.¹ In the acute phase, the *T. cruzi* infection generates great tissue inflammation, and there is an initial response of the innate immune system in an attempt to fight parasitemia.²

However, the infection persists and the adaptive immune system activates the T lymphocytes, as well as the auxiliary and cytotoxic T cells, which produce cytokines, such as gamma interferon (IFN- γ), which can in turn lead to intracellular parasitic death by inducing an increase in the reactive oxygen species and nitrogen, which are microbicides. This infection also increases the expression of the tumor necrosis factor (TNF- α) and specific antibodies to combat *T. cruzi*, which control parasitism, with a low-grade infection being established.³

Keywords

Exercise; Chagas Disease; MicroRNAs.

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Still in the acute phase of the disease, there is an increase in the expression of the vasoactive peptide endothelin-1 (ET-1) and cardiotrophin-1 (CT-1), both inducing cardiac hypertrophy, as well as an increase in the expression of interleukin-1 beta. (IL-1 β), inducing an inflammatory and pro-hypertrophic response of the myocardium, which may initiate cardiac hypertrophy even at this stage.^{4,5}

Over the years, parasitemia is reduced; however, parasitic antigens persist, generating a diffuse inflammatory infiltrate and myocarditis, with the presence of CD4 + and CD8 + T lymphocytes and macrophages that continue to express TNF- α and IFN- γ .³ IFN- γ has an essential function to control and fight against parasites, but it also contributes to cardiac pathogenesis, as it damages the myocardium through several molecular mechanisms generating myocardial dysfunction.⁶

Thus, the disease evolves and passes to the chronic phase, which can be subdivided into two forms: indeterminate and symptomatic. In the indeterminate form, individuals can go for years without manifesting any type of more serious symptom, where there is a balance between parasitemia and the host's immune system. However, about 30% of these patients develop a symptomatic or determined form, which can trigger dysfunctions in different organs, including the heart, developing Chronic Chagas Cardiomyopathy (CCC) associated with myocarditis and cardiac myofibrillar fibrosis, thereby reducing cardiac electrical conductivity and generating myocardial remodeling.⁷

CCC generates inflammation of the cardiac tissue, causing focal or diffuse myocarditis, hypertrophy, or dilation of the left ventricle and progressive death of some cardiomyocytes, necrosis, and collagen deposit,⁸ thereby increasing the fibrotic tissue, leading to a reduction in its contractile capacity. This outcome is mostly associated with arrhythmias and heart failure,⁹ but microRNAs (miRNAs) may also participate in these mechanisms. In general, the molecular mechanisms that govern these processes are poorly understood.

MiRNAs are small RNAs, with only 18 to 25 nucleotides in length;¹⁰ non-coding proteins; and regulators of post-transcriptional gene expression with the function of inhibiting or degrading its target genes.^{11,12} It has been shown that several types of physical exercise training (PET) modulate the expression of miRNAs.¹³ Nevertheless, articles that analyze the effects of PET on the expression of miRNAs in CD are still scarce in the literature. Thus, our literature review sought to analyze the miRNAs expressed in CD and to compare this finding with the miRNAs expressed during or after PET.

Chagas Disease and miRNAs

Few studies in the literature have analyzed the expression profile of miRNAs in CD, either in the acute or in the chronic

phase, as well as the signaling pathways that are regulated by miRNAs in this neglected disease. Therefore, this study included all of the studies that evaluated the expression pattern of miRNAs in CD (Table 1).

Chagas Disease (acute phase) and miRNAs

During the acute phase of CD, the researchers evaluated the expression of miRNAs at 15, 30, and 45 days post-infection, and identified that miRNAs were differentially expressed during parasitemia and that changes in the QT interval were upregulated: miR-20, miR-20b, miR-21, miR-142, miR-146a, miR-146b, miR-155, miR-182, miR-203, and miR-222, and downregulated: miR-139, miR-145, miR-149, miR-322, and miR-503.¹⁴

Another study performed an *in silico* analysis to identify the differential expression of miRNAs and their target genes in several biological processes during the acute phase of *T. Cruzi* infection, demonstrating that some miRNAs may be associated with the pathological process, such as miR-238-3p, miR-149-5p, miR-143-3p, miR-145-5p, and miR-486-5p. Other miRNAs may be associated with cardiovascular immunity and function, for example: miR-10a-5p, miR-16-5p, miR-30c-5p, miR-34a-5p, miR-138-5p, miR-146a-5p, miR-149, miR-191-5p, miR-204-5p, miR-320b and miR-653-3p, as well as miRNAs related to the tissue fibrosis process: miR-34a-5p, miR-142-3p, miR-200b-3p, and 203a-3p.¹⁵

Chagas Disease (chronic phase) and miRNAs

The expression of miRNAs from the cardiac tissue of patients with CCC after heart transplantation was analyzed and compared with the expression of miRNAs from the cardiac tissue of healthy donor individuals. Of all miRNAs analyzed, five miRNAs had their expression reduced (miR-1, miR-133a, miR-133b, miR-208a, and miR-208b) in patients with CCC when compared to the control group.¹⁶ By contrast, the circulating miR-208a in a plasma sample was overexpressed in patients with CD; however, these were in the undetermined chronic phase.¹⁷

The overexpression of MiR-19a, miR-21, and miR-29b has been described in patients with CCC when compared to healthy individuals. In fact, in the histological analysis of

the cardiac tissue of patients in the final stage of CCC, it was identified that, in addition to the miRNAs mentioned above, the miR-30a and miR-199b are also overexpressed in the CD.¹⁸

These studies demonstrate that many miRNAs participate in several processes in the CD both in the acute and chronic phase; however, further studies are needed to elucidate the role of these miRNAs and the signaling pathways they are regulating in the CD, including the importance of therapies or treatments that can modulate the pattern of expression shown in the disease.

Chagas Disease and Physical Exercise Training: miRNAs as potential modulators

Several types of PET have been described as modulators of the expression of many miRNAs,¹³ in experimental and clinical studies, such as swimming PET,²⁰ marathon,²¹ running on a treadmill,²² and resistance training (RT)²³ (Table 2).

Some studies have also reported the importance of PET modulating the expression of miRNAs in pathological situations, as well as in diabetics,^{24,25} in obesity,²⁶ after myocardial infarction,²⁷ and with heart failure;²² however, the role of PET-modulating miRNAs in CD has not yet been illustrated. The literature presents only studies that have shown beneficial effects of PET on CD, but they did not analyze the miRNA profile.

Performing only aerobic PET with moderate intensity (50% to 70% of maximum heart rate), three days a week, for 30 minutes, in 12 weeks, obtained a significant increase in maximum cardiorespiratory and metabolic capacity (VO₂), increased time in exercise, distance covered, and improvement in emotional aspects,²⁸ as well as association with an RT program, obtained similar beneficial results.²⁹

In another study, with a similar PET protocol, an improvement in functional capacity was also evidenced, with an improvement in ejection fraction and respiratory strength, improvement in diastolic pressure in the left ventricle and in the quality of life of Chagas patients after 8 months of training.³⁰

A cardiac rehabilitation program consisting of the same PET protocol mentioned above, with RT and stretches, adding nutritional guidance and pharmacological counseling

Table 1 – MicroRNAs in Chagas Disease

MicroRNAs	Source	Findings	Reference
↓ miR-1, miR-133a, miR-133b, miR-208a, miR-208b	Heart samples	Association with connective tissue disorders and fibrosis	16
↑ miR-208b	Plasma samples	Association with cardiovascular dysfunction and myocardial hypertrophy	17
↑ miR-20, miR-20b, miR-21, miR-142, miR-146a, miR-146b, miR-155, miR-182, miR-203, miR-222 ↓ miR-139, miR-145, miR-149, miR-322, miR-503,	Heart samples	Association with heart rate-corrected QT (QTc) interval. Ventricular depolarization and repolarization.	14
↑ miR-19a, miR-21, miR-29b, miR-30a, miR-199b	Heart samples and cell model	Association with fibrosis and cardiac remodeling	18
↑ miR-16, miR-26b, miR-190b, miR-3586, let-7f-2 ↓ miR-190b	H9c2 cells, infected with <i>T. Cruzi</i>	Association with cell growth, hypertrophy, and cell survival	19

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Table 2 – MicroRNAs in Physical Exercise Training (pre-clinical and clinical studies)

MicroRNAs	Target	Source	Types of Exercises	Reference
In vivo experimental models				
↑ miR-27a, miR-155 ↓ miR-143	ACE, AT1R	Heart samples	Wistar-Kyoto rats Exercise training on treadmill	39
↑ miR-17-3p	TIMP-3 PTEN	Heart samples	C57Bl/6 mice Ramp swimming training model Voluntary wheel training	40
↑ miR-222	HIPK1	Heart samples	Ramp swimming model Voluntary wheel training	41
↑ miR-19b, miR-30e, miR-133b, miR-208a ↓ miR-99b, miR-100, miR-191a, miR-22, miR-181a	IGF-1 PI3K/AKT/mTOR MAPK	Heart samples Plasma	Wistar albino rats Swimming training	42
↑ miR-29a, miR-101a	TG-β fos COL1A1	Heart samples	Intermittent run exercise	43
↑ miR-27a, miR-27b ↓ miR-143	ACE ACE2	Heart samples	Wistar rats Swimming training	44
↑ miR-126	PI3KR2	Heart samples Plasma	Zucker rats Swimming training	26
↓ miR-214	SERCA2A	Heart samples	Wistar rats Resistance training	23
↑ miR-1 ↓ miR-214	NCX SERCA2A	Heart samples	Wistar rats Swimming training	27
↑ miR-29c ↓ miR-1, miR-133a, miR133b	COL1A1 COL3A1	Heart samples	Wistar rats Swimming training	45
↑ miR-126	SPRED1 PI3KR2	Heart samples	Wistar rats Swimming training	46
↑ miR-21, miR-144, miR-145 ↓ miR-124	PTEN PIK3A TSC2	Heart samples	Wistar rats Swimming training	20
↑ miR-336-5p, miR-130b-5p, let7d-3p, miR-466c-5p, miR-324-3p, miR-146b-5p, miR-132-3p, miR-21-5p, miR-187-3p, miR-29b-5p, miR-324-5p, miR-214-5p, miR-140-5p, miR-152-5p, miR-99b-5p, miR-130a-5p, miR-455-5p, miR-27b-3p, miR-23b-3p, miR-652-5p, miR-199a-3p, miR-223-5p, miR-421-3p, miR-27a-5p, miR-24-5p, miR-34a-3p, miR-140-3p, miR-125b-5p, miR-145a-5p, miR-192-5p, miR-139-5p, miR-199a-5p, miR-674-3p, miR-191-5p, miR-28-3p, miR-195-5p, miR-598, miR-429, miR-224, miR-425, miR-221 ↓ miR-701-5p, miR-220, miR-144-3p, miR-694, miR-485-3p, miR-136-5p, miR-384-3p, miR-376c-3p, miR-208b-3p, miR-411-3p, miR-141-5p, miR-1894-3p, miR-9a, miR-687, miR-451-5p	TNF-α COL1A1 MMP9 PTEN AKT1 AMPK BCL2	Heart samples	Wistar rats Aerobic run training	22
↑ miR-503, miR-465b-5p, miR-542-3p ↓ miR-652		Heart samples	C57Bl6 mice Swimming training	47
↓ miR-26b, miR-143	IGF1R GATA-4 NFAT1C GSK3B	Heart samples	Balb/c mice Aerobic metal wheels training	48
↑ miR-21, miR-30b ↓ miR-1	BCL-2 p53 PDCD4	Heart samples	Swimming training	49

Continuação

↑ miR-23a, miR-27a	PTEN Casp7 FoxO1	Skeletal muscle samples	Resistance exercise	50
↑ miR-29c ↓ miR-1	COL1A1 COL3A1	Heart samples	Swimming training	51
↑ miR-382		Serum, tissues, and cell samples	IR mice Aerobic exercise	25
MicroRNAs	Targets	Source	Types of Exercises	Reference
Clinical studies				
↑ miR-126, miR-133	CPK	Plasma	Single symptom-limited spiroergometry test Marathon run Eccentric resistance exercise	52
↓ miR-486	PTEN	Serum	Systematic-cycling at 70% VO2max	53
↑ miR-1, miR-126, miR-133a, miR-134, miR-146a, miR-208a, miR-499-5p	CPK NT-proBNP hsCRP	Plasma	Marathon run Immediately after run	21
↑ miR-1, miR-133a, miR-206, miR-208b, miR-499		Plasma	Marathon run Immediately after run	54
↑ miR-1, miR-133a, miR-206		Plasma	Marathon run Immediately after run	55
↑ let-7d-3p, let-7f-3p miR-29a-3p, miR-34a-5p, miR-125b-5p miR-132-3p, miR-143-3p, miR-148a-3p, miR-223-3p, miR-223-5p miR-424-3p, miR-424-5p		Serum	Marathon run Immediately after run	56
↑ miR-1, miR-30a, miR-133a ↓ miR-26a, -29b		Plasma	Marathon run Immediately after run	57
↑ miR-1, miR-133a, miR-206		Plasma	Marathon run Immediately after run	58
↑ miR-1, miR-133a, miR-133b, miR-139-5p, miR-143, miR-145, miR-223, miR-330-3p, miR-338-3p, miR-424 ↓ miR-30b, miR-106a, miR-146, miR-151-3p, miR-151-5p, miR-221, miR-652, let-7i ↑ miR-103, miR-107 ↓ miR-21, miR-25, miR-29b, miR-92a, miR-133a, miR-148a, miR-148b, miR-185, miR-342-3p, miR-766, let-7d		Plasma	Cycle ergometry test 1-3 hs after exercise Systematic endurance cycle ergometry training	59
↑ miR-1, miR-133a, miR-133b, miR-206 miR-485-5p, miR-509-5p, miR-517a miR-518f, miR-520f, miR-522, miR-553, miR-888		Plasma	High intensity interval exercise Immediately after	60
↑ miR-181b, miR-214 ↑ miR-1, miR-133a, miR-133b, miR-208b		Plasma	Uphill treadmill test (concentric) Immediately after Downhill treadmill test (eccentric) 2-6 hs after exercise	61
↑ miR-149 ↓ miR-146a, miR-221		Serum	Resistance exercise 3 days after exercise	62
↑ miR-1, miR-133a, miR-133b, miR-206, miR-208b, miR-499		Plasma	Systematic resistance training 36-72 hs after training	63
↑ miR-1, miR-133a, miR-133b, miR-181a ↓ miR-9, miR-23a, miR-23b, miR-31 ↑ miR-1, miR-29b	HDAC4 NRF1	Skeletal muscle samples	Cycle ergometer, Cycling	64

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Continuação

↑ miR-136, miR-200c, miR-376a, miR-377, miR-499b, miR-558 ↓ miR-28, miR-30d, miR-204, miR-330, miR-345, miR-375, miR-449c, miR-483, miR-509, miR-520a, miR-548a, miR-628, miR-653, miR-670, miR-889, miR-1245a, miR-1270, miR-1280, miR-1322, miR-3180	Skeletal muscle samples	Resistance training	65
↑ miR-451 ↓ miR-26a, miR-29a, miR-378	Skeletal muscle samples	Resistance exercise	66
↑ miR-125a, miR-145, miR-181b, miR-193a, miR-197, miR-212, miR-223, miR-340, miR-365, miR-485, miR-505, miR-520d, miR-629, miR-638, miR-939, miR-940, miR-1225, miR-1238 ↓ let-7i, miR-16, miR-17, miR-18a, miR-18b, miR-20a, miR-20b, miR-22, miR-93, miR-96, miR-106a, miR-107, miR-126, miR-130a, miR-130b, miR-151, miR-185, miR-194, miR-363, miR-660	Serum	Cycle ergometer exercise	67
↑ miR-7, miR-15a, miR-21, miR-26b, miR-132, miR-140, miR-181a, miR-181b, miR-181c, miR-338, miR-363, miR-939, miR-940, miR-1225 ↓ let-7e, miR-23b, miR-31, miR-99a, miR-125a, miR-125b, miR-126, miR-130a, miR-145, miR-151, miR-199a, miR-199b, miR-221, miR-320, miR-451, miR-486, miR-584, miR-652	PBMC	Cycle ergometer exercise	68
↑ let-7f, miR-21, miR-29c, miR-223 ↓ let-7f, miR-21, miR-29c, miR-223	PBMC	Running exercise	69
↑ miR-7, miR-29a, miR-29b, miR-29c, miR-30e, miR-142, miR-192, miR-338, miR-363, miR-590 ↓ let-7e, miR-126, miR-130a, miR-151, miR-199a, miR-221, miR-223, miR-326, miR-328, miR-652	PBMC	Cycle ergometer exercise	70
↑ miR-15a, miR-29b, miR-29c, miR-30e, miR-140, miR-324, miR-338, miR-362, miR-532, miR-660 ↓ miR-23b, miR-130a, miR-151, miR-199a, miR-221	Serum	Cycle ergometer exercise	71
↑ miR-1, miR-486, miR-494	Serum	(Endurance athletes, runners, cyclists, and triathletes) Cardiopulmonary exercise test	72
↑ miR-21, miR-146a, miR-221, miR-222 ↑ miR-20a, miR-21, miR-146a, miR-221, miR-222	Serum	Rowing training, 5Km, 1-3 h per session, 20-24 strokes/min)	73
↑ miR-376a ↓ miR-16, miR-27a, miR-28	Plasma	Aerobic run exercise training (4 days/week)	74
↑ miR-19a, miR-19b, miR-20a, miR-26b, miR-143, miR-195	p-AKT p-S6K1 Serum	Resistance exercise	75
↑ miR-222	HIPK1 Plasma	Bicycle Ergometry Test	41
↑ miR-221 ↓ miR-208b, miR-221, miR-21, miR-146a, miR-210	Serum	Basketball Exercise	76

for patients with CD, demonstrated an increase in the physical and functional capacity, improving the quality of life of Chagas patients.³¹

In another important study, researchers performed PET three times a week for six months on Chagas patients. They demonstrated that the exercise group increased peak exercise oxygen consumption and maximum minute ventilation, improving the functional capacity of these patients.³²

However, even demonstrating that PET has beneficial effects for patients with CD, it is difficult to analyze the effects of this type of training at the tissue, cell, and molecular levels, given that these studies were performed in humans, where biopsies would be necessary. Therefore, to investigate the possible mechanisms associated with these beneficial effects of PET on CD, some studies have been carried out on experimental models of CD *in vivo*.

Balb/c mice performed PET on a treadmill before being infected by *T. Cruzi*. It was observed that PET reduced the peak of parasitemia, concluding that PET can promote beneficial changes in the immune system and obtain better responses to infections.³³

In other studies, the same finding as in the previous study was reported; however, they also observed that trained mice obtained greater protection from the metabolic activity of NADH in myenteric neurons and greater synthesis of TNF- α and TGF- β .³⁴ This contributed to the survival and/or protection of 10.3% of myenteric neurons and their immunoreactive production of nitric oxide neuronal synthase, in fact, the trained group obtained a greater expression of TNF- α during the acute phase of *T. Cruzi* infection, providing benefits to the host and improving the immune system to preserve nitrergic neurons.³⁵

In this context, in another study, researchers observed that the PET group obtained a greater expression of TNF- α , IFN γ , IL-6, and chemokines MCP-1 and CX3CL1 during acute infection, and also obtained better physical capacity, increased anaerobic threshold, increased activity of catalase and superoxide dismutase and reduced lipid and protein oxidation in cardiac tissue, demonstrating that PET can be an interesting strategy to increase the efficiency of endogenous antioxidant mechanisms, reducing oxidative damage in these animals.³⁶

Another study showed that PET before infection in Wistar rats, increased the time to reach fatigue and anaerobic threshold, reduced the expression of TNF- α , CCL-2, MCP-1, and CX3CL1, as well as lipid and protein oxidation, and increased the expression of IL-10, catalase, and superoxide dismutase, indicating that PET induces a protective phenotype, increasing the host's defenses against the parasitic agent, including the attenuation of the pathological remodeling process associated with musculoskeletal myositis.³⁷

Finally, in another study, Swiss mice were infected by *T. Cruzi* after PET with moderate intensity on a treadmill, being carried out for 9 weeks. Researchers identified that PET was able to reduce the latent parasitemia of the infected animals they trained, corroborating with previous studies, and even obtained less production of pro-inflammatory cytokines (TNF- α , INF γ , IL-12) and type-1 monocyte chemotactic protein (MCP-1) during the first days of infection.³⁸

Thus, it is suggested that PET has a therapeutic potential for the prevention and complementary treatment of CD and CCC through the modulation of the immune system. However, clinical studies lack morphometric, cellular, and molecular analyzes, mainly through the analysis of miRNAs for a better understanding of the beneficial effects of PET on signaling pathways in humans with CD, while preclinical studies, *in vivo*, need studies that evaluate the effects of PET with CD and CCC already installed and not only in the pre-infection stage.

Overlaps between miRNAs in CD and PET

Additionally, this study also performed an analysis using the Venn diagram to identify miRNAs that were modulated by PET in both clinical and pre-clinical studies that can possibly modulate miRNAs in CD.

There were only 7 miRNAs expressed in CD, 95 miRNAs expressed in PET clinical studies, and 36 miRNAs expressed in PET pre-clinical studies. Interestingly, the present study identified 7 miRNAs that had modulations in both CD and PET clinical studies, 3 common miRNAs modulated in CD and PET pre-clinical studies and, mainly, 12 common miRNAs modulated in CD, PET clinical studies, and PET pre-clinical studies (Figure 1). These 12 miRNAs are: miR-1, miR-21, miR-26b, miR-29b, miR-133a, miR-133b, miR-139, miR-145, miR-146a, miR-208a, miR-208b, and miR-222.

Nevertheless, of these 12 common miRNAs, only miR-133b, miR-139, and miR-208a were identified with a different expression pattern in CD and PET; all 3 miRNAs are downregulated in CD and upregulated in PET (Figure 2).

MiR-133b controls the connective tissue growth factor (CTGF)⁷⁷ and can suppress cardiac remodeling;⁷⁸ therefore, PET can be an excellent alternative to control cardiac remodeling, possibly through the modulation of miR-133b and the modification of some signaling pathways.

MiR-139 is associated with hypertrophic cardiomyopathy, regulating the expression of c-Jun, a transcriptional factor that binds in the promoter region of some genes to induce cardiac hypertrophy; thus, the overexpression of this miRNA reduces the expression of c-Jun, and consequently attenuates the pathological cardiac hypertrophy,⁷⁹ which may be a signaling pathway by which PET suppresses the pathological hypertrophy in CD, since PET also increases the expression of this miRNA.^{22,59}

In this context, miR-208a regulates the expression of some transcriptional factors, such as GATA-4, which is associated with the activation of pro-hypertrophic cardiac genes.⁸⁰ In CD, this miRNA is downregulated,¹⁶ while PET can increase its expression,^{21,42} thus demonstrating that it may possibly be a molecular mechanism by which PET attenuates cardiac hypertrophy in this disease.

Conclusions

miRNAs participate in several processes in the pathogenesis of CD. Much evidence shows the beneficial effects of PET on CD; however, there still are no articles in the literature that demonstrate the changes in the molecular mechanisms of miRNAs that PET induces in CD. Therefore, further studies are necessary to elucidate these mechanisms.

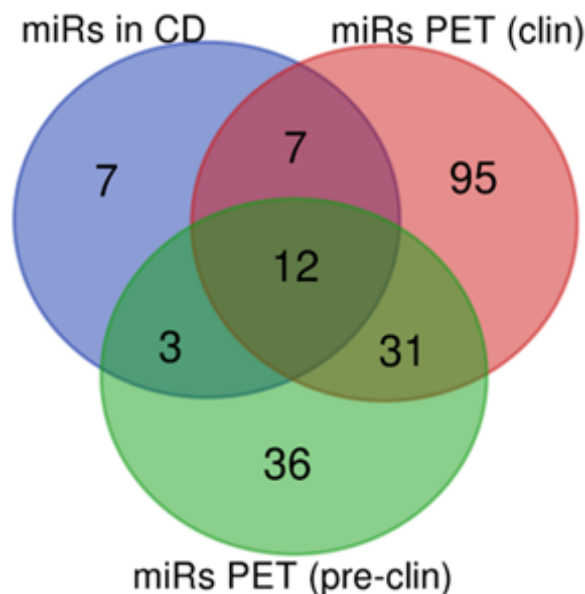


Figure 1 – Venn diagram shows overlaps between miRNAs: miRNAs (miRs) in Chagas Disease (blue), miRs PET clin: clinical studies (pink) and miRs PET pre-clin: pre-clinical studies (green).

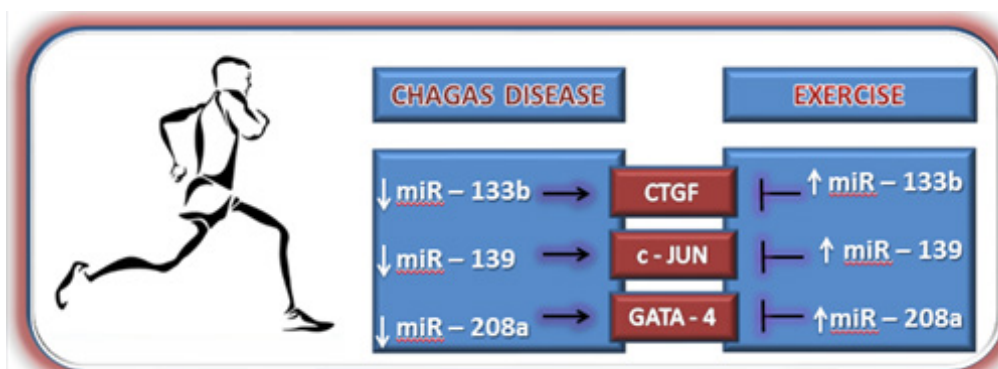


Figure 2 – miRNAs expressed in CD that can likely be modulated by PET.

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Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Improta-Caria AC; Analysis and interpretation of the data and Critical revision

of the manuscript for intellectual content: Improta-Caria AC, Aras Júnior R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References

- Bestetti RB, Cardinalli-Neto A. Sudden cardiac death in Chagas' heart disease in the contemporary era. *Int J Cardiol.* 2008;131(1):9-17. doi: 10.1016/j.ijcard.2008.05.024.
- Oliveira AC, Peixoto JR, Arruda LB, Campos MA, Gazzinelli RT, Golenbock DT, et al. Expression of functional TLR4 confers proinflammatory responsiveness to *Trypanosoma cruzi* glycoinositolphospholipids and higher resistance to infection with *T. cruzi*. *J Immunol.* 2004;173(9):5688-96. doi: 10.4049/jimmunol.173.9.5688.
- Nogueira LG, Santos RH, Fiorelli AI, Mairana EC, Benvenuti LA, Bocchi EA, et al. Myocardial gene expression of T-bet, GATA-3, Ror- γ t, FoxP3, and hallmark cytokines in chronic Chagas disease cardiomyopathy: an essentially unopposed TH1-type response. *Mediators Inflamm.* 2014;2014:914326. doi: 10.1155/2014/914326.
- Petersen CA, Burleigh BA. Role for interleukin-1 beta in *Trypanosoma cruzi*-induced cardiomyocyte hypertrophy. *Infect Immun.* 2003;71(8):4441-7. doi: 10.1128/IAI.71.8.4441-4447.2003.
- Petersen CA, Krumholz KA, Burleigh BA. Toll-like receptor 2 regulates interleukin-1beta-dependent cardiomyocyte hypertrophy triggered by *Trypanosoma cruzi*. *Infect Immun.* 2005;73(10):6974-80. doi: 10.1128/IAI.73.10.6974-6980.2005.
- Cunha Neto E, Dzau VJ, Allen PD, Stamatou D, Benvenuti L, Higuchi ML, et al. Cardiac gene expression profiling provides evidence for cytokinopathy as a molecular mechanism in Chagas' disease cardiomyopathy. *Am J Pathol.* 2005;167(2):305-13. doi: 10.1016/S0002-9440(10)62976-8.
- Rossi MA. The pattern of myocardial fibrosis in chronic Chagas' heart disease. *Int J Cardiol.* 1991;30(3):335-40. doi: 10.1016/0167-5273(91)90012-e.
- Soares MB, Lima RS, Souza BS, Vasconcelos JF, Rocha LL, Santos RR, et al. Reversion of gene expression alterations in hearts of mice with chronic chagasic cardiomyopathy after transplantation of bone marrow cells. *Cell Cycle.* 2011;10(9):1448-55. doi: 10.4161/cc.10.9.15487.
- Bocchi EA, Bestetti RB, Scanavacca MI, Cunha Neto E, Issa VS. Chronic Chagas Heart Disease Management: From Etiology to Cardiomyopathy Treatment. *J Am Coll Cardiol.* 2017;70(12):1510-1524. doi: 10.1016/j.jacc.2017.08.004.
- Ha M, Kim VN. Regulation of microRNA biogenesis. *Nat Rev Mol Cell Biol.* 2014;15(8):509-24. doi: 10.1038/nrm3838.
- Ambros V. The functions of animal microRNAs. *Nature.* 2004;431(7006):350-5. doi: 10.1038/nature02871.
- Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet.* 2010;11(9):597-610. doi: 10.1038/nrg2843.
- Caria ACI, Nonaka CKV, Pereira CS, Soares MBP, Macambira SG, Souza BSF. Exercise Training-Induced Changes in MicroRNAs: Beneficial Regulatory Effects in Hypertension, Type 2 Diabetes, and Obesity. *Int J Mol Sci.* 2018;19(11):3608. doi: 10.3390/ijms19113608.
- Navarro IC, Ferreira FM, Nakaya HI, Baron MA, Vilar-Pereira C, Pereira IR, et al. MicroRNA Transcriptome Profiling in Heart of *Trypanosoma cruzi*-Infected Mice: Parasitological and Cardiologic Outcomes. *PLoS Negl Trop Dis.* 2015;9(6):e0003828. doi: 10.1371/journal.pntd.0003828.
- Ferreira LRP, Ferreira FM, Laugier L, Cabantous S, Navarro IC, Cândido DS, et al. Integration of miRNA and gene expression profiles suggest a role for miRNAs in the pathobiological processes of acute *Trypanosoma cruzi* infection. *Sci Rep.* 2017;7(1):17990. doi: 10.1038/s41598-017-18080-9.
- Ferreira LR, Frade AF, Santos RH, Teixeira PC, Baron MA, Navarro IC, et al. MicroRNAs miR-1, miR-133a, miR-133b, miR-208a and miR-208b are dysregulated in Chronic Chagas disease Cardiomyopathy. *Int J Cardiol.* 2014;175(3):409-17. doi: 10.1016/j.ijcard.2014.05.019.
- Linhares-Lacerda L, Granato A, Gomes-Neto JF, Conde L, Freire-de-Lima L, Freitas EO, et al. Circulating Plasma MicroRNA-208a as Potential Biomarker of Chronic Indeterminate Phase of Chagas Disease. *Front Microbiol.* 2018;9:269. doi: 10.3389/fmicb.2018.00269.
- Nonaka CKV, Macêdo CT, Cavalcante BRR, Alcântara AC, Silva DN, Bezerra MDR, et al. Circulating miRNAs as Potential Biomarkers Associated with Cardiac Remodeling and Fibrosis in Chagas Disease Cardiomyopathy. *Int J Mol Sci.* 2019;20(16):4064. doi: 10.3390/ijms20164064.
- Monteiro CJ, Mota SL, Diniz LF, Bahia MT, Moraes KC. Mir-190b negatively contributes to the *Trypanosoma cruzi*-infected cell survival by repressing PTEN protein expression. *Mem Inst Oswaldo Cruz.* 2015;110(8):996-1002. doi: 10.1590/0074-02760150184.
- Ma Z, Qi J, Meng S, Wen B, Zhang J. Swimming exercise training-induced left ventricular hypertrophy involves microRNAs and synergistic regulation of the PI3K/AKT/mTOR signaling pathway. *Eur J Appl Physiol.* 2013;113(10):2473-86. doi: 10.1007/s00421-013-2685-9.
- Baggish AL, Park J, Min PK, Isaacs S, Parker BA, Thompson PD, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol (1985).* 2014;116(5):522-31. doi: 10.1152/japplphysiol.01141.2013.
- Souza RW, Fernandez CJ, Cunha JP, Piedade WP, Soares LC, Souza PA, et al. Regulation of cardiac microRNAs induced by aerobic exercise training during heart failure. *Am J Physiol Heart Circ Physiol.* 2015;309(10):H1629-41. doi: 10.1152/ajpheart.00941.2014.
- Melo SF, Barauna VG, Carneiro MA Jr, Bozi LH, Drummond LR, Natali AJ, et al. Resistance training regulates cardiac function through modulation of miRNA-214. *Int J Mol Sci.* 2015;16(4):6855-67. doi: 10.3390/ijms16046855.
- Rowlands DS, Page RA, Sukala WR, Giri M, Ghimbovski SD, Hayat I, et al. Multi-omic integrated networks connect DNA methylation and miRNA with skeletal muscle plasticity to chronic exercise in Type 2 diabetic obesity. *Physiol Genomics.* 2014;46(20):747-65. doi: 10.1152/physiolgenomics.00024.2014.
- Liu SX, Zheng F, Xie KL, Xie MR, Jiang LJ, Cai Y. Exercise Reduces Insulin Resistance in Type 2 Diabetes Mellitus via Mediating the lncRNA MALAT1/MicroRNA-382-3p/Resistin Axis. *Mol Ther Nucleic Acids.* 2019;18:34-44. doi: 10.1016/j.omtn.2019.08.002.
- Gomes JL, Fernandes T, Soci UP, Silveira AC, Barretti DL, Negrão CE, et al. Obesity Downregulates MicroRNA-126 Inducing Capillary Rarefaction in Skeletal Muscle: Effects of Aerobic Exercise Training. *Oxid Med Cell Longev.* 2017;2017:2415246. doi: 10.1155/2017/2415246.
- Melo SF, Barauna VG, Neves VJ, Fernandes T, Lara LS, Mazzotti DR, et al. Exercise training restores the cardiac microRNA-1 and -214 levels regulating Ca²⁺ handling after myocardial infarction. *BMC Cardiovasc Disord.* 2015;15:166. doi: 10.1186/s12872-015-0156-4.
- Lima MM, Rocha MO, Nunes MC, Sousa L, Costa HS, Alencar MC, et al. A randomized trial of the effects of exercise training in Chagas cardiomyopathy. *Eur J Heart Fail.* 2010;12(8):866-73. doi: 10.1093/eurjhf/hfq123.
- Fialho PH, Tura BR, Sousa AS, Oliveira CR, Soares CC, Oliveira JR, et al. Effects of an exercise program on the functional capacity of patients with chronic Chagas' heart disease, evaluated by cardiopulmonary testing. *Rev Soc Bras Med Trop.* 2012;45(2):220-4. doi: 10.1590/s0037-86822012000200016.
- Mediano MF, Mendes FS, Pinto VL, Silva GM, Silva PS, Carneiro FM, et al. Cardiac rehabilitation program in patients with Chagas heart failure: a single-arm pilot study. *Rev Soc Bras Med Trop.* 2016;49(3):319-28. doi: 10.1590/0037-8682-0083-2016.
- Mediano MFF, Mendes FSNS, Pinto VLM, Silva PSD, Hasslocher-Moreno AM, Sousa AS. Reassessment of quality of life domains in patients with compensated Chagas heart failure after participating in a cardiac rehabilitation program. *Rev Soc Bras Med Trop.* 2017;50(3):404-407. doi: 10.1590/0037-8682-0429-2016.

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32. Mendes FSN, Mediano MFF, Souza FCC, Silva PS, Carneiro FM, Holanda MT, et al. Effect of Physical Exercise Training in Patients With Chagas Heart Disease (from the PEACH STUDY). *Am J Cardiol.* 2020;125(9):1413-1420. doi: 10.1016/j.amjcard.2020.01.035.
33. Schebeleski-Soares C, Occhi-Soares RC, Franzói-de-Moraes SM, Dalálio MMO, Almeida FN, Toledo MJO, et al. Preinfection aerobic treadmill training improves resistance against *Trypanosoma cruzi* infection in mice. *Appl Physiol Nutr Metab.* 2009;34(4):659-65. doi: 10.1139/H09-053.
34. Moreira NM, Moraes SM, Dalálio MM, Gomes ML, Sant'ana DM, Araújo SM. Moderate physical exercise protects myenteric metabolically more active neurons in mice infected with *Trypanosoma cruzi*. *Dig Dis Sci.* 2014;59(2):307-14. doi: 10.1007/s10620-013-2901-9.
35. Moreira NM, Zanoni JN, Dalálio MMO, Araújo EJA, Braga CF, Araújo SM. Physical exercise protects myenteric neurons and reduces parasitemia in *Trypanosoma cruzi* infection. *Exp Parasitol.* 2014;141:68-74. doi: 10.1016/j.exppara.2014.03.005.
36. Novaes RD, Gonçalves RV, Penitente AR, Bozi LH, Neves CA, Maldonado IR, et al. Modulation of inflammatory and oxidative status by exercise attenuates cardiac morphofunctional remodeling in experimental Chagas cardiomyopathy. *Life Sci.* 2016;152:210-9. doi: 10.1016/j.lfs.2016.03.053.
37. Novaes RD, Gonçalves RV, Penitente AR, Cupertino MC, Maldonado IRSC, Talvani A, et al. Parasite control and skeletal myositis in *Trypanosoma cruzi*-infected and exercised rats. *Acta Trop.* 2017;170:8-15. doi: 10.1016/j.actatropica.2017.02.012.
38. Lucchetti BFC, Zanluqui NG, Raquel HA, Lovo-Martins MI, Tatakihara VLH, Belém MO, et al. Moderate Treadmill Exercise Training Improves Cardiovascular and Nitrogenic Response and Resistance to *Trypanosoma cruzi* Infection in Mice. *Front Physiol.* 2017;8:315. doi: 10.3389/fphys.2017.00315.
39. Gu Q, Wang B, Zhang XF, Ma YP, Liu JD, Wang XZ. Contribution of renin-angiotensin system to exercise-induced attenuation of aortic remodeling and improvement of endothelial function in spontaneously hypertensive rats. *Cardiovasc Pathol.* 2014;23(5):298-305. doi: 10.1016/j.carpath.2014.05.006.
40. Shi J, Bei Y, Kong X, Liu X, Lei Z, Xu T, et al. miR-17-3p Contributes to Exercise-Induced Cardiac Growth and Protects against Myocardial Ischemia-Reperfusion Injury. *Theranostics.* 2017;7(3):664-676. doi: 10.7150/thno.15162.
41. Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, et al. miR-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell Metab.* 2015;21(4):584-95. doi: 10.1016/j.cmet.2015.02.014.
42. Ramasamy S, Velmurugan G, Rajan KS, Ramprasad T, Kalpana K. MiRNAs with apoptosis regulating potential are differentially expressed in chronic exercise-induced physiologically hypertrophied hearts. *PLoS One.* 2015;10(3):e0121401. doi: 10.1371/journal.pone.0121401.
43. Xiao L, He H, Ma L, Da M, Cheng S, Duan Y, et al. Effects of miR-29a and miR-101a Expression on Myocardial Interstitial Collagen Generation After Aerobic Exercise in Myocardial-infarcted Rats. *Arch Med Res.* 2017;48(1):27-34. doi: 10.1016/j.arcmed.2017.01.006.
44. Fernandes T, Hashimoto NY, Magalhães FC, Fernandes FB, Casarini DE, Carmona AK, et al. Aerobic exercise training-induced left ventricular hypertrophy involves regulatory MicroRNAs, decreased angiotensin-converting enzyme-angiotensin II, and synergistic regulation of angiotensin-converting enzyme 2-angiotensin (1-7). *Hypertension.* 2011;58(2):182-9. doi: 10.1161/HYPERTENSIONAHA.110.168252.
45. Soci UP, Fernandes T, Hashimoto NY, Mota GF, Amadeu MA, Rosa KT, et al. MicroRNAs 29 are involved in the improvement of ventricular compliance promoted by aerobic exercise training in rats. *Physiol Genomics.* 2011;43(11):665-73. doi: 10.1152/physiolgenomics.00145.2010.
46. Silva ND Jr, Fernandes T, Soci UP, Monteiro AW, Phillips MI, Oliveira EM. Swimming training in rats increases cardiac MicroRNA-126 expression and angiogenesis. *Med Sci Sports Exerc.* 2012;44(8):1453-62. doi: 10.1249/MSS.0b013e31824e8a36.
47. McPherson NO, Owens JA, Fullston T, Lane M. Preconception diet or exercise intervention in obese fathers normalizes sperm microRNA profile and metabolic syndrome in female offspring. *Am J Physiol Endocrinol Metab.* 2015;308(9):E805-21. doi: 10.1152/ajpendo.00013.2015.
48. Martinelli NC, Cohen CR, Santos KG, Castro MA, Biolo A, Frick L, et al. An analysis of the global expression of microRNAs in an experimental model of physiological left ventricular hypertrophy. *PLoS One.* 2014;9(4):e93271. doi: 10.1371/journal.pone.0093271.
49. Zhao Y, Ma Z. Swimming training affects apoptosis-related microRNAs and reduces cardiac apoptosis in mice. *Gen Physiol Biophys.* 2016;35(4):443-450. doi: 10.4149/gpb_2016012.
50. Wang B, Zhang C, Zhang A, Cai H, Price SR, Wang XH. MicroRNA-23a and MicroRNA-27a Mimic Exercise by Ameliorating CKD-Induced Muscle Atrophy. *J Am Soc Nephrol.* 2017;28(9):2631-2640. doi: 10.1681/ASN.2016111213.
51. Silveira AC, Fernandes T, Soci ÚPR, Gomes JLP, Barretti DL, Mota GGF, et al. Exercise Training Restores Cardiac MicroRNA-1 and MicroRNA-29c to Nonpathological Levels in Obese Rats. *Oxid Med Cell Longev.* 2017;2017:1549014. doi: 10.1155/2017/1549014.
52. Uhlemann M, Möbius-Winkler S, Fikenzer S, Adam J, Redlich M, Möhlenkamp S, et al. Circulating microRNA-126 increases after different forms of endurance exercise in healthy adults. *Eur J Prev Cardiol.* 2014;21(4):484-91. doi: 10.1177/2047487312467902.
53. Aoi W, Ichikawa H, Mune K, Tanimura Y, Mizushima K, Naito Y, et al. Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men. *Front Physiol.* 2013;4:80. doi: 10.3389/fphys.2013.00080.
54. Mooren FC, Viereck J, Krüger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. *Am J Physiol Heart Circ Physiol.* 2014;306(4):557-63. doi: 10.1152/ajpheart.00711.2013.
55. Gomes CP, Oliveira GP Jr, Madrid B, Almeida JA, Franco OL, Pereira RW. Circulating miR-1, miR-133a, and miR-206 levels are increased after a half-marathon run. *Biomarkers.* 2014;19(7):585-9. doi: 10.3109/1354750X.2014.952663.
56. Gonzalo-Calvo D, Dávalos A, Montero A, García-González Á, Tyshkovska I, González-Medina A, et al. Circulating inflammatory miRNA signature in response to different doses of aerobic exercise. *J Appl Physiol.* 2015;119(2):124-34. doi: 10.1152/jappphysiol.00077.2015.
57. Clauss S, Wakili R, Hildebrand B, Kääs S, Hoster E, Klier I, et al. MicroRNAs as Biomarkers for Acute Atrial Remodeling in Marathon Runners (The miRathon Study--A Sub-Study of the Munich Marathon Study). *PLoS One.* 2016;11(2):e0148599. doi: 10.1371/journal.pone.0148599.
58. Min PK, Park J, Isaacs S, Taylor BA, Thompson PD, Troyanos C, et al. Influence of statins on distinct circulating microRNAs during prolonged aerobic exercise. *J Appl Physiol.* 2016;120(6):711-20. doi: 10.1152/jappphysiol.00654.2015.
59. Nielsen S, Åkerström T, Rinnov A, Yfanti C, Scheele C, Pedersen BK, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One.* 2014;9(2):e87308. doi: 10.1371/journal.pone.0087308.
60. Cui SF, Wang C, Yin X, Tian D, Lu QJ, Zhang CY, et al. Similar Responses of Circulating MicroRNAs to Acute High-Intensity Interval Exercise and Vigorous-Intensity Continuous Exercise. *Front Physiol.* 2016;7:102. doi: 10.3389/fphys.2016.00102.
61. Banzet S, Chennaoui M, Girard O, Racinais S, Drogou C, Chalabi H, et al. Changes in circulating microRNAs levels with exercise modality. *J Appl Physiol.* 2013;115(9):1237-44. doi: 10.1152/jappphysiol.00075.2013.
62. Sawada S, Kon M, Wada S, Ushida T, Suzuki K, Akimoto T. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. *PLoS One.* 2013;8(7):e70823. doi: 10.1371/journal.pone.0070823.

63. Zhang T, Birbrair A, Wang ZM, Messi ML, Marsh AP, Leng I, et al. Improved knee extensor strength with resistance training associates with muscle specific miRNAs in older adults. *Exp Gerontol.* 2015;62:7-13. doi: 10.1016/j.exger.2014.12.014.
64. Russell AP, Lamon S, Boon H, Wada S, Güller I, Brown EL, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. *J Physiol.* 2013;591(18):4637-53. doi: 10.1113/jphysiol.2013.255695.
65. Ogasawara R, Akimoto T, Umeno T, Sawada S, Hamaoka T, Fujita S. MicroRNA expression profiling in skeletal muscle reveals different regulatory patterns in high and low responders to resistance training. *Physiol Genomics.* 2016;48(4):320-4. doi: 10.1152/physiolgenomics.00124.2015.
66. Davidsen PK, Gallagher IJ, Hartman JW, Tarnopolsky MA, Dela F, Helge JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol.* 2011;110(2):309-17. doi: 10.1152/jappphysiol.00901.2010.
67. Radom-Aizik S, Zaldivar F Jr, Oliver S, Galassetti P, Cooper DM. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol.* 2010;109(1):252-61. doi: 10.1152/jappphysiol.01291.2009.
68. Radom-Aizik S, Zaldivar F Jr, Leu SY, Adams GR, Oliver S, Cooper DM. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci.* 2012;5(1):32-8. doi: 10.1111/j.1752-8062.2011.00384.x.
69. Dias RG, Silva MS, Duarte NE, Bolani W, Alves CR, Lemos JR Jr, et al. PBMCs express a transcriptome signature predictor of oxygen uptake responsiveness to endurance exercise training in men. *Physiol Genomics.* 2015;47(2):13-23. doi: 10.1152/physiolgenomics.00072.2014.
70. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol.* 2013;114(5):628-36. doi: 10.1152/jappphysiol.01341.2012.
71. Radom-Aizik S, Zaldivar FP Jr, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: implications for atherosclerotic vascular disease. *Brain Behav Immun.* 2014;39:121-9. doi: 10.1016/j.bbi.2014.01.003.
72. Denham J, Prestes PR. Muscle-Enriched MicroRNAs Isolated from Whole Blood Are Regulated by Exercise and Are Potential Biomarkers of Cardiorespiratory Fitness. *Front Genet.* 2016;7:196. doi: 10.3389/fgene.2016.00196.
73. Baggish AL, Hale A, Weiner RB, Lewis GD, Systrom D, Wang F, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol.* 2011;589(16):3983-94. doi: 10.1113/jphysiol.2011.213363.
74. Zhang T, Brinkley TE, Liu K, Feng X, Marsh AP, Kritchevsky S, et al. Circulating MiRNAs as biomarkers of gait speed responses to aerobic exercise training in obese older adults. *Aging.* 2017;9(3):900-913. doi: 10.18632/aging.101199.
75. Margolis LM, Rivas DA, Berrone M, Ezzyat Y, Young AJ, McClung JP, et al. Prolonged Calorie Restriction Downregulates Skeletal Muscle mTORC1 Signaling Independent of Dietary Protein Intake and Associated microRNA Expression. *Front Physiol.* 2016;7:445. doi: 10.3389/fphys.2016.00445.
76. Li Y, Yao M, Zhou Q, Cheng Y, Che L, Xu J, et al. Dynamic Regulation of Circulating microRNAs During Acute Exercise and Long-Term Exercise Training in Basketball Athletes. *Front Physiol.* 2018;9:282. doi: 10.3389/fphys.2018.00282.
77. Gjymishka A, Pi L, Oh SH, Jorgensen M, Liu C, Protopapadakis Y, et al. miR-133b Regulation of Connective Tissue Growth Factor: A Novel Mechanism in Liver Pathology. *Am J Pathol.* 2016;186(5):1092-102. doi: 10.1016/j.ajpath.2015.12.022.
78. Li N, Zhou H, Tang Q. miR-133: A Suppressor of Cardiac Remodeling? *Front Pharmacol.* 2018;9:903. doi: 10.3389/fphar.2018.00903.
79. Ming S, Shui-Yun W, Wei Q, Jian-Hui L, Ru-Tai H, Lei S, et al. miR-139-5p inhibits isoproterenol-induced cardiac hypertrophy by targetting c-Jun. *Biosci Rep.* 2018;38(2):BSR20171430. doi: 10.1042/BSR20171430.
80. Callis TE, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, et al. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. *J Clin Invest.* 2009;119(9):2772-86. doi: 10.1172/JCI36154.



Left Heart Hypoplasia Evolving Up to 21 Years, After Total Cavopulmonary Operation Performed at 5 Years of Age

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Introduction

Hypoplasia of the left heart is characterized by very small dimensions of the left cardiac cavities, represented by the left atrium, mitral valve, left ventricle, aortic ring and ascending aorta.¹ Systemic circulation thus becomes dependent on the ductus arteriosus with reverse flow from the hypertensive pulmonary artery to the descending aorta, and also to the ascending aorta. Coronary circulation is also dependent on this reverse flow, which is why there is a high chance of myocardial infarction, even in the first days of life. It is easy to imagine that, on decreased pulmonary arterial pressure or ductus arteriosus caliber, there is an unfavorable evolution towards low cardiac output. The right heart is enlarged and atrial septal defect invariably accompanies this defect. When this atrial defect appears to be of reduced dimensions, known as restrictive, it causes retrograde pulmonary hypertension. On the other hand, when larger, it may favor the faster involution of pulmonary hypertension, with congestive symptoms and low output. In the rare cases of intact atrial septum, anomalous pulmonary vein drainage remains in order of maintenance and viability of circulation. Left heart hypoplasia is the fourth most common heart disease in the neonatal period, with high mortality, even in this period, and corresponds to 1.5% of all congenital heart diseases.

How it is externalized and evolves: Dynamic instability favors the advent of very early signs and symptoms in life, in the first hours or days of life. These signs are characterized by congestive condition (with large atrial defect) or low systemic output (decreased pulmonary arterial pressure and/or constriction of the ductus arteriosus), with pallor, dyspnea, discomfort, irritability and variable cyanosis. The most favorable picture corresponds to the one with restrictive atrial septal defect, which, in view of the maintenance of pulmonary hypertension, the cardiac output is maintained at a satisfactory level.

Larger pulses in the lower limbs and decreased pulses in the upper limbs, alongside discrete systolic murmur with a second accentuated heart sound in the pulmonary area, overload of the right cardiac chambers on the

electrocardiogram and cardiomegaly resulting from the right cavities, constitute diagnostic elements. In the restrictive form, cyanosis predominates, without murmurs and pulmonary venocapillary congestion expresses the reason for retrograde pulmonary hypertension, responsible for maintaining systemic flow.

How it is Treated

Clinic: The prophylactic use of prostaglandin (0.05 to 0.1 mcg/kg/min), right after birth, is a key measure for the preservation of systemic flow through the ductus arteriosus. Vasoactive drugs such as dobutamine, dopamine and adrenaline are added together in order to maintain adequate pulmonary pressure, and to maintain cardiac output.

If they need endotracheal intubation, it is essential that the fraction of inspired oxygen does not exceed 25%, to avoid pulmonary vasodilation with a consequent decrease in cardiac output. These measures support clinical stabilization (oxygen saturation in 80 to 85%) to avoid preoperative complications, of greater surgical risk, such as myocardial infarction, arrhythmias, ventricular dysfunction, tricuspid regurgitation and low systemic output.

Surgery: Two main techniques are indicated for the palliative correction of left heart hypoplasia. The most used one is the classic Norwood operation (transformation to anomaly-type pulmonary atresia and dependent on the modified Blalock-Taussig technique) or by the Sano variant (transformation to anomaly-type double outlet right ventricle with non-valved tube connection, 5 mm in diameter, between the right ventricle and the pulmonary trunk). In both techniques, the pulmonary trunk is sectioned transversely, next to the bifurcation of the pulmonary arteries, and the ascending aorta is anastomosed to it, thus creating a wide connection between the right ventricle and the neo-aorta. Hybrid operation can also be performed, with stent placement in the ductus arteriosus, banding of the pulmonary arteries and expansion of the atrial septal defect. The greatest advantage of this technique lies in the elimination of circulatory arrest, decreasing the operative risk in this first stage. Indication of this hybrid technique is particularly important in unfavorable clinical situations involving high-risk patients, such as in the absence of atrial septal defect, low body weight, cardiogenic shock, at ages older than 14 days and in centers with high operative mortality.

How it evolves after the operation: The balance between pulmonary and systemic resistance must be maintained throughout the postoperative period. This aspect is best achieved with the Norwood-Sano operation, since in this variant there is no diversion of blood from the systemic circulation through the classic Blalock-Taussig technique. Thus, the postoperative period becomes more stable, both

Keywords

Hypoplastic Left Heart Syndrome; Fontan Procedure; Cardiac Surgical Procedures.

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coronary and splanchnic perfusion increase, and right ventricular volume overload and mortality decrease, until the Glenn operation. The disadvantage of this technique is a 6 mm ventriculotomy in the ventricular outflow tract that can predispose to ventricular dysfunction, arrhythmias and pulmonary insufficiency. Regarding the hybrid technique, evolutionary problems may arise, such as constriction of the ductus arteriosus, stenosis of the pulmonary arteries due to previous bandages and even the inadequate development of the ascending aorta.

In the evolution of any of the recommended techniques, heart failure and hypoxemia, which are more pronounced, are feared. Hence the early indication, about 6 months of age for the 2nd stage, by the bidirectional Glenn operation and the 3rd stage, for about 18 to 24 months of age, in order to complete the total cavopulmonary operation.

The total mortality of patients with hypoplasia of the left heart according to natural history, in the first month of life, has now been alleviated for about 40 to 60% of them until the completion of the Fontan²⁻⁵ principle. In subsequent evolution, mortality is also high, about 25% of them in 10 years and up to 55% in 30 years.^{2,3}

The purpose of this presentation is to show a good long-term evolution, overcoming all the recommended operative phases, and to highlight the necessary prerogatives for this good evolution.

Case description

Clinical data

A 21-year-old patient has been followed up since birth with diagnosis of left heart hypoplasia, who underwent Norwood operation at 4 days of life, 5-month bidirectional Glenn technique and total cavopulmonary anastomosis at 5 years with a non-fenestrated external tube. Since then, he has evolved without symptoms, using warfarin, spironolactone and enalapril.

Physical examination: eupneic, acyanotic, normal pulses. Weight: 80 kg, Height: 185 cm, BP: 110/80 mm Hg, CF: 65 bpm, O₂ saturation = 95%. Discreet jugular turgescence and aorta slightly palpated at the suprasternal notch.

In the precordium, apical impulse was not palpable and there were no systolic impulses at the left external border (LEB). The cardiac sounds were normal in intensity and a mild systolic murmur was heard, +/+ +/4 intensity, rough, in the low LEB. The liver was not palpable and the lungs were clean.

Complementary Exams

Electrocardiogram showed sinus rhythm and qR morphology in V1 and negative T waves from V1 to V3, indicative of severe right ventricular overload. There were no left ventricular potentials, with RS morphology in V6. AP: +10°, AQRs: +100°, AT: +70° (Figure 1).

Chest radiography shows normal cardiac area and pulmonary vascular network. There was a slight protrusion of the aortic arch, and a rectified medium arch (Figure 1).

Echocardiogram showed dilated inferior vena cava (22 mm), external tube between the inferior vena cava and the right pulmonary artery with a laminar flow at a speed of 0.68 m/s, anastomosis of the superior vena cava with the right pulmonary artery with a maximum velocity of 0.48 m/s. The left atrioventricular connection was absent. Right ventricular cavity in connection with the neo-aorta (former pulmonary trunk and valve). Wide interatrial communication with flow from left to right. Hypertrophic and dilated right ventricle with preserved systolic function. Left ventricle markedly hypoplastic. Confluent pulmonary arteries (Figure 1).

Abdominal tomography: Hepatosplenomegaly with normal and homogeneous density parenchyma. Normal caliber hepatic and portal veins. Varicose splenic veins. No dilation of intra or extrahepatic bile ducts. Other abdominal structures without morphological abnormalities.

Clinical diagnosis: Left heart hypoplasia syndrome submitted to total cavopulmonary operation 16 years ago, in good long-term evolution.

Clinical Characteristics

a. Clinical reasoning: The clinical elements were compatible with the good evolution of the Fontan operation performed 16 years ago, due to absence of symptoms and complications, and a favorable clinical condition. Systolic murmur auscultated on the left sternal border was not of pathological importance because it was discreet, supported by the absence of valve insufficiencies on echocardiogram. The expected marked right ventricular overload, as this has become the systemic ventricle, is not accompanied by dysfunction, which is why the patient's good clinical evolution has been preserved.

Management: The favorable clinical evolution in this group of patients with hypoplasia of the left heart always results from continuous preservation of right ventricular function, even when subjected to a higher-pressure load and, for this reason, vasodilator medication was administered according to the myocardial structure. Anticoagulants required due to slow systemic venous flow abnormalities accompany all patients undergoing the Fontan operation, preventing the formation of evolutionary thrombi in this system.

Discussion

Left heart hypoplasia is undoubtedly the most feared congenital cardiac anomaly, even with the decrease in mortality, as found in all evolutionary stages between the operations necessarily performed. There was an improvement in the immediate management at birth in preserving the clinical condition with more adequate systemic output, with the use of prostaglandin E1 and vasoactive drugs. As a result, the newborn has been operated in a better clinical condition, so the initial Norwood-Sano technique has also become less risky, and about 90% has survived in this phase.⁵ Subsequent developments, up to the Glenn and Fontan operation, are also accompanied by fewer complications, which in greater numbers manage to be followed up in the long term, as

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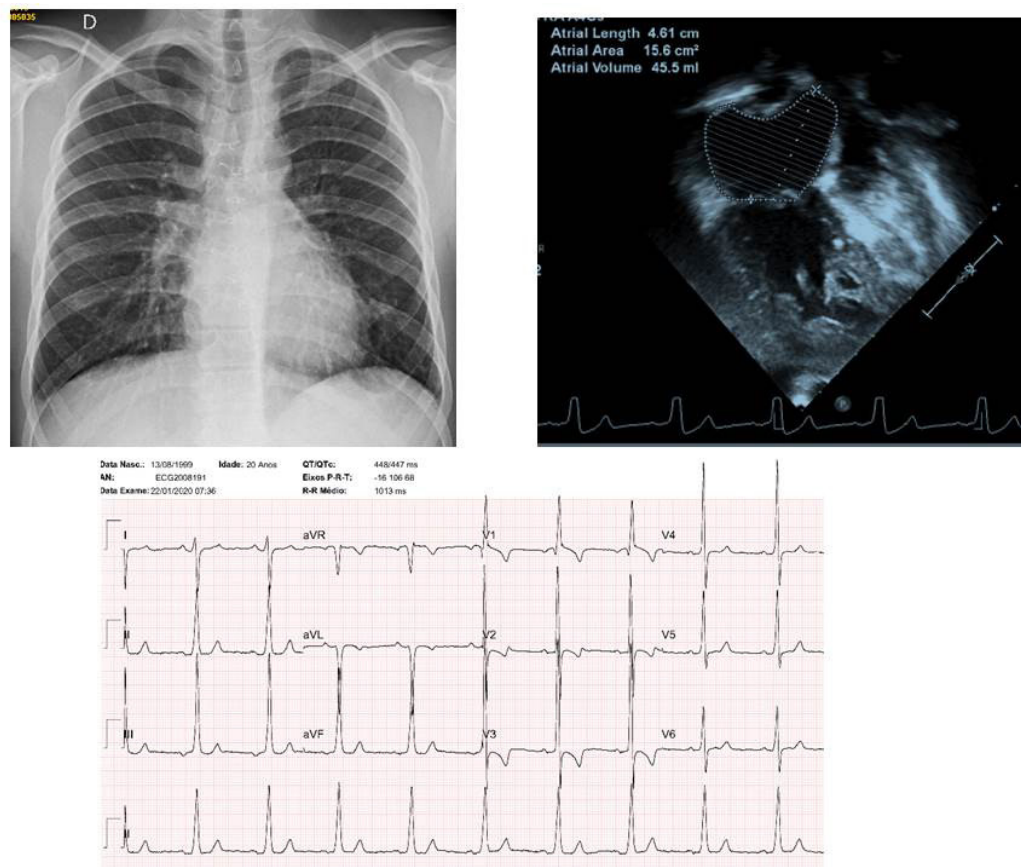


Figure 1 – Electrocardiogram highlights the marked overload of the right ventricle; chest X-ray shows normal cardiac area and pulmonary vascular network with slight enlargement of the aorta; and the 4-chamber echocardiogram showed marked hypoplasia of the left ventricular cavity, being normal the systemic right ventricle.

the patient in question. However, only 40 to 50% of these patients have the chance of undergoing the Fontan palliative operation.^{2,5} Thus, the morbidity of patients with hypoplasia of the left heart remains high, indicating that more care should be taken between the operative phases.² Evolution after the Fontan operation obeys the requirements of the functional palliative technique with problems related to greater venous congestion, lower systemic cardiac output but, in the preservation of good ventricular function, it turns out to be more favorable, as observed. Under observation, of 1052 patients with single ventricular type heart defects, operated on at the Mayo Clinic between 1973 and 2012, survival after 10, 20 and 30 years after the Fontan operation was 74%, 61% and 43%. Evolutionary problems refer to high left atrial pressure (>13 mm Hg), prolonged pleural drainage (>21 days), arrhythmias, renal failure, protein-losing enteropathy, cardiac dysfunction and surgical valve interventions.

Without a doubt, the challenges remain, but with noticeable improvements since Norwood changed the natural history of the left heart hypoplasia syndrome defects in 1982.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Atik E.

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References

1. Atik E, Moreira VM. Hipoplasia do coração esquerdo. Atik E, Moreira VM, editors. *Imagens e correlações em cardiologia pediátrica*. São Paulo: Roca; 2011. p. 336-42.
2. Roeleveld PP, Axelrod DM, Klugman D, Jones MB, Chanani NK, Rossano JW, et al. Hypoplastic left heart syndrome: from fetus to fontan. *Cardiol Young*. 2018;28(11):1275-88. doi: 10.1017/S104795111800135X.
3. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, et al. 40-year follow-up after the fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol*. 2015;66(15):1700-10. doi: 10.1016/j.jacc.2015.07.065.
4. Khairy P, Fernandes SM, Mayer JEJ, Triedman JK, Walsh EP, Lock JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with fontan surgery. *Circulation*. 2008;117(1):85-92. doi: 10.1161/CIRCULATIONAHA.107.738559.
5. Bautista-Hernandez V, Avila-Alvarez A, Marx GR, Del Nido PJ. Current surgical options and outcomes for newborns with hypoplastic left heart syndrome. *An Pediatr*. 2019;91(5):352.e1-352.e9. doi: 10.1016/j.anpedi.2019.09.007.



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Theophylline for Attenuating Ticagrelor-Related Dyspnea

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Introduction

Dyspnea is one of the most frequent adverse reaction of ticagrelor, leading to premature discontinuation in 15-20% of the patients.¹ The mechanism is unclear, but it is thought to be related to increased tissue adenosine concentrations or to the direct reversible inhibition of P2Y₁₂ receptors on sensory neurons.²

Theophylline has been used as a bronchodilator since 1922, and its effects seem to be partly mediated through nonselective adenosine receptors blockade.³

The authors hypothesized that theophylline could attenuate the dyspnea caused by ticagrelor administration and reported their initial clinical experience with 10 patients.

Methods

Inclusion criteria were: 1) Presence of moderate or severe dyspnea after at least one dose of ticagrelor, not explained by cardiac or pulmonary causes; 2) Follow-up in a Cardiac Intensive Care unit; 3) Patient's formal agreement to the compassionate use of theophylline.

A single dose of 200-mg theophylline was administered, diluted in 100 ml-0.9% saline infusion over 20 min. All patients had a thorough clinical exam, electrocardiogram and echocardiogram performed before drug administration, and continuous monitoring of O₂ saturation, electrocardiogram, and noninvasive blood pressure. Electrocardiogram and echocardiograms were performed at bedside, with the sole intention of excluding alternative causes of dyspnea such as ongoing ischemia, heart failure, or bronchospasm.

Assessment of symptoms and physical exam was performed before and immediately after infusion. Each patient provided specific verbal authorization for compassionate use of theophylline in this situation. All patients granted consent for publication of anonymous data.

Results

From January/2017 to December/2019, 1,437 patients were admitted to the hospital with acute coronary syndromes, of whom 29 (3.1%) had moderate to severe dyspnea during admission

presumably related to ticagrelor administration. A total of 10 patients were empirically treated with 200-mg IV theophylline because their symptoms were deemed to be sufficiently important to require therapeutic maneuvers (Table 1). The median age was 75 years (IQ range 61-80 years), six patients had previous myocardial infarctions, five patients had type 2 diabetes mellitus, four patients were smokers, and none had previous pulmonary obstructive chronic disease. In six patients, symptoms begun after orally receiving the 180-mg bolus dose, including two patients with previous administration of clopidogrel.

After theophylline administration, all patients reported attenuation of the shortness of breath, although two patients only reported a partial relief. In one of the patients with partial response, a second 200-mg bolus dose was administered one hour later with complete resolution of symptoms. All patients were treated with a different P2Y₁₂ inhibitor after the event. One patient (patient #3) further received 200-mg bid theophylline treatment, orally, along with ticagrelor, before the authors decided to switch to clopidogrel prior to discharge. No patient presented stent thrombosis or other thrombotic events during admission. An 82-year-old patient, with non-ST elevation myocardial infarction conservatively treated and discharged with clopidogrel, was readmitted after 20 days with a repeated myocardial infarction and cardiogenic shock and died despite successful revascularization.

Discussion

For the first time, the favorable effects of theophylline are reported in the resolution of ticagrelor-related dyspnea in patients with acute coronary syndromes. Although this initial clinical experience was strikingly positive, these findings should be considered exploratory due to the lack of a control group.

Although mechanisms behind dyspnea alleviation may be multifactorial, these preliminary findings represent a strong case for the adenosine hypothesis of dyspnea caused by reversible P2Y₁₂ inhibition (Figure 1). In an elegant double-blind, placebo-controlled study, Wittfeldt et al.⁵ showed that a 5-mg/kg dose of theophylline attenuated the effects of an incremental adenosine infusion of 40 volunteers treated with 180-mg ticagrelor on coronary blood flow velocity and dyspnea symptoms, measured by the Borg scale. The present results extend these findings to a population of patients with acute coronary syndromes and using a smaller dose of theophylline.

Theophylline is a xanthine derivative that has been commonly used in the treatment of asthma for several decades, although its precise molecular mechanism of action is uncertain.^{3,6} Among the proposed therapeutical mechanisms, it has been shown that theophylline promotes nonselective phosphodiesterase inhibition, antagonism of adenosine receptors and anti-inflammatory effects, such as interleukin-10 release, prevention of translocation of nuclear factor kappa B (NF- κ B) transcription factor, and activation of histone deacetylases, which enhances

Keywords

Ticagrelor; Theophylline; Acute Coronary Syndrome.

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Table 1 – Patients' characteristics. All patients received ticagrelor as the initial antiplatelet agent with an oral bolus dose of 180 mg, except patients #8 and #9, who received clopidogrel first and then switched to ticagrelor 90 mg bid

Patient	Age (years)	Weight (kg)	Sex	Acute Coronary Syndrome	Baseline O ₂ Saturation (%)	Initial P2Y ₁₂ inhibitor	Dyspnea onset (hours after 180 mg bolus dose)	Attenuation of dyspnea	Discharge P2Y ₁₂ inhibitor
1	56	75	Male	STEMI	98	Ticagrelor	48	Complete	Prasugrel
2	80	54	Male	STEMI	99	Ticagrelor	36	Partial	Clopidogrel
3	76	80	Female	STEMI	93	Ticagrelor	2	Complete	Clopidogrel
4	57	83	Male	STEMI	99	Ticagrelor	40	Complete	Prasugrel
5	78	68	Male	NSTEMI	97	Ticagrelor	2	Complete	Clopidogrel
6	48	85	Male	STEMI	95	Ticagrelor	12	Partial	Clopidogrel
7	71	100	Male	NSTEMI	97	Ticagrelor	2	Complete	Prasugrel
8	82	75	Male	STEMI	95	Clopidogrel	2	Complete	Clopidogrel
9	73	68	Female	NSTEMI	98	Clopidogrel	3	Complete	Clopidogrel
10	83	72	Male	NSTEMI	97	Ticagrelor	1	Complete	Clopidogrel

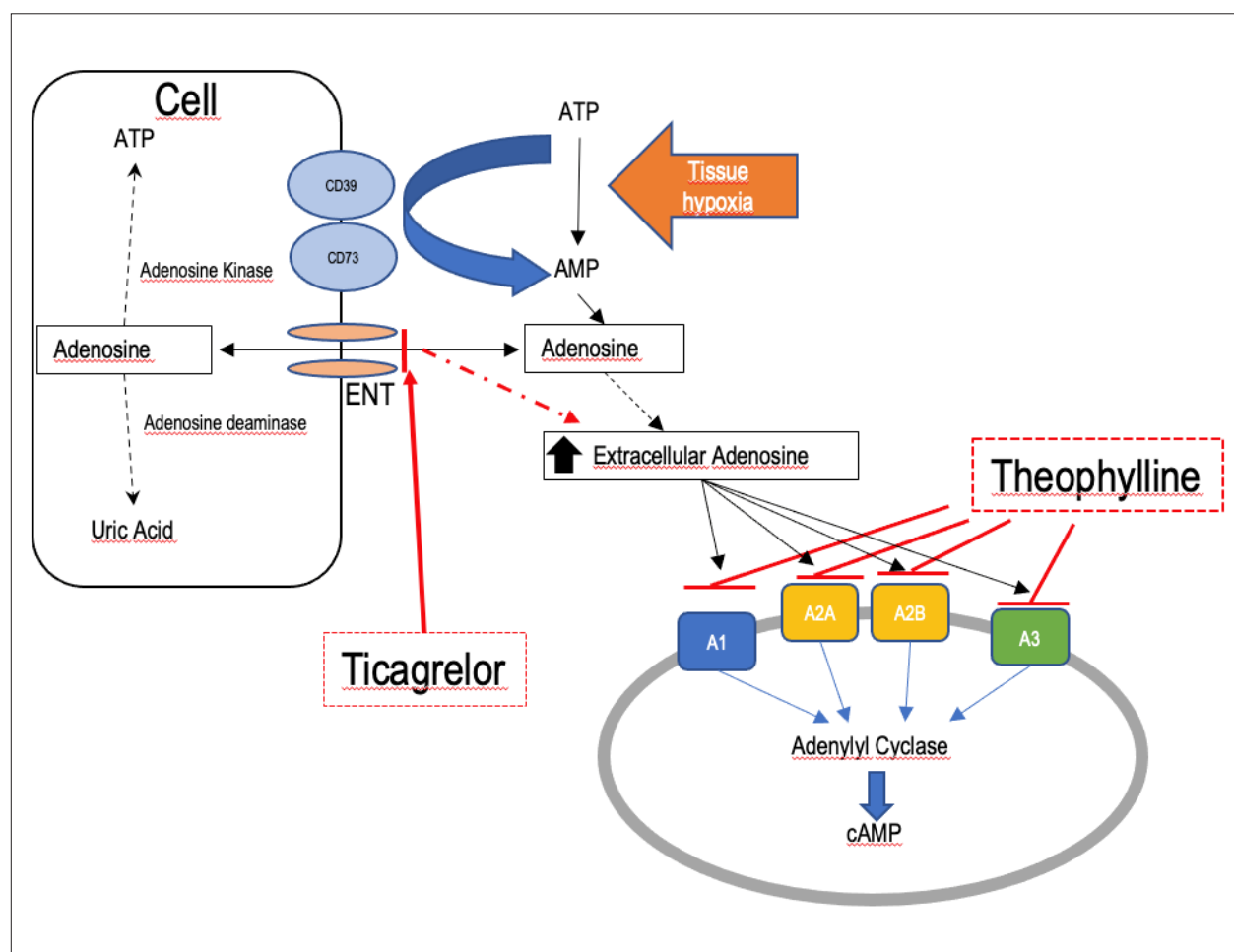


Figure 1 - Tissue damage and hypoxia stimulates adenosine formation in extracellular space by degradation of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) through the action of nucleotidases such as CD39 and CD73. Rapid degradation of adenosine intracellularly occurs by adenosine kinase and adenosine deaminase, after being taken up through sodium-independent nucleoside transporters (equilibrative nucleoside transporter (ENT)). As ticagrelor inhibits the ENT membrane, adenosine accumulates in the extracellular space, leading to adenosine-mediated effects, such as stimulation of lung neuroreceptors, probably through binding to adenosine membrane receptors (A1, A2A, A2B, and A3), and later to interaction with adenylyl cyclase and formation of cyclic adenosine monophosphate (cAMP). Theophylline blockade of adenosine receptors probably explains inhibition of adenosine-mediated effects.⁴

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the anti-inflammatory effect of corticosteroids. The authors believe that the attenuation of ticagrelor-induced dyspnea occurs through nonselective blockade of adenosine membrane receptors, preventing intracellular formation of cyclic adenosine monophosphate (Figure 1) in the interstitial lung tissue, considering that there is no objective bronchospasm or local inflammatory activity in this clinical setting.

There were no adverse effects from the theophylline administration, but the selected doses were smaller than those recommended for acute asthma (5 mg/kg). There are no reports of a prothrombotic response to theophylline. In fact, some studies suggest enhanced platelet inhibition with this drug.⁷

Although the present findings require confirmation in clinical trials, a fixed combination of theophylline and ticagrelor could represent an important step for avoiding frequent discontinuations of ticagrelor treatment.

Author Contributions

Conception and design of the research, Acquisition of data, Statistical analysis e Writing of the manuscript: Sanmartin-

Fernandez M; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Sanmartin-Fernandez M, Zamorano JL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Arora S, Shemisa K, Vaduganathan M, Qamar A, Gupta A, Garg SK, et al. Premature ticagrelor discontinuation in secondary prevention of atherosclerotic CVD: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(19):2454-64. doi: 10.1016/j.jacc.2019.03.470.
2. Unverdorben M, Parodi G, Pistolesi M, Storey RF. Dyspnea related to reversibly-binding P2Y12 inhibitors: a review of the pathophysiology, clinical presentation and diagnostics. *Int J Cardiol*. 2016;202:167-73. doi: 10.1016/j.ijcard.2015.08.162.
3. Biaggioni I, Paul S, Puckett A, Arzubaga C. Caffeine and theophylline as adenosine receptor antagonists in humans. *J Pharmacol Exp Ther*. 1991;258(2):588-93.
4. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol*. 2014;63(23):2503-9. doi: 10.1016/j.jacc.2014.03.031.
5. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. *J Am Coll Cardiol*. 2013;61(7):723-7. doi: 10.1016/j.jacc.2012.11.032.
6. Barnes PJ. Theophylline. *Pharmaceuticals*. 2010;3(3):725-47. doi: 10.3390/ph3030725.
7. Hardwick RA, Hellums JD, Peterson DM, Moake JL, Olson JD. The effect of PGI2 and theophylline on the response of platelets subjected to shear stress. *Blood*. 1981;58(4):678-81.



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Is It Time for a New Standard Therapy for Heart Failure with Reduced Ejection Fraction?

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Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) leads to mortality and impairment in one's quality of life, and causes a major impact on the healthcare system. Despite trials showing the benefits of angiotensin receptor–neprilysin inhibitor (ARNI) over angiotensin-converting enzyme inhibitors (ACEi), and the superiority of sodium-glucose cotransporter-2 inhibitors (SGLT2i) over placebos, current guidelines still recommend ACEi, mineralocorticoid receptor antagonists (MRA), and beta-blockers as first-line therapy in HFrEF.¹⁻³ In this letter, we will discuss the potential benefits and risks of adopting ARNI and SGLT2i as first-line therapies in HFrEF.

What are the potential benefits and risks of adopting ARNI as a first-line therapy in HFrEF?

In the PARADIGM-HF trial, HFrEF patients treated with ARNI had a significant reduction in the primary outcome of cardiovascular mortality or HF hospitalization (21.8% vs. 26.5%; number needed to treat (NNT) = 21) compared with enalapril.¹ Moreover, ARNI significantly reduced the all-cause mortality (17.0% vs. 19.8%; NNT = 36).¹ A sub-analysis of the PARADIGM-HF trial has also shown that ARNI significantly improved one's quality of life compared with enalapril.⁴ Regarding safety, sacubitril/valsartan led to higher proportions of hypotension and non-serious angioedema, but lower proportions of renal impairment, hyperkalemia, and cough compared with enalapril.¹ The benefits of ARNI over enalapril were further confirmed in patients with HFrEF hospitalized for acute decompensated HF in the PIONEER-HF trial, which showed a significant reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients treated with ARNI since week one.⁵ A reduction in a composite of HF rehospitalization or cardiovascular death was also found to be significant in patients treated with ARNI in an exploratory analysis of the PIONEER-HF trial.⁶ Finally, a sub-analysis of the PIONEER trial showed that ARNI was well-tolerated and

superior to enalapril in improving clinical outcomes, regardless of ACE inhibitor, ARB treatment, or previous HF history.⁷

Real world data from the Change the Management of Patients with Heart Failure registry (CHAMP-HF) has also shown an association between ARNI therapy and early improvements in health status compared to patients not treated with ARNI.⁸ In the EVALUATE-HF trial, which aimed to access if ARNI compared with enalapril improved central aortic stiffness and cardiac remodeling, ARNI led to a significant reduction in secondary echocardiographic end-points, suggesting that ARNI may induce reverse cardiac remodeling.⁹

Data from the Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION) study, showed that first-line initiation of ARNI in *de novo* HFrEF did not change the adoption rate of guideline-directed HF therapies.¹⁰ Moreover, in this study, patients with *de novo* HFrEF that initiated ARNI had fewer side-effects and lower rates of treatment discontinuations compared to patients with prior HFrEF.¹⁰ Moreover, in *de novo* HFrEF, ARNI led to a faster and greater decrease in cardiac biomarkers, such as NT-proBNP and high-sensitivity troponin-T, and lower rates of HF and all-cause rehospitalization when compared to patients with prior HFrEF.¹⁰ Finally, a previous study showed that ARNI was cost-effective when compared with enalapril in HFrEF from the healthcare perspective of the United Kingdom, Denmark, and Colombia.¹¹

As reviewed in this letter, previous evidence supports that ARNI improves overall quality of life and reduces the risk of cardiovascular mortality, HF hospitalization, and NT-proBNP in patients with HFrEF. Furthermore, ARNI leads to an improvement in health status and to reverse cardiac remodeling, and does not change the adoption of guideline-directed therapies in HFrEF. However, some authors criticize some aspects of the PARADIGM-HF trial, including its target dose of enalapril (10 mg twice daily),⁴ whereas the European Society of Cardiology and the Brazilian Society of Cardiology HF guidelines support a maximum tolerated target dose. Nonetheless, the dose targeted by the trial followed the American College of Cardiology guidelines, with patients having achieved a good level of median dose, similar to previous randomized trials. Another issue is that the PARADIGM-HF trial investigated the effectiveness of an ARNI dose of 100-200 mg, while the effectiveness of lower doses, such as 50 mg, which may be the maximum tolerated dose for some patients, has yet to be tested.⁴

Although future studies are needed to bring a strong conclusion for the adoption of ARNI as a first-line therapy in HFrEF, in our view, the benefits mentioned above make a strong case for the adoption of sacubitril-valsartan as a first-line

Keywords

Heart Failure; Stroke Volume; Drug Therapy; Mortality; Hospitalization; Ventricular Modeling; Neprilysin; Angiotensins

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therapy in HFrEF instead of ACEi, in the absence of a history of angioedema or significant hypotension.

What are the potential benefits and risks of adopting SGLT2i as a first-line therapy in HFrEF?

The DAPA-HF trial compared dapagliflozin, an SGLT2i, with a placebo in class II, III, and IV HFrEF patients with or without diabetes.² In this study, patients treated with dapagliflozin had a 26% reduction in the risk of cardiovascular death or worsening HF, compared with standard care alone, with an NNT = 21.² An exploratory analysis of the DAPA-HF has also confirmed the improvement of primary outcome, regardless of the patient's status of diabetes.¹² Regarding safety, the frequency of adverse events was similar between the dapagliflozin and placebo group.³ Because of the diuretic action of SGLT2i, concerns were raised about whether these drugs could be safely used in HFrEF patients treated with loop diuretics and MRA.¹³ However, a recently published sub-analysis of the DAPA-HF trial showed that symptom improvement and treatment toleration did not differ across subgroups with different diuretic usage.¹³ Further studies also investigated if the benefit of dapagliflozin in primary outcomes was related to background HF therapy. However, a previous study showed that in the DAPA-HF trial, dapagliflozin reduced the primary outcome regardless of background therapy.¹⁴ Moreover, Solomon et al.¹⁵ showed that the effectiveness and safety of dapagliflozin were similar in patients who were taking sacubitril/valsartan with patients who were taking the placebo in the DAPA-HF trial, which suggests that the combination of these agents could further reduce the occurrence of mortality or hospitalization in patients with HFrEF.¹⁵ Furthermore, a meta-analysis of Turgeon et al.,¹⁶ which included two trials that analyzed over 4,000 patients with HFrEF, showed that dapagliflozin significantly improved the patient's quality of life when compared with the placebo.¹⁶

Recently, another SGLT2i, empagliflozin, met its primary endpoint in the EMPEROR-Reduced trial.³ In this trial, HFrEF patients treated with empagliflozin had a 25% reduction in the risk of cardiovascular death or hospitalization for HF and a 30% reduction in the risk of hospitalization for HF.³ Furthermore, the empagliflozin-treated group had a slower rate of decline in the glomerular filtration rate.³ Regarding safety, uncomplicated genital infection was more common in patients treated with empagliflozin.³ Data from the EMPATROPISM trial has also shown that empagliflozin significantly improves LV volumes, LV mass, LV systolic function, functional capacity, and quality of life when compared with the placebo in non-diabetic patients with HFrEF.¹⁷ A meta-analysis, that analyzed data from DAPA-HF and EMPEROR-Reduced trials, showed that dapagliflozin and empagliflozin reduced all-cause and cardiovascular death, and improved renal outcomes, further confirming the important role of SGLT2i in HFrEF.¹⁸ In addition, this study showed that the benefits of SGLT2i in HFrEF were independent of the patient's status of diabetes, age, sex, or ARNI therapy.¹⁸ Regarding cost-effectiveness, dapagliflozin proved to be cost-effective for patients with HFrEF based on the UK, German, and Spanish healthcare perspective.¹⁹

Although the SGLT2i reduce the risk of cardiovascular death and worsening HF, and are well tolerated, to date, there are still no recommendations of its use in HF guidelines. In our view, SGLT2i can be safely instituted as a new pillar of first-line therapy in HFrEF patients.

A new standard therapy in HFrEF

ARNI and SGLT2i are well-tolerated and cost-effective drugs that reduce the risk of mortality and hospitalization, improve the quality of life, and may lead to reverse cardiac remodeling when compared to conventional therapy. To illustrate the importance of these therapies, a cross-trial study compared the effects of ARNI, beta-blocker, MRA, and SGLT2i (called comprehensive therapy) with ACEi or ARB and beta-blocker only (called conventional therapy).²⁰ In this study, patients treated with comprehensive therapy were 62% less likely to experience cardiovascular death or HF hospitalization.²⁰ Furthermore, comprehensive therapy was superior in reducing cardiovascular death, HF hospitalization, and all-cause mortality alone.²⁰ This study also estimated that comprehensive therapy provided additional years free from cardiovascular death or first hospitalization for HF and extended survival.²⁰ A proposal of a new first-line therapy for patients with HFrEF is illustrated in Figure 1.

Conclusion

Current HF guidelines still do not recommend the first-line therapy proposal discussed in this paper. Although the cost of new drugs is always an important issue in prescriptions, mainly in less developed and developing countries, such as Brazil, in our view, compelling evidence reviewed in this paper supports the recommendation of ARNI and SGLT2i as first-line therapies in HFrEF. Hence, future HF guidelines should endorse a combination of ARNI, beta-blocker, MRA, and SGLT2i as the new standard first-line therapy for HFrEF in patients without contraindications to these medications. To ensure the adoption of these new therapies, physicians can present their benefits and cost-effectiveness to patients. Beyond that, public health agencies and private insurance plans should recognize the cost-effectiveness of these new drugs and develop measures to help their implementation.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Correia ETO, Barbeta LMS, Mesquita ET; Acquisition of data and Analysis and interpretation of the data: Correia ETO, Barbeta LMS.

Potential Conflict of Interest

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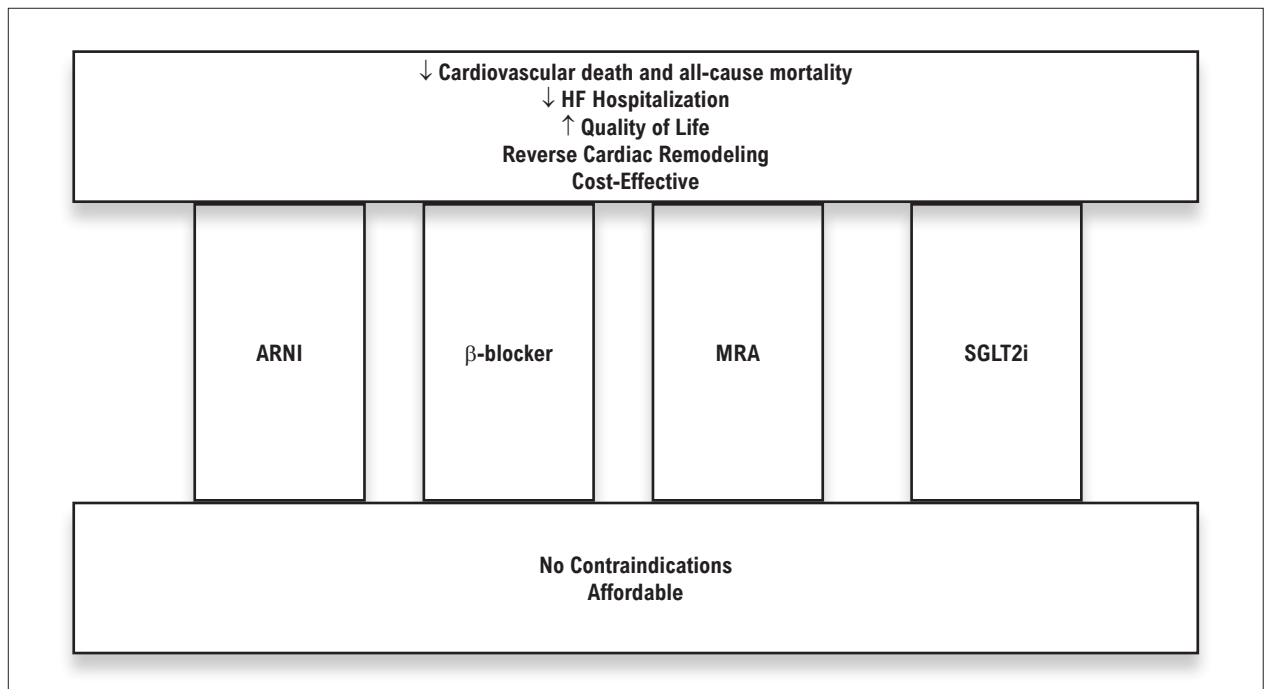


Figure 1 – Proposal of a new first-line therapy for patients with Heart Failure with Reduced Ejection Fraction. The bottom bar illustrates the conditions needed to institute a combination of angiotensin receptor–neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors. The upper bar illustrates the benefits and cost-effectiveness of this combination. ARNI - angiotensin receptor–neprilysin inhibitor; HF: heart failure; MRA: mineralocorticoid receptor antagonists; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

- McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *New England Journal of Medicine*. 2014 Sep 11;371(11):993–1004.
- McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381: 1995–2008.
- Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* [Internet]. [cited 2020 Aug 03]. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2022190>
- Chandra A, Lewis EF, Claggett BL, Desai AS, Packer M, Zile MR, et al. Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial. *JAMA Cardiol*. 2018 01;3(6):498–505.
- Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. *New England Journal of Medicine*. 2019 Feb 7;380(6):539–48.
- Morrow David A., Velazquez Eric J., DeVore Adam D., Desai Akshay S., Duffy Carol I., Ambrosy Andrew P., et al. Clinical Outcomes in Patients With Acute Decompensated Heart Failure Randomly Assigned to Sacubitril/Valsartan or Enalapril in the PIONEER-HF Trial. *Circulation*. 2019 May 7;139(19):2285–8.
- Ambrosy AP, Braunwald E, Morrow DA, DeVore AD, McCague K, Meng X, et al. Angiotensin Receptor–Neprilysin Inhibition Based on History of Heart Failure and Use of Renin–Angiotensin System Antagonists. *J Am Coll Cardiol*. 2020 Sep 1;76(9):1034–48.
- Khariton Y, Fonarow GC, Arnold SV, Hellkamp A, Nassif ME, Sharma PP, et al. Association Between Sacubitril/Valsartan Initiation and Health Status Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail*. 2019;7(11):933–41.
- Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, et al. Effect of Sacubitril–Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA*. 2019 Sep 17;322(11):1077–84.
- Senni M, Wachter R, Witte KK, Straburzynska-Migaj E, Belohlavek J, Fonseca C, et al. Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (de novo) heart failure: a subgroup analysis of the TRANSITION study. *European Journal of Heart Failure*. 2020;22(2):303–12.
- McMurray JJV, Trueman D, Hancock E, Cowie MR, Briggs A, Taylor M, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. *Heart*. 2018 Jun 1;104(12):1006–13.

Research Letter

12. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. *JAMA*. 2020 Mar 27; 323(14):1353-68.
13. Jackson Alice M, Dewan Pooja, Anand Inder S, Belohlávek Jan, Bengtsson Olof, de Boer Rudolf A., et al. Dapagliflozin and Diuretic Use in Patients with Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation* [Internet]. [cited 2020 Aug 4]. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047077>
14. Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J*. 2020 Jul 1;41(25):2379-92.
15. Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, et al. Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan: The DAPA-HF Trial. *JACC Heart Fail*. 2020 Oct;8(10):811-8.
16. Turgeon R, Barry A, Ellis U. Impact of SGLT2 inhibitors MPACT of life in patients with heart failure with reduced ejection fraction : a systematic review and meta-analysis. *Canad J Cardiol*. 2020; 1;36(10):S68-9.
17. Santos-Gallego Carlos G, Vargas-Delgado Ariana P, Requena Juan A, Garcia-Ropero A, Mancini Donna, Pinney S, et al. Randomized Trial of Empagliflozin in Non-Diabetic Patients with Heart Failure and Reduced Ejection Fraction. *J am Coll Cardiol*. 2020. [Internet]. [cited 2020 Nov 14];0(0). Available from: <https://www.jacc.org/doi/10.1016/j.jacc.2020.11.008>
18. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials.Abstract. *Lancet* [Internet]. [cited 2020 Sep 3]. Available from: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31824-9/abstract](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31824-9/abstract)
19. McEwan P, Darlington O, McMurray JJV, Jhund PS, Docherty KF, Böhm M, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur J Heart Fail*. [Internet]. [cited 2020 Aug 17]. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.1978>
20. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020 Jul 11;396(10244):121-8.



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Transbaffle Puncture Using Multimodality Imaging and 3-D Mapping with CT Image Integration in a Patient with Atrial Flutter Post-Senning Procedure

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The complex post-surgical anatomy after the Senning procedure presents several challenges for catheter ablation. Transbaffle approach allows access to the pulmonary venous atrium and better catheter manipulation. However, this modified transseptal puncture can be challenging to perform.

The authors present the case of a 29-year-old woman who underwent a Senning procedure for dextro-transposition of the great arteries. The patient had recurrent episodes of atrial flutter despite adequate antiarrhythmic therapy and was referred for catheter ablation.

Since the vast majority of the arrhythmias are related to the pulmonary venous atrium and catheter manipulation through a retrograde approach is difficult, a transbaffle puncture was performed.¹⁻³

Angiography in the systemic Senning baffle was first carried out (Figure 1A). Images from a CT scan were merged with real-time 3-D electroanatomical mapping of the systemic venous atrium (CARTO 3, Biosense Webster) (Figure 2). The transseptal needle was connected to the mapping system, allowing for the visualization of the needle tip (Figure 2). Under transesophageal echocardiography (Figure 3) and fluoroscopy (Figures 1B and 1C), the transbaffle puncture was safely performed.

Activation mapping in the pulmonary venous atrium revealed a counterclockwise activation pattern along the tricuspid valve (Figure 4A). Radiofrequency was delivered on both sides of the cavotricuspid isthmus, terminating the tachycardia with subsequent confirmation of bidirectional block (Figure 4B).

Multimodality imaging and 3-D electroanatomical mapping, together with CT scan provide real-time anatomical landmarks, crucial for an effective and safe transbaffle puncture, increasing the probability of a successful catheter ablation after Senning procedures.

Author Contributions

Conception and design of the research: Palma A, Sousa PA, Silva PV; Acquisition of data and Writing of the manuscript: Palma A; Analysis and interpretation of the data: Palma A, Sousa PA; Critical revision of the manuscript for intellectual content: Sousa PA, Silva PV, Pires A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Keywords

Transseptal Puncture; Senning Surgery; Catheter Ablation; Atrial Flutter; Arterial Switch Operation.

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Image

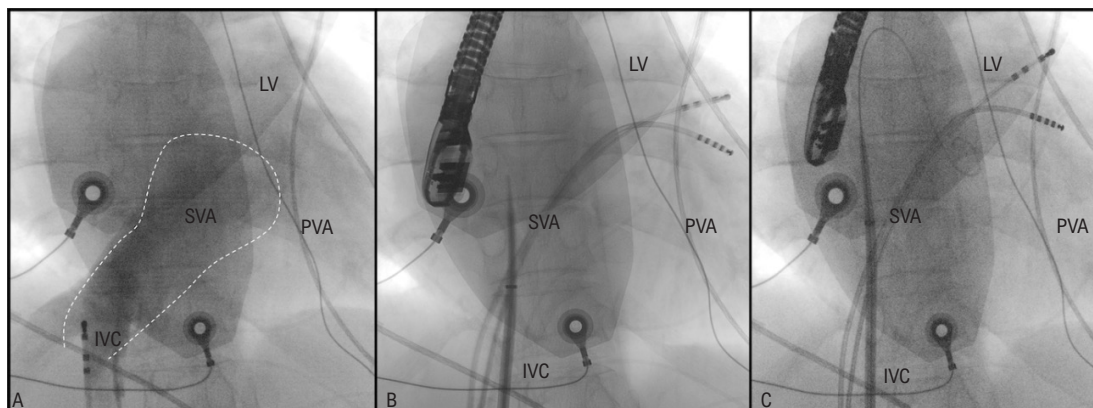


Figure 1 – A: Angiography of the systemic Senning baffle reveals unobstructed flow with no intra-atrial shunting. Dashed line highlights the boundaries of systemic venous atrium (SVA). B and C: Fluoroscopic images, in the postero-anterior view, demonstrating the transbaffle puncture. A transseptal needle (BRK-1, St. Jude Medical, Inc., Minneapolis, Minnesota) is directed superiorly and anteriorly (12 o'clock). Guided by multimodality imaging, the superior portion of the systemic baffle is highlighted and stained with contrast, allowing for visualization of the needle as it crosses into the pulmonary venous atrium (PVA). An 8.5-F sheath (SLO Swartz braided trans-septal guided, St. Jude Medical, Inc.) is advanced into the PVA. IVC: inferior vena cava; LV: left ventricle.

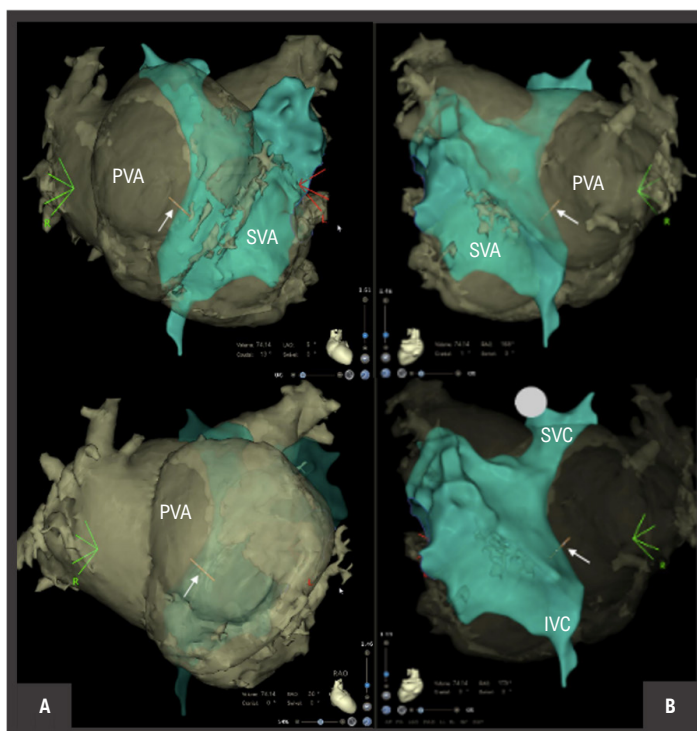


Figure 2 – A 3-D electroanatomical mapping (CARTO 3, Biosense Webster, Inc.) of the systemic (SVA) and pulmonary venous atria (PVA), together with CT scan. Left side (A) shows a posterior view and right side (B) an anterior view. The systemic Senning baffle is highlighted in navy green color. The white arrow indicates the needle through the site of the transbaffle puncture. IVC: inferior vena cava; SVC: superior vena cava.

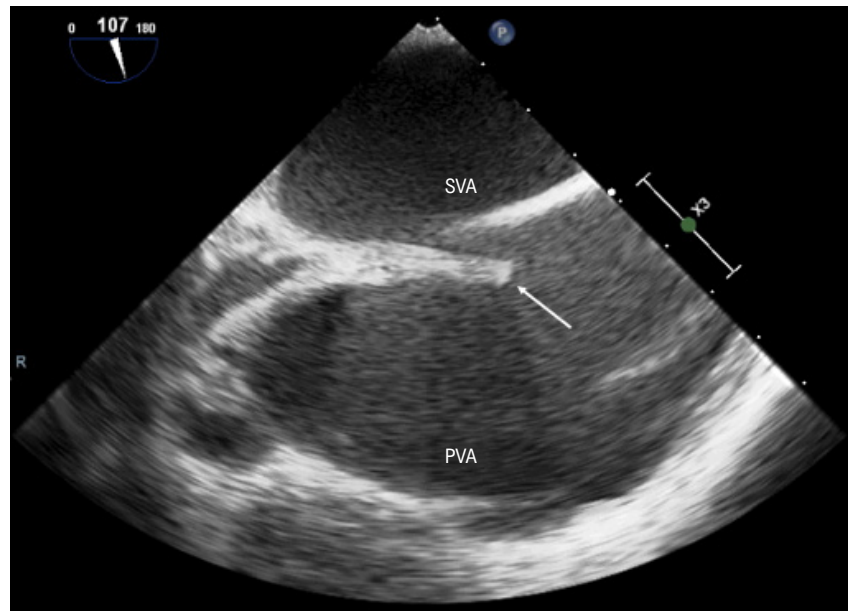


Figure 3 – Transesophageal echocardiography, showing the transbaffle puncture site. The white arrow corresponds to the sheath. PVA: pulmonary venous atrium; SVA: systemic venous atrium.

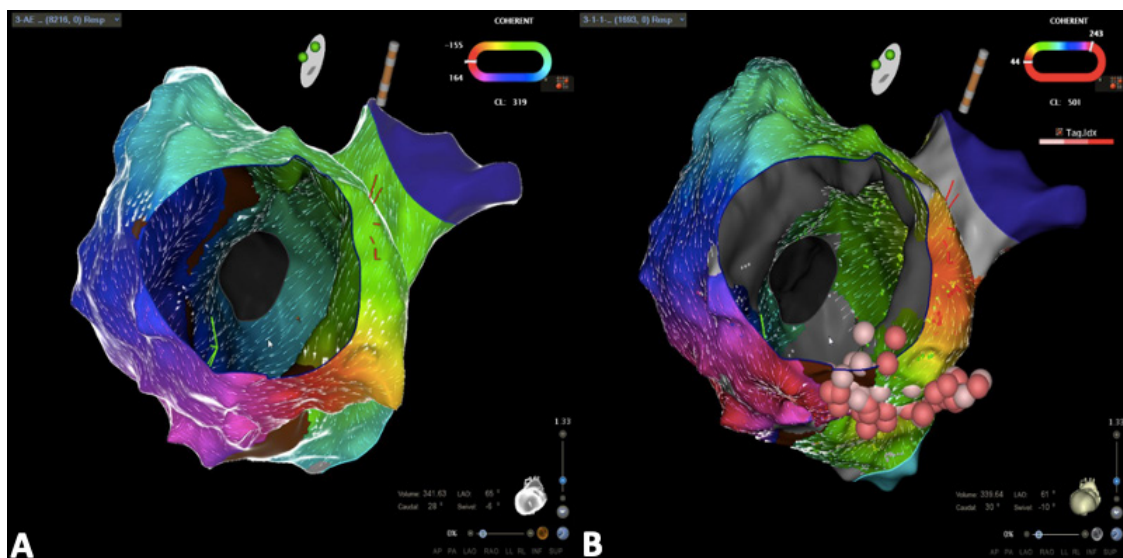


Figure 4 – Maps performed with the Coherent mapping algorithm and the PentaRay catheter (Biosense Webster, Inc). A- Pulmonary venous atrium activation map including 8,216 points and 319ms of the tachycardia cycle length, revealing a counterclockwise motion around the tricuspid annulus (red indicates the areas with earliest local activation time, while orange, yellow, green, blue, and purple indicate progressively delayed activation). B- This high-density activation map, performed while pacing at 500ms from the posterior septum of the systemic venous atrium, was performed after radiofrequency delivery (red dots). It included 1,693 points and confirmed the presence of a bidirectional block, with no activation passage through the cavotricuspid isthmus line.

References

1. Baysa SJ, Olen M. Arrhythmias following the Mustard and Senning operations for dextro-transposition of the great arteries - clinical aspects and catheter ablation. *Card Electrophysiol Clin.* 2017; 9(2):255–71.
2. Laredo M, Waldmann V, Soulat G, Amet D, Maryon E, Iserin L. Transbaffle/transconduit puncture using a simple CARTO-guided approach without echocardiography in patients with congenital heart disease. *J Cardiovasc Electrophysiol* 2020; 31(8):2049-60.
3. Uhm J-S, Kim NK, Kim TH, Joung B, Nan-Pak H, Lee MH. How to perform transconduit and transbaffle puncture in patients who have previously undergone the Fontan or Mustard operation. *Heart Rhythm* 2017; 15(1):145-50.



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Risk Stratification for Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

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We have read with great interest the article by Mattos et al.¹ regarding risk stratification in hypertrophic cardiomyopathy (HCM).¹ The authors compared the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines with the 2014 European Society of Cardiology (ESC) guidelines in Brazilian HCM patients and found low agreement between the two systems. A total of 90 patients with HCM were included and 15 (17%) of them received an implantable cardioverter-defibrillator (ICD). Two (2%) patients experienced appropriate shock, 6 (7%) experienced sudden cardiac death (SCD) and 6 (7%) had non-cardiac death. According to the 2011 ACCF/AHA criteria, 43 (48%) patients received Class IIa recommendation for ICD, 3 (3%) received Class IIb and 44 (49%), Class III. If the ESC HCM risk-SCD score was applied, 12 (14%) patients received Class IIa recommendation for ICD (high risk, $\geq 6\%$), 11 (12%) received Class IIb (intermediate risk, $\geq 4\%$ - $<6\%$) and 67 (74%), Class III (low risk, $<4\%$). The calculated kappa coefficient (0.355, $p=0.0001$) confirmed the low agreement between the two guidelines. In specific, the ESC model left unprotected all patients who experienced SCD or aborted SCD with only 2 of them (25%) being classified as IIb. The 2011 ACCF/AHA criteria recommended ICD (Class IIa) for half of these patients, but an ICD was recommended in much more patients than actually needed. The findings of this study highlight the inadequacy of precise risk stratification strategies and challenge current decision making.

This is not the first time that the accuracy for prediction of SCD in HCM is proven to be underpowered.²⁻⁴ HCM is the most common cause of SCD in young individuals and the burden of such a loss due to wrong non-invasive risk stratification on the one hand, and the unnecessary insertion of a device on the other, urge us to do better.

Our group proposed the additional contribution of programmed ventricular stimulation (PVS) during

a comprehensive electrophysiology study (EPS) in the current risk stratification strategies in order to address their underperformance.⁴ The study population included 203 HCM patients, and like in the study by Mattos et al.,¹ the majority were low-to-intermediate risk for SCD (60% had a single risk factor). An ICD was implanted in 92 (45.3%) patients and the primary endpoint (SCD and/or appropriate ICD therapies) occurred in 20 patients (9.9%). The important finding of the study was that PVS was positive in all but one patient who experienced the primary endpoint, while the 2011 AACF/AHA and the 2014 ESC guidelines misclassified 3 and 9 patients, respectively. In our population, the 2011 ACCF/AHA guidelines would have led to the implantation of 171 ICDs, while the ESC guidelines would have led to the implantation of 53, and PVS alone in 79 patients. The combination of each of these guidelines with the PVS protocol would increase these numbers to 187 and 110 patients, respectively, without missing any primary endpoint. Especially when combined with the ESC guidelines, optimal sensitivity and specificity was achieved in the most cost-effective manner. Another important advantage of EPS turned out to be the proper characterization of syncope mechanism.

The use of PVS in risk stratification of primary prevention for SCD in HCM is Class III in the 2014 European and the 2011 ACCF/AHA guidelines, with the main argument being the risks of such an invasive procedure and its cost, based on unsupported level of evidence C. However, our method was feasible and safe in all cases, while misclassification or inappropriate implantation of ICDs is much more devastating and costly. The underperformance of the ESC and ACCF/AHA guidelines may be due to their inability to express the exact mechanism of arrhythmogenesis in this disease. Cardiac magnetic resonance imaging (CMR) has been a valuable tool in the evaluation of HCM, as the presence of late gadolinium enhancement fibrosis is considered a strong independent predictor for malignant ventricular arrhythmias.⁵ The use of CMR findings in risk stratification has been taken into consideration in the 2020 ACC/AHA guidelines.

In conclusion, proper identification of patients at highest risk for sudden death deserving lifesaving ICD therapy, while controlling overtreatment, remains the holy grail in HCM. Mattos et al.¹ provide additional evidence in the current literature of the inadequacies of risk scores and highlight the need for the introduction of more sensitive and specific criteria. Programmed ventricular stimulation could be a life-saving addition to our armamentarium against sudden cardiac death.

Keywords

Hypertrophic Cardiomyopathy; Sudden Cardiac Death; Defibrillators, Implantable; Prevention and Control; Syncope.

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References

1. Mattos BP, Scolari FL, Garbin HI. Discrepancy between international guidelines on the criteria for primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Arq Bras Cardiol.* 2020;115(2):197-204.
2. Wang J, Zhang Z, Li Y, Xu Y, Wan K, Chen Y. Variable and limited predictive value of the European Society of Cardiology hypertrophic cardiomyopathy sudden-death risk model: a meta-analysis. *Can J Cardiol.* 2019;35(2):1791-9.
3. Liu J, Wu G, Zhang C, Ruan J, Wang D, Zhang M et al. Improvement in sudden cardiac death risk prediction by the enhanced ACC/AHA strategy in Chinese patients with hypertrophic cardiomyopathy. *Heart Rhythm* 2020;17(10):1658-63.
4. Gatzoulis KA, Georgopoulos S, Antoniou CK, Anastasakis A, Dilaveris P, Arsenos P et al. Programmed ventricular stimulation predicts arrhythmic events and survival in hypertrophic cardiomyopathy. *Int. J Cardiol.* 2018;254:175-181.
5. Kariki O, Antoniou CK, Mavrogeni S, Gatzoulis KA. Updating the risk stratification for sudden cardiac death in cardiomyopathies: the evolving role of cardiac magnetic resonance imaging. An approach for the electrophysiologist. *Diagnostics.* 2020;10(8):541.

Reply

Sudden cardiac death (SCD) is considered the most dramatic complication of hypertrophic cardiomyopathy (HCM) with an estimated annual incidence of 0.5–1%.¹ Over the years, the ACC/AHA and the ESC have published consensus guidelines providing different approaches for SCD risk stratification based on independent clinical predictors. Despite the relatively low accuracy of these markers, current strategies are considered to have a reasonable discriminatory power for the recognition of high-risk patients. However, prognostic assessment is challenging in HCM, especially in low to moderate risk patients. SCD may arise in the absence of known risk factors and some approaches show conflicting results in different populations.² Moreover, methodological discrepancies between the North American and the European guidelines may determine discordant levels of recommendation regarding implantable cardioverter defibrillator (ICD) in primary prevention.³ Therefore, risk stratification is still imprecise and requires further investigation.

The 2018 manuscript of Gatzoulis et al.⁴ reevaluates the role of electrophysiological study for prognostic assessment in a low to intermediate risk single-center HCM cohort stratified according to contemporary guidelines. The authors conclude that programmed ventricular stimulation (PVS) combined with current models add sensitivity and negative predictive value to risk stratification.⁴ Results are interesting but need to be confirmed in larger prospective trials. PVS has been downgraded to class III in current guidelines due to the low sensitivity and potential risks. Similarly, fractionation of right ventricle electrograms has been related to SCD but was not assimilated due to the invasive nature of the procedure, which may impact feasibility in some settings.⁵ Electrical instability is transitory in HCM and should be periodically evaluated such as other predictors with dynamic characteristics.^{2,5} The guidelines

recommend the reassessment of SCD risk during follow-up. Clinical and more easily acquired non-invasive approaches favor routine patient evaluation.

In the recent 2020 ACC/AHA guideline, an algorithm was introduced with three novel non-invasive predictors: late gadolinium enhancement fibrosis on cardiac magnetic resonance, left ventricular apical aneurysm and reduced ejection fraction.¹ All of them are directly or indirectly related to the impaired myocardial architecture, mainly replacement fibrosis. There is a trend towards the assimilation of novel and more accurate non-invasive technologies for routine HCM prognostic evaluation projected for the near future. Perhaps, invasive protocols will be gradually neglected to the past based on a cost-effectiveness appraisal. However, PVS may find a role in cases with discordant risk stratification between guidelines regarding ICD recommendation, and may contribute in cases with cardiac-related unexplained syncope.

Finally, the cell disarray evaluation with diffusion tensor cardiac magnetic resonance imaging, genotyping, microRNA profile and other promising biomarkers, as well as the non-invasive assessment of myocardial ischemia, will assure a more reliable assessment of the anatomical and electrical substrate of the disease.^{2,6} Nevertheless, their incorporation into daily clinical practice should take into account locally available resources and will certainly represent another great challenge. A search for new paradigms is in course in HCM and a more precise electrical evaluation of SCD mechanisms is needed and may add or even outperform our current risk-stratification.

Beatriz Piva e Mattos

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References

1. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. *Circulation* 2020;142(25):e533–57. <https://doi.org/10.1161/CIR.0000000000000937>.
2. Pelliccia F, Gersh BJ, Camici PG. Gaps in evidence for risk stratification for sudden cardiac death in hypertrophic cardiomyopathy. *Circulation* 2021;143(2):101–3. <https://doi.org/10.1161/CIRCULATIONAHA.120.051968>.
3. Mattos BP, Scolari FL, Garbin HI. Discrepancy between international guidelines on the criteria for primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Arq Bras Cardiol* 2020;115(2):197–204. <https://doi.org/10.36660/abc.20190161>.
4. Gatzoulis KA, Georgopoulos S, Antoniou CK, Anastakis A, Dilaveris P, Arsenos P, et al. Programmed ventricular stimulation predicts arrhythmic events and survival in hypertrophic cardiomyopathy. *Int J Cardiol* 2018;254:175–81. <https://doi.org/10.1016/j.ijcard.2017.10.033>.
5. O'Mahony C, Elliott PM. Prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Heart* 2014;100(3):254–60. <https://doi.org/10.1136/heartjnl-2012-301996>.
6. Scolari FL, Faganello LS, Garbin HI, Piva e Mattos B, Biolo A. A systematic review of microRNAs in patients with hypertrophic cardiomyopathy. *Int J Cardiol* 2020;327:146–54. <https://doi.org/10.1016/j.ijcard.2020.11.004>.



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Position Statement on Exercise During Pregnancy and the Post-Partum Period – 2021

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Position Statement on Exercise During Pregnancy and the Post-Partum Period – 2021	
The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2020.	
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1. Introduction

The Department of Ergometry, Exercise, Nuclear Cardiology and Cardiovascular Rehabilitation (DERC), through its commission on Health and Diagnosis of Cardiovascular Diseases in Women and in association with the Sports Cardiology Study Group (GECESP) and the Cardiopulmonary Rehabilitation and Metabolic Study Group (GERCPM), has prepared this position paper in accordance with Brazilian Society of Cardiology norms to guide health professionals regarding the prescription of physical exercise during pregnancy and the postpartum period, as well as to strengthen the relationship between specialists in related areas (especially clinicians, cardiologists and obstetricians), including exercise management in pregnant athletes and pregnant women with comorbidities. At the end of this document, details about exercising during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease-2019 (COVID-19) pandemic will be addressed.

Exercise has proven benefits for maternal and fetal health, although women, especially those with comorbidities, often curtail physical activity or remain sedentary during pregnancy due to fear of clinical and obstetric complications. Thus, it should be made clear that exercise has a number of advantages for pregnant women, such as improved functional capacity, reduced fatigue, lower risk of depression, excessive weight gain prevention, and better control of metabolic and cardiovascular disorders (eg, preeclampsia, hypertensive disorders and gestational diabetes mellitus). Preeclampsia, hypertensive disorders and gestational diabetes mellitus are now considered emerging or sex-specific risk factors and are associated with an increased risk of cardiovascular disease (CVD).

Planned consultations with an obstetrician represent a great opportunity to raise awareness about and encourage a healthier lifestyle. In general, women who are active during pregnancy continue to be active in the postpartum period, enjoying the benefits of exercise on long-term cardiovascular health. During the COVID-19 pandemic, sedentary lifestyles have increased, and exercise should be recommended more intensely for pregnant women, including the usual precautions to prevent contamination and the spread of the virus. Pregnant women, especially those with comorbidities, should be referred to specialists to help control risk factors for CVD and receive exercise prescriptions.

This paper will describe the benefits and indications of exercise during pregnancy and the postpartum period, the standardization of clinical assessment prior to exercise prescription, guidance about prescription, criteria for stopping exercise and special conditions during COVID-19 pandemic.

2. Exercise During Pregnancy

2.1. Benefits and Indications

Pregnancy causes hormonal and anatomical changes that lead to lumbar hyperlordosis, loosening of the pelvic ligaments, fluid retention in connective tissue and increased body weight. Consequently, overload in the lumbar spine and low back pain occur in approximately 60% of pregnant women, negatively interfering in sleep quality, physical disposition, work performance, social life, domestic activities, and leisure.¹ There is also a tendency to curtail physical activity during pregnancy, especially in the third trimester, which worsens the anatomical implications of pregnancy. Obstetrics/gynecology and cardiology groups have published recommendations and guidelines about exercise during pregnancy to promote maternal, fetal and neonatal health.²⁻⁴ Exercise reduces fat mass percentage, increases the transfer of oxygen (O₂) and reduces diffusion of carbon dioxide (CO₂) through the placenta, favoring fetal development. Additionally, regular exercise decreases the risk of gestational diabetes mellitus (GDM) by approximately 50%, and the risk of preeclampsia, gestational hypertension, excessive weight gain and depression by up to 40%.⁵⁻⁸

Pregnant women with no disorders should begin exercising as soon as they feel ready, considering that fatigue and the unwanted symptoms of early pregnancy can be disruptive. Supervised exercise is considered safe for the mother and the fetus, with no reported increase in congenital anomalies, premature births or low birth weight.⁹⁻¹² It is important for the patient to be evaluated by an obstetrician and/or cardiologist before beginning an exercise program.

Table 1 shows the recommendations for exercise during pregnancy from a recently published international guideline, describing their evidence levels and quality.³ The strength of the recommendations was determined using the Grading of Recommendations Assessment, Development and Evaluation system¹³, classifying them as strong or weak according to: (1) balance between benefits and hazards, (2) overall evidence quality, (3) outcome importance, (4) resource usage (cost), (5) viability, and (6) acceptability.

Table 1 – Recommendations for exercise during pregnancy, including the quality and strength of the evidence

Indications	Recommendation	Evidence quality
All women without contraindications should be physically active throughout pregnancy (subgroups a, b, c)	Strong	Moderate
Previously inactive women	Strong	Moderate
Women with gestational diabetes	Weak	Low
Pre-gestational BMI ≥ 25 kg/m ²	Strong	Low
Pregnant women should have a minimum of 150 min of moderate-intensity exercise/week, totaling at least 3 days/week	Strong	Moderate
The exercise regimen of pregnant women should include aerobics and resistance exercise of varying intensities, to which stretching and yoga can be added	Strong	High
Daily pelvic floor training (Kegel exercises) to reduce the risk of urinary incontinence	Weak	Low

Adapted from Mottola et al.³ BMI: body mass index

2.2. Cardiovascular and Respiratory Adaptations at Rest and during Exercise

Knowledge of cardiovascular and respiratory adaptations is of great importance for understanding common cardiorespiratory symptoms during pregnancy and for assisting in the differential diagnosis of symptoms related to decompensation of previously stable heart diseases, as well as for managing exercise during this period.

Rest: In pregnancy, blood volume increases secondary to an increase in plasma and red blood cells, leading to hemodilution, especially toward the end of the gestational period. Even at rest, there is an increase in stroke volume and heart rate (HR), causing an increase in cardiac output.^{14,15} There is also a change in cardiac excitability, leading to a greater occurrence of extrasystole. Increased estrogen promotes a decrease in vascular tone, including a decrease in peripheral vascular resistance and a consequent reduction in blood pressure (BP), especially diastolic BP. Although peripheral vascular resistance remains low, fluid variations near delivery cause BP lability and promote lower limb edema during this stage.¹⁶ These changes, which usually produce a greater sensation of palpitation at rest and post-exercise dizziness, should be considered predisposing factors for the decompensation of pre-existing heart diseases.¹⁷

Increasing oxygen levels are an important mechanism of maternal adaptation, since they facilitate transfer to the fetus through the placenta. The increased metabolic demands of the fetus, uterus and maternal organism result in increased oxygen consumption (VO₂), carbon dioxide production and basal metabolic rate, causing hyperventilation, which is also influenced by progesterone. There is a significant increase in minute ventilation (V_E) and tidal volume, with an increase in the partial pressure of O₂ in arterial blood and a decrease in the partial pressure of CO₂. Residual functional capacity decreases, mainly due to displacement of the diaphragm, which increases the sensation of respiratory discomfort, even at rest. These changes explain the “physiological dyspnea” observed in about 60% to 70% of healthy pregnant women,

common around the 30th week, as well as a reduced ability to hold their breath, which limits activities such as diving and anaerobic exercise (eg, sprinting).¹⁸ Physiological adaptations during pregnancy are described in Figure 1.

Exercise: During exercise, systolic volume, cardiac output, HR and V_E also increase, and an increase in aerobic capacity and higher performance can already occur during the first trimester of pregnancy. Although the HR of pregnant women is higher at rest, it does not increase the same way during exercise, and VO₂ does not increase proportionally with higher loads, especially when the effort includes supporting body weight. Thus, functional capacity is limited as pregnancy progresses. The increase in V_E exceeds the increase in VO₂, but the arteriovenous difference in O₂ decreases, which provides greater delivery of oxygen to the fetus. However, during high-intensity exercise the blood flow may be diverted from the uterus to the muscles, which can be harmful to fetal development.^{18,19}

From an anatomical point of view, there is an increase in the left ventricular cavity, although wall thickness is not increased. A study of 105 pregnant women found that 35% developed an increase in left ventricular trabeculation, with 8% fulfilling the criteria for non-compacted myocardium. Similar changes have been reported in other situations where there is an increase in cardiac output, such as in athletes (which is reversible after returning to baseline hemodynamic conditions), and should not be confused with pathological changes.²⁰

2.3. Exercise Assessment

Recommendations for and impediments to exercise (Figure 2) during pregnancy are usually determined by an obstetrician after clinical evaluation and identification of contraindications, such as pre-existing diseases, medical or obstetric complications, etc. (Table 2).³ Women with CVD should also be accompanied by a cardiologist. Currently, the partnership between cardiology and obstetrics/gynecology allows the early identification and modification of risk factors for CVD.²¹

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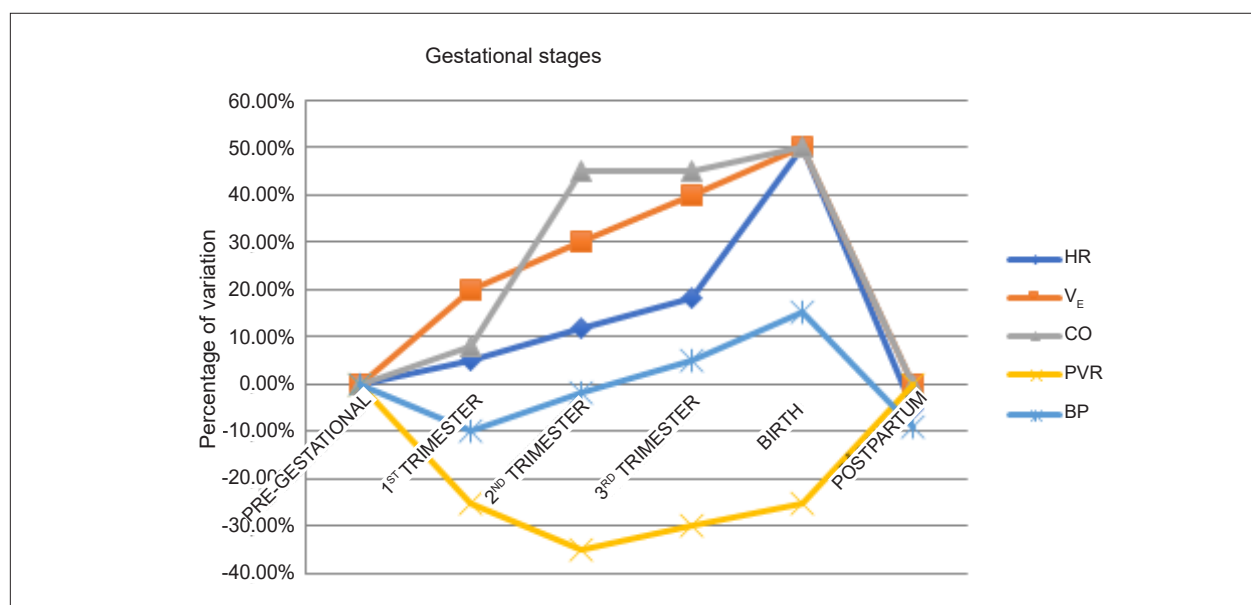


Figure 1 – Physiological changes during pregnancy.
CO: cardiac output; HR: heart rate; BP: blood pressure;
PVR: peripheral vascular resistance; VE: minute ventilation.

The Physical Activity Readiness Medical Examination, developed by the Canadian Society for Exercise Physiology for exercise evaluation and guidance during pregnancy, has been very well accepted by medical societies worldwide for its practicality. It includes the following sections: **a)** a pre-exercise health survey (completed by the patient); **b)** exercise contraindications; **c)** a health assessment (completed by the attending physician) to be used by the exercise physiologist; **d)** instructions for prescribing aerobic and muscle conditioning exercises, thus providing recommendations for a safe and personalized prescription, as well as indicators for exercise cessation.²²

After a thorough anamnesis and clinical examination, exercise can be recommended and supervised during pregnancy. Routine cardiac exams are not indicated for all pregnant women, only those whose clinical condition warrants them. Although electrocardiography (ECG) is not part of the prenatal routine, it should be used when investigating heart disease, monitoring pregnant women with previous CVD and assessing arrhythmias.²³ ECGs are also recommended for patients who have clinical and obstetric contraindications to exercise (Table 2).

Transthoracic ECG is the preferred imaging method when CVD is suspected; it is non-invasive, easy to perform, and widely available.²⁴ It is recommended for patients with previous heart disease, symptoms suggestive of heart disease, or abnormal previous ECG findings.

The one-repetition maximum (1RM) strength test is not recommended for functional assessment in pregnant women. If absolutely necessary for cardiovascular evaluation and after excluding contraindications, the patient can perform a submaximal exercise test (up to 85% of the maximum expected HR), which is considered safe by the Brazilian and

European Societies of Cardiology. However, due to a lack of studies it cannot be recommended for characterizing ischemic heart disease. Performing an ECG during a submaximal exercise test on a bicycle ergometer can improve specificity in the detection of coronary artery disease, (ie, by adding imaging to the findings of the submaximal exercise test). Pharmacological stress with dobutamine during pregnancy is contraindicated.^{24,25}

Regarding exercise prescription, especially for patients at higher cardiovascular risk, a submaximal exercise test is more efficient when associated with expired gases analysis, ie, the cardiopulmonary exercise test (CPET), which determines functional limitations and the ventilatory threshold, providing a more accurate, safe and objective prescription.^{26,27} To evaluate pregnant women, there is no good correlation between training load and HR.²⁸ Pregnant women with heart disease (valve disease or congenital heart disease) undergo the CPET at a submaximal level in specific situations, after excluding absolute contraindications. It is not recommended as a routine exam.

Analyzing the physical fitness of pregnant women can help identify those who have developed or are at risk of developing cardiovascular complications, such as systemic arterial hypertension or preeclampsia. The 6-minute walk test (6MWT) is a validated assessment of cardiorespiratory reserve in high-risk adults and non-pregnant women (for perioperative evaluation or chronic pathologies). Although it is submaximal, safe, viable and applicable in pregnant women at term, its use is not widespread. Since 6MWT reference ranges have been established for healthy pregnant women, individual assessment of functional capacity is possible, which can help personalize exercise programs.^{29,30} The 6MWT is recommended for the cardiorespiratory assessment of pregnant women.

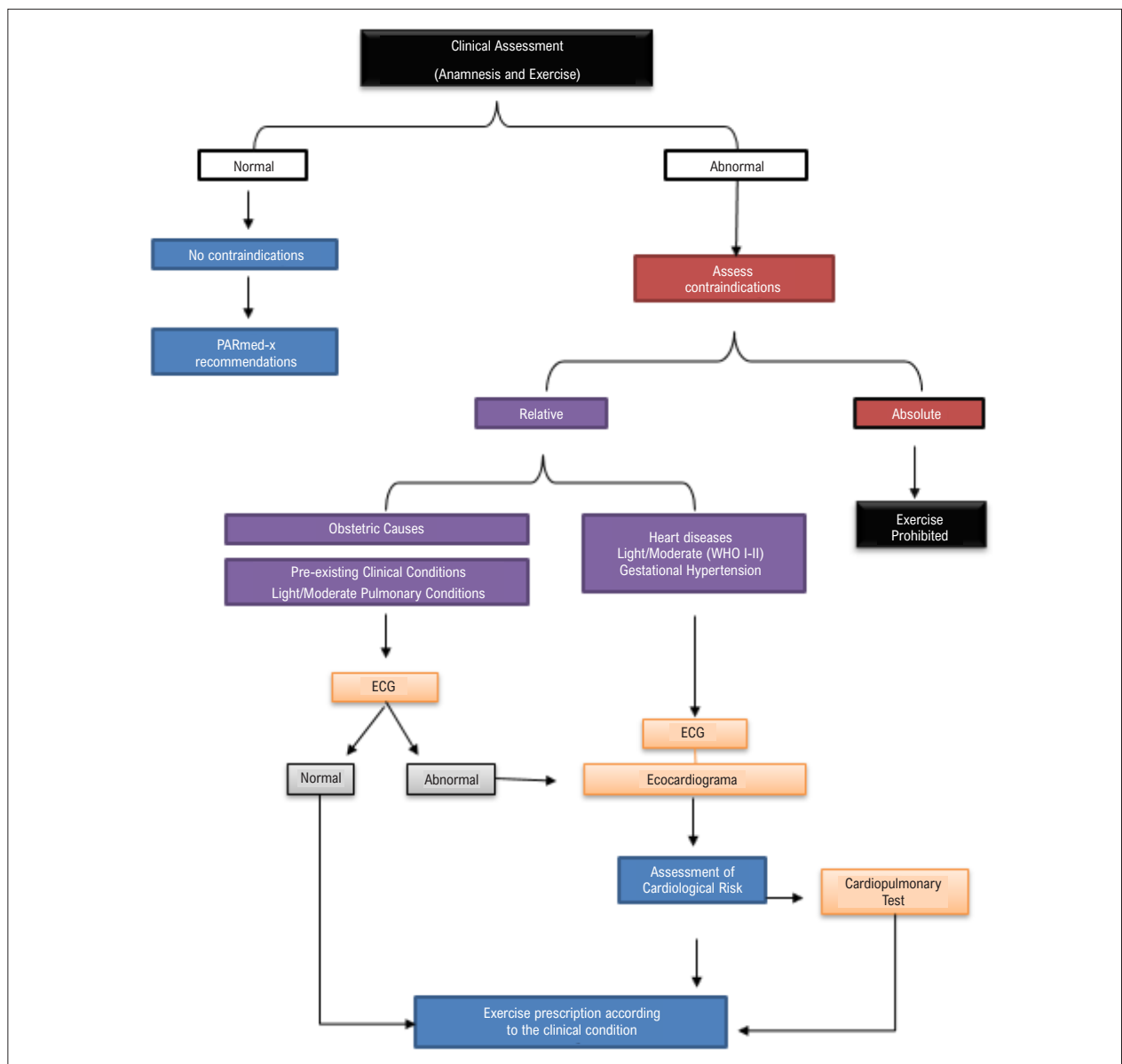


Figure 2 – Exercise assessment for pregnant women.
ECG: electrocardiogram; WHO: World Health Organization. Clinical Assessment (Anamnesis and Exercise)

Therefore, when there are pre-existing diseases and clinical or obstetric contraindications related to exercise, more specific cardiological examinations are required before exercising during pregnancy.

2.3.1. Risk Stratification for Pregnant Women with Heart Disease

Patients with CVD should be stratified for exercise risk. The risk of complications in pregnancy depends on the underlying cardiac diagnosis, but an association of other comorbidities should also be considered. Therefore, risk estimates must be individualized.

Functional capacity and the clinical stability of heart disease are important factors when analyzing the risk of maternal complications, although it is often difficult to distinguish physiological signs and symptoms during pregnancy from those secondary to decompensated heart disease, such as edema, dyspnea, palpitation and dizziness. However, complaints such as palpitations, worsening functional capacity, nocturnal cough, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, precordial pain on exertion, or syncope should be followed up.²⁴

In pregnant women with heart disease, a more detailed approach with specific exams is required, such as oxygen saturation, blood biochemistry (natriuretic peptide levels), echocardiogram

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Table 2 – Contraindications for physical activity during pregnancy

OBSTETRIC CAUSES	
ABSOLUTE	RELATIVE
Membrane rupture	History of premature birth
Premature labor	Recurrent loss of pregnancy
Placenta previa after 28 weeks of gestation	Twin pregnancy >28 weeks
Multiple pregnancy (triplets or higher-order)	
Unexplained persistent vaginal bleeding	
Cervical weakness	
Intrauterine growth restriction	
CLINICAL CAUSES	
ABSOLUTE	RELATIVE
Chronic arterial hypertension (uncontrolled)/ preeclampsia	Gestational hypertension
Severe cardiovascular disease (WHO III-IV)	Mild/moderate cardiovascular disease (WHO I-II)
Restrictive lung disease	Mild/moderate lung disease
Type I diabetes mellitus, thyroid disease (uncontrolled)	Extreme obesity, malnutrition or eating disorder Symptomatic anemia

WHO: World Health Organization.

(ventricular function, valve involvement, intrapulmonary pressure and aortic diameter), an exercise test or submaximal CPET (exercise capacity) and Holter monitoring (arrhythmias).²⁵

The risk of heart disease during pregnancy can be stratified according to World Health Organization (WHO) parameters (Table 3).³¹⁻³³ Women with heart disease are at increased risk for obstetric complications, including premature delivery, preeclampsia and postpartum hemorrhage. Fetal complications also occur in 18 to 30% of patients with heart disease, with neonatal mortality between 1 and 4%. Maternal and fetal events are highly correlated.^{34,35}

WHO classifications III and IV contraindicate exercise during pregnancy, and the other classes must be assessed individually (Figure 2).

2.4. Exercise Prescription

Exercise is here conceptualized as programmed physical activity, which involves repetitive body movement, aiming to improve or maintain one or more components of physical capacity.³⁶

As a general rule, exercise programs must consider the pregnant woman's physiological condition and incorporate these basic components: frequency, intensity, type and time (FITT). Frequency indicates the number of sessions per week, time indicates the duration of session, the types include aerobic and/or resistance, and intensity refers to the work level, which can be classified as light, moderate or intense.³⁶

2.4.1. Exercise Types and their Prescription for Pregnant Women

Aerobic exercise: Aerobic exercise metabolizes O₂ as the main source of energy and involves cardiorespiratory demand.

It comprises the flexion and extension of large muscle groups in a rhythmic manner for a prolonged time. However, when performed at high intensity, it may involve predominantly anaerobic metabolism, requiring other energy substrates to maintain effort, and a consequent risk of greater accumulation of lactic acid. Aerobic capacity, also known as VO₂, reflects the cardiovascular system's ability to transport and deliver O₂ to skeletal muscles, in addition to the muscles' efficiency at extracting it from the bloodstream and using it as an energy source for exercise.³⁶

Regular aerobic exercise helps maintain functional capacity, control weight and prevent GDM and gestational hypertension. During pregnancy, low impact aerobic exercise, such as walking, swimming, stationary cycling, or water aerobics, is considered safe.⁴ Exercise performed on the floor or in a "dry" environment is more difficult during pregnancy, causing greater metabolic demand, osteoarticular overload and balance difficulties, because they are related to body weight, which progressively increases. Thus, aquatic exercise is considered preferential during this period. The effects of and recommendations about aquatic exercise will be addressed separately.

Since one of the main responses to aerobic exercise is increased HR and respiratory rate, the intensity can be based on HR control, which, despite its limitations in pregnant women, is the closest index of functional capacity. Based on healthy populations in both sexes, several methods for defining the intensity of aerobic exercise have been proposed, and these can be applied during normal pregnancies, including appropriate adjustments due to overload during that period.³⁶

For healthy pregnant women, moderate-intensity exercise is recommended, although it is important to point out that the

Table 3 – Modified World Health Organization classification system according to maternal cardiovascular risk

WHO modified	I	II	II-III	III	IV
Diagnostic	Small or light: - Pulmonary stenosis - Patent ductus arteriosus - Mitral valve prolapse (simple injuries successfully repaired) - Isolated atrial or ventricular ectopics	- Untreated atrioventricular septal defect - Corrected tetralogy of Fallot - Supraventricular arrhythmias - Turner's syndrome without aortic dilation	- Mild ventricular dysfunction (EF >45%) - Hypertrophic cardiomyopathy - Valve disease not considered WHO class I or IV (mild mitral stenosis, moderate aortic stenosis) - Marfan syndrome without aortic dilation - Corrected coarctation - Atrioventricular septal defect	- Moderate ventricular dysfunction (EF 30% to 45%) - Previous peripartum cardiomyopathy without residual ventricular dysfunction - Mechanical valve - Fontan circulation - Uncorrected cyanotic heart disease - Other complex heart diseases - Moderate mitral stenosis - Asymptomatic severe aortic stenosis - Systemic right ventricle with preserved function or mild dysfunction - Moderate aortic dilation (40 to 45 mm in Marfan syndrome; 45 to 50 mm in bicuspid aortic valve; aorta index 20 to 25 mm/m ² in Turner syndrome; <50 mm in tetralogy of Fallot - Ventricular tachycardia	- Pulmonary arterial hypertension - Severe ventricular dysfunction (EF <30% or NYHA class III-IV) - Peripartum cardiomyopathy with residual ventricular dysfunction - Severe mitral stenosis - Symptomatic severe aortic stenosis - Systemic right ventricle with moderate or severe dysfunction - Severe aortic dilation (>45 mm in Marfan's syndrome; >50 mm in bicuspid aortic valve; aorta index >25 mm/m ² in Turner's syndrome; >50 mm in tetralogy of Fallot - Ehlers-Danlos severe (re) coarctation - Fontan operation with complications
Maternal cardiac event rate	2.5% to 5%	5.7% to 10.5%	10% to 19%	19% to 27%	40% to 100%
Risk	No increased maternal risk of death detected and no/slightly increased risk of morbidity	Slightly increased risk of maternal death or moderate increase in morbidity	Increased risk of maternal death or moderate to severe increase in morbidity	Significant increase in risk of maternal death or severe morbidity	Extreme risk of maternal death or severe morbidity

Adapted from Regitz-Zagrosek et al.²⁵ EF: ejection fraction; NYHA: New York Heart Association; WHO: World Health Organization.

selected intensity is the combined responsibility of the doctor and exercise professional or physical therapist and can be reduced in previously sedentary women or those with comorbidities.³⁷

The intensity of the exercise can be determined by calculating the percentage of the age-predicted maximum heart rate (HRmax) or the heart rate reserve (HRR). The percentage of maximum VO₂ values and predicted metabolic load (MET) can also be used (Table 4).³⁶ However, to obtain the HRR and maximum VO₂, it is necessary to perform a maximum exercise test, which is not recommended for pregnant women. There are easier and more practical methods of prescribing exercise, such as subjective perceived exertion with a Borg scale³⁸ (Table 5) and the talk test, ie, an exercise intensity at which the individual can talk, but not sing (Table 6).^{3,37,39}

Previously active women should continue regular aerobic exercise for at least 30 minutes, 4 to 5 times a week. Sedentary women can begin, for example, with 15 minutes of aerobic

exercise 3 times a week and gradually increase the time until reaching the recommended 150 minutes/week or 30 minutes/day.³⁷

a) Resistance exercise: loads specific muscle groups with weight to increase strength over time. When joint movement is associated with muscle contractions, the exercise is considered dynamic, when it is not the exercise is considered static (isometric). Resistance exercise can be performed with free weights, on weight machines, with elastic bands and even with one's own body weight.³⁶ The exercises must be adjusted in each gestational stage, adapting to the woman's anatomical changes. Resistance exercise increases muscle tone, strength and endurance, which facilitates adaptation to postural changes, reducing musculoskeletal pain and preventing possible falls during pregnancy. It has been shown that regular strength training results in up to 14% higher lumbar resistance in pregnant women.⁴⁰

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Table 4 – Aerobic exercise intensity levels for healthy individuals

Intensity	%VO ₂ max	%HRmax	%HRR	MET* (absolute)	Borg Scale
Very light	<37	<57	<30	<2	<9
Light	37-45	57-64	30-40	2-3.9	9-11
Moderate	46-64	65-76	40-60	4-6	12-13
Intense	65-91	76-96	60-90	6,1-8,8	14-17
Very intense	>91	>96	>90	>8.9	>17

Adapted from the ACSM.³⁶ *MET: metabolic unit, which for non-pregnant women is equivalent to oxygen consumption of 3.5 ml/kg⁻¹.min⁻¹ while resting in a supine/sitting position. In the presented suggestions, oxygen consumption (VO₂) values should ideally be obtained by a direct cardiopulmonary test and not estimated by regression equations derived from conventional exercise testing protocols; %VO₂max: percentage of maximal oxygen consumption; %HRmax: percentage of age-predicted maximum heart rate; %HRR: percentage of heart rate reserve; Borg scale: linear scale of perceived exertion, graded from 6 to 20.

Table 5 – Borg scale of perceived exertion (graded from 6 to 20)

Borg Scale	Exercise perception
6	
7	
8	Very easy
9	
10	Easy
11	
12	Relatively easy
13	
14	Slightly tiring
15	
16	Tiring
17	
18	Very tiring
19	
20	Exhausting

Adapted from Borg.³⁸

Examples of resistance exercise include weight training, functional training, Pilates and yoga.⁴ Gentle stretching and yoga also promote muscle relaxation and are particularly useful in improving posture and relieving lower back and pelvic pain, although they should be performed with caution due to greater ligament laxity during pregnancy and the consequent risk of injury.^{3,4,39} Pilates provides satisfactory results when preparing the abdomen and pelvic floor for labor, in addition to reducing the risk of urinary incontinence. Pelvic muscle training has been found to reduce the occurrence of urinary incontinence by up to 50% in the prenatal period and 35% in the postnatal period.⁴¹

The intensity of the resistance exercise is defined according to the percentage of 1RM that the individual can perform,

which is reflected in the number of possible repetitions with a given load. Table 7 describes the intensity ranges for resistance exercise training.³⁶

Moderate-intensity resistance exercise is recommended for pregnant women three to five times a week, in sessions lasting 15 to 20 min, approximately two to three sets of 10 to 15 repetitions.^{3,36,37} The number of repetitions and the load must be adjusted according to the individual's previous muscle conditioning, ie, approximately 10 repetitions at the highest intensity/load. It is preferable to work with large muscle groups, using elastic bands or machines with light weights rather than free weights because of the greater difficulty balancing due to changes in center of gravity. Very high loads and intense isometrics are not recommended, since concomitant performance of the Valsalva maneuver can result in increased intra-abdominal pressure and a consequent decrease in blood flow to the fetus, in addition to further overload of the pelvic floor, increased risk of prolapse, and anal and urinary incontinence.^{19,22}

b) General exercise recommendations for healthy pregnant women

include aerobic and moderate-intensity resistance exercise. It is important to remember that the time calculated for the training session should include a mild-intensity warm-up and cool-down period. Exercise prescription for pregnant women according to the FITT components is summarized in Table 8.

2.4.2. Aquatic Exercise

Aquatic exercise has been shown to be beneficial and safe during pregnancy. The aquatic environment provides buoyancy, which facilitates movement, reduces body weight and osteoarticular overload, and provides a feeling of well-being while eliminating the risk of falls. It also facilitates heat dissipation and thermoregulation, which reduces the chance of hyperthermia, which is unwanted during exercise due to the risk of fetal malformation.⁴² Thus, aquatic exercise (represented mainly by water aerobics) is the exercise of choice in this period and can include aerobic and resistance components.

Hydrostatic pressure, the main favorable effect of immersion for pregnant women, is proportional to depth

Table 6 – Alternative methods of prescribing aerobic exercise for pregnant women*

METHOD	DESCRIPTION
Perceived exertion (Borg scale)	Exercise with relatively easy or slightly tiring self-perceived exertion. Borg score of 12 or 13 recommended
Talk test	Exercising at an intensity where breathing is labored but controlled, so that a sentence can be completed without pauses
Percentage of HRmax	Exercise at 60%-80% of HRmax Target HR = % x HRmax HRmax = 208 - (0.7 x age) ** or 220 - age ***
Heart rate reserve (Karvonen)	Exercise at 45%-60% of HRR (HR peak - HR rest) Target HR = resting HR + % x (peak HR - resting HR)

HR: heart rate; HRmax: maximum heart rate; HRR: heart rate reserve. *Considering a moderate intensity, **Tanaka's formula, *** Karvonen's formula.³⁶

Table 7 – Resistance exercise intensity levels

Intensity	1RM percentage*	Number of repetitions
Light	30% to 50%	15 to 20
Moderate	50% to 70%	10 to 15
Intense	70% to 85%	8 to 10

*1RM: maximum repetition.

Table 8 – Exercise prescription for healthy pregnant women according to FITT

FREQUENCY	INTENSITY	TYPE	TIME
3 to 5 days/week	Moderate	Aerobic (low impact)	20 to 30 minutes per session (goal - a total of 150 minutes/week) 10 to 15 minutes heating and cooling
	- 60% to 80% HRmax or		
	- % of other validated method (HRR, VO2) or		
	- 12 to 13 Borg scale or		
3 to 5 days/week	- Corresponding to 4 - 6 MET	Resistance	15 to 20 minutes
	Moderate		10 to 15 minutes of warm-up and cool-down
	2 to 3 sets and 10 to 12 repetitions		

HRmax: maximum heart rate; HRR: heart rate reserve; MET: metabolic unit; VO2: oxygen consumption.

and acts uniformly on the body surface, redistributing fluids from extravascular to intravascular space, which leads to rapid expansion of plasma volume, stroke volume and CO, as well as increased uteroplacental blood flow and diuresis. A study found that uterine tonus and fetal HR do not change during immersion or after aquatic exercise, demonstrating that neither uteroplacental circulation nor the fetal energy substrate are impaired.⁴³

From a metabolic point of view, hormonal changes (increased natriuretic factor and decreased antidiuretic hormone levels secondary to receptor stimulation) increase

diuresis for up to 4 hours. This effect contributes to a reduction in peripheral edema and lower BP levels after exertion.⁴⁴

In comparison to floor (ie, dry medium) exercises, it has been observed that maternal HR, BP and temperature increases are lower in water and should be adjusted to the training range (approximately 15 beats per minute less). Aerobic performance seems to be better because, with less body weight, relative oxygen consumption is higher.^{45,46}

To achieve these benefits, the chest should remain immersed to the xiphoid process or just below, with a water temperature between 28 and 30°C (never exceeding 33.4°C)

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and the sessions should last approximately 45 min, especially for untrained women. Foot support should be provided for those who are not good swimmers.

It has been demonstrated that swimming is safe during pregnancy, provided the recommended volume and intensity limits are observed. Interestingly, a recent study suggested that swimming in cold water (approximately 20°C, without artificial heating) can benefit both the mother and the fetus, since it is associated with decreased stress and cortisol levels (which are increased at rest), as well as an increased pain threshold.⁴⁷ It should be noted, however, that this study was conducted with northern European women, who are more accustomed to such conditions.

Although SCUBA diving appears to be safe for pregnant women, it is not for the fetus. During sudden decompression, the fetal pulmonary circulation cannot filter bubbles, leading to the risk of gas embolism and fetal malformations. Therefore, SCUBA diving should be avoided, although snorkeling is allowed.⁴⁸

The FITT recommendations for aquatic exercises during pregnancy are summarized in Table 9.

2.5. Exercises for Special Populations

2.5.1. Hypertensive Disorders in Pregnancy

Hypertensive disorders occur in up to 10% of pregnancies and are associated with increased cardiovascular risk throughout life.⁴⁹ They involve risk factors similar to those of the general population (advanced maternal age, ethnicity, family history of hypertension and sedentary lifestyle). The disorders are classified in Table 10.

Gestational hypertension affects 5 to 8% of pregnancies and is characterized by systolic BP >140 mmHg and/or diastolic BP >90 mmHg. BP should be measured in a sitting position or in the left lateral position. Preeclampsia is a multisystem disorder that also occurs in 5% to 8% of pregnancies, although it is more frequent in the first pregnancy, multiple pregnancies, hydatidiform mole, antiphospholipid syndrome, arterial hypertension, kidney disease, or pre-existing diabetes. It is frequently associated with fetal growth restriction due to

placental insufficiency (25% of cases), being a common cause of prematurity (27%) and intrauterine fetal death (4%). The main and most effective treatment is childbirth.²⁵

The literature shows that regular exercise improves cardiovascular health during pregnancy and can decrease the risk of developing hypertensive disorders during pregnancy by up to 30%.^{37,49,50} Regular physical activity prior to pregnancy is related to a lower occurrence of preeclampsia, with 22% and 35% reductions in relative risk for women with moderate and high physical activity levels, respectively.⁵¹ This risk is even lower with combined physical activity before and early in pregnancy. When assessing the dose-response effect of physical activity, 5 to 6 h per week reduces the risk of preeclampsia by up to 40%, but no further reduction has been reported with higher activity levels.^{25,50}

According to Brazilian and international guidelines, exercise is contraindicated in pregnant women with uncontrolled preexisting hypertension or a suspected/confirmed diagnosis of preeclampsia, and there is a relative contraindication for gestational hypertension.^{49,50}

Other than consensus among specialists, no BP values have been established as exercise limits during pregnancy. The Brazilian Cardiovascular Rehabilitation Guideline recommends that an exercise session should not be started when resting BP levels are above 160/100 mmHg and it should be stopped BP reaches 220/105 mmHg in individuals with heart disease or hypertension.⁵²

Based on these concepts, some precautions should be respected:

1. For pregnant women with controlled BP (<140/90 mmHg), mild-intensity exercise is recommended in sedentary patients, although a moderate level is acceptable for physically active women. BP measurements should be performed before, during and after exercise, interrupting activities when values above 160/100 mmHg are reached. The Valsalva maneuver should be avoided throughout pregnancy.

a. First trimester: at this stage, a reduction in BP levels is common, and many women tend not to use any specific medication for it. Discontinuation of antihypertensive drugs

Table 9 – Aquatic exercise guidelines

FREQUENCY	INTENSITY	TYPE	TIME
3 to 5 days/week	Moderate (for aerobic and resistance components)	Aqua aerobics or swimming	Up to 45 minutes/session

Water temperature between 28 and 30°C; immersion level near the xiphoid process

Table 10 – Classification of hypertensive disorders in pregnancy²⁵

Hypertensive Pregnancy Disorders	
Pre-existing hypertension	Precedes pregnancy or develops before the 20th week of pregnancy. Persists for more than 42 days after delivery. May be associated with proteinuria
Gestational hypertension	Develops after the 20th week of pregnancy and resolves up to 42 days after delivery
Preeclampsia	Gestational hypertension with significant proteinuria: >0.3 g/24 h and/or albumin-creatinine ratio >30 mg/mmol

should be avoided; however, dosage adjustments may be necessary when water intake is increased. This will assist in correct hydration and body temperature control while exercising. Exercise intensity must be reduced at times.

b. Second trimester: during this period, BP stabilizes and rises again, and further therapeutic adjustments may be necessary. This trimester is the most hemodynamically stable and allows for slight load increases for women with adequate weight and controlled BP levels. Supine exercises should be avoided after this stage.

c. Third trimester: the mechanical compression that the uterus exerts on the aorta and inferior vena cava increases dramatically, resulting in greater stasis and edema in the lower limbs. BP is likely to increase due to water retention. Increased monitoring of BP levels is necessary, and exercise intensity should decrease. Self-limitations should guide exercise intensity and adherence during in this period. We suggest maintaining pelvic musculature conditioning, stretching and low- or very low-intensity aerobic exercise, as long as blood pressure levels remain within acceptable limits ($\leq 160/100$ mmHg). If there is any unexpected increase in blood pressure, exercise should be stopped.

2.5.2. Diabetes Mellitus

GDM has short- and long-term complications for both mother and baby. Early diagnosis is important so that interventions can be carried out to reduce the deleterious effects of hyperglycemia. A high frequency of maternal dystocia and birth trauma is observed, with a greater chance of developing gestational hypertension or preeclampsia. In the long run, about 50% of these women develop type 2 DM and are at increased risk of post-term pregnancy; the child is also more likely to develop metabolic syndrome in childhood and adulthood.⁵³⁻⁵⁵

Lifestyle changes, such as diet and exercise, are the basis for treating GDM and are important allies when associated with drug treatment. In contrast, studies show that sedentary behavior increases the risk of GDM.^{53,56}

In GDM, studies have shown that targeted exercise reduces negative maternal and fetal outcomes. However, this has not been proven for pregnant women with pre-existing DM.^{53,57,58} Nevertheless, in both populations, low- to moderate-intensity resistance and aerobic exercise helps with glycemic control and reduces the need for insulin, in addition to the other previously reported physical and psychological benefits.^{53,58}

Special attention should be paid to contraindications to exercise, such as pre-proliferative retinopathy, uncontrolled hyperglycemia, hypoglycemia unawareness, advanced peripheral neuropathy and dysautonomia. Thirty-minute sessions of light- to moderate-intensity aerobic and resistance exercise at least three times a week are recommended for pregnant women with DM.^{57,59,60}

One of the greatest risks for diabetic patients is hypoglycemia, which can occur during or after exercise. Capillary blood glucose monitoring should be performed before and after exercise, especially in pregnant women who are beginning an exercise program and after adjustments to the therapeutic

regimen. At the beginning of exercise, capillary glycemia should be between 100 and 200 mg/dL. At levels below 100 mg/dL, 15 to 30 g of fast-absorbing carbohydrates should be consumed, which should be repeated after 30 min. Exercises must not be performed on an empty stomach or for more than 3 h without food. In cases of hyperglycemia with capillary levels above 250 mg/dL, exercise is contraindicated due to the risk of complications such as diabetic ketoacidosis.^{57,60}

Some glycemic control issues for patients with type 1 diabetes should be highlighted when HbA1c levels are less than 7.5%.⁶¹ Patients must not exercise at the peak of insulin action, and insulin should not be applied in areas that will be most required during physical exertion due to greater absorption at the site.^{57,59,60} Uncontrolled type 1 DM is an absolute contraindication to exercise.

Although pregnancy is a challenging period for women who develop diabetes, it is also a greater motivation for healthy lifestyle changes, which can persist after birth and help prevent the onset of type 2 DM.

2.5.3. Obesity

Pregnancy is included in the list of risk factors for obesity, predisposing women to GDM, type 2 DM, systemic arterial hypertension, CVD and cancer. The children of obese mothers also have a higher incidence of obesity and its metabolic and cardiovascular implications. There is also evidence that obese or overweight women have lower rates of breastfeeding initiation and duration, which is disadvantageous for their children's growth and development.⁶²⁻⁶⁴

Obesity increases the probability of prolonged labor, probably due to lower myometrial tone, post-term pregnancy, cesarean delivery, prolonged hospitalization and puerperal infections. Contributing factors to the higher frequency of cesarean delivery include cephalopelvic disproportion and dystocia due to an increase in soft tissue in the maternal pelvis.⁶⁵ In vaginal deliveries, the higher prevalence of macrosomia contributes to shoulder dystocia, causing perineal lacerations and brachial plexus paralysis in the newborn.⁶⁴

Because obesity or excessive weight gain are linked to increased maternal and fetal complications during pregnancy, childbirth and the postpartum period, adherence to a balanced diet and regular exercise (preferably supervised) is strongly recommended.⁶⁵⁻⁶⁷ The main goal during pregnancy is not weight loss, but appropriate weight gain, avoiding excess in the third trimester. Maternal weight is an independent risk factor for preeclampsia, which doubles with each increase of 5 to 7 kg/m² in pre-gestational body mass index.⁶⁸ Prenatal physical training reduces weight gain and the risk of GDM for overweight and obese pregnant women.⁶⁴

Several studies have demonstrated the safety of moderate-intensity exercise throughout pregnancy when there are no medical or obstetric contraindications.^{3,69} In obese pregnant women, light- to moderate-intensity aerobic exercise is recommended when prescribed at 35% to 60% of the HRR, which will depend on their previous cardiorespiratory condition. The benefits of endurance training can also be seen in this group.^{37,39}

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A key challenge is controlling adherence to regular physical activity, even in supervised programs.⁶⁹ In view of all the favorable effects for both mother and fetus, overweight or obese women should be encouraged to abandon a sedentary lifestyle. In the postpartum period, exercise and a healthy diet must be encouraged, not only to lose excess gestational weight, but to achieve more appropriate weight goals for future pregnancies.

2.5.4. Athletes

Athletic training presupposes great volumes of high-intensity exercise. In addition to the limitations imposed by pregnancy, ethical issues make it difficult to conduct studies, which results in little robust evidence on the safety of high-intensity exercise during pregnancy. However, some pregnant women choose to continue this level of training, including participation in competitions.

Active women who continue to exercise during pregnancy have lower resting HR and greater stroke volume, with better tolerance for high-intensity exertion, including during the puerperium, which facilitates a return to pre-pregnancy conditions and perhaps even better performance.⁷⁰ Such data are relevant for athletes who intend to continue their careers and resume high-level training in the short term.

On the other hand, it must be considered that there is a decrease in functional residual capacity, a reduction in hepatic glycogen and greater difficulty in adapting to anaerobic exercise, with greater plasma accumulation of lactic acid and a decrease in glucose availability, especially during prolonged exercise. Compared to sedentary women, active women and their babies have lower weight, although this is due to the decreased body fat percentage, which damages neither mother nor child.⁷¹

Training and endurance tests, such as marathons, should be avoided because there is a risk of maternal hyperthermia in exercise sessions over 60 min (which can cause malformations of the neural tube if it occurs between the 4th and 6th week) and fetal hypoglycemia (identified by a transient decrease in fetus reactivity).⁷² When exercising in hot and humid environments, careful attention should be paid to hydration and caloric intake, which should be adjusted for increased metabolic needs to maintain fetal homeostasis.

Sports that involve collision with other players (basketball, football) or objects (hockey, volleyball) and falls (jumping, riding, cycling, skiing) are also discouraged, since they can cause placental detachment and/or fetal hypoxia or slowdown due to direct trauma.^{3,19}

Despite these considerations, some elite athletes have continued to train and compete during pregnancy, winning titles in sports such as tennis, beach volleyball, track and field, marathons, mountain climbing and skiing, without no reported maternal-fetal complications.^{65,73,74}

Although little data is available in the literature, a Norwegian study found that a group of elite athletes who continued training at a high volume and intensity on the 17th week of pregnancy benefitted (with no increased risks) from returning to competition after childbirth compared with a group that

trained with a lower workload, which suggests that well-trained women can maintain normal exercise intensity during pregnancy.⁷⁵ Another study carried out an exercise test until exhaustion (HR >90% of the predicted maximum) in three groups of pregnant women: inactive, active and very active (athletes), reporting decreased uterine artery flow and mild and transient fetal bradycardia (<3 min) in a small number of women. However, the meaning of this finding is unknown, considering that there was no damage to the fetus before or after the test or a greater occurrence of complications.⁷⁶

In any case, the data are still scarce and further studies on pregnant athletes who continue high-intensity training are needed, provided that ethical principles and maternal-fetal safety are maintained. Although some groups believe that exercise recommendations for pregnant athletes could be more liberal, there is insufficient data to state that high-intensity exercise is safe during pregnancy. It is up to the doctor to understand the psychological and financial impact that these conditions can cause on the athlete's well-being and career, advising her about the risks of complications and even unwanted terminations or irreversible damage to the baby. A shared decision is the best decision.

2.5.5. Heart Disease

The changes that occur during pregnancy are dynamic, like an exercise test, with cardiovascular and systemic changes that can compromise the stability of heart disease. The increase in stroke volume, HR, CO and uterine blood flow and reduction in hematocrit and cardiac reserve may be sufficient to cause hemodynamic instability, not only at the beginning, but also throughout the gestational period.^{25,77} Regular consultations with a cardiologist should assist with clinical control in these patients.

Although regular exercise is recommended for primary and secondary prevention of CVD, heart disease in pregnant women has not been widely documented. Studies with this patient profile are scarce, given the complexity of most CVDs, such as congenital heart disease, heart valve disease, and pulmonary hypertension, conditions that endanger the life of the mother and fetus. Exercise prescription in this population should be based mainly on assessing cardiovascular risk during pregnancy. Important predictors of maternal cardiovascular events have been demonstrated in the literature, such as New York Heart Association (NYHA) functional class III and IV, moderate to severe obstructive lesions of the left heart, previous cardiac events, reduced left ventricular ejection fraction (<40%), moderate to severe systemic atrioventricular valve regurgitation, moderate to severe pulmonary atrioventricular valve regurgitation, pulmonary arterial hypertension, use of cardiac medication prior to pregnancy, cyanosis (oxygen saturation <90%), smoking, mechanical valve prosthesis, and corrected or uncorrected cyanotic heart disease.²⁴

An interesting study by Jastrow et al. of 227 women with heart disease (312 pregnancies) used a risk score called Cardiac Disease in Pregnancy (CARPREG), whose variables are described in Table 11, to follow-up and determine the association with maternal and fetal outcomes. In the evaluated group, maternal cardiac injuries were predominantly congenital

(81.4%), with a low risk score (score = 0) in 66.3%, and an intermediate risk (score = 1) in 33.7%. Maternal cardiac events complicated 7.4% of the pregnancies, with pulmonary edema being the most frequent (3.8%). Intermediate scores were associated with a higher rate of maternal cardiac outcomes ($19.0\% \times 1.4\%$, odds ratio [OR] = 15.6, 95% CI), with adverse events occurring in 27.5% of the neonates. The CARPREG risk index showed high sensitivity and negative predictive value for cardiac complications in pregnant women with heart disease.⁷⁸ However, when this index was applied to a sample of patients with rheumatic heart disease, it overestimated the number of events in pregnant women classified as CARPREG 1 and >1, in addition to underestimating the risk in low-risk patients (CARPREG 0).⁷⁹

There are other indexes for assessing maternal-fetal risk, the most accurate of which are currently used by the WHO, as described above. Exercise is proscribed for pregnant women in WHO risk categories III and IV.²⁵ For other cases, a detailed heart disease assessment is suggested, including consideration of the patient's cardiorespiratory condition and the physiological changes peculiar to each gestational period, to assess the risks and benefits of exercise for the mother and fetus. The interaction between cardiology and obstetrics is very important in evaluating these patients and prescribing their exercise.

The use of functional tests in this scenario, such as exercise tests and the CPET, is controversial. Submaximal tests have been suggested for specific situations, including valve disease and congenital heart disease.²⁵

HR, BP and peripheral oxygen saturation (by pulse oximetry) can guide prescription of the type and intensity of exercise, which should be applied by specialized trained professionals. To ensure that exercise is stopped when necessary, special attention must be paid to the warning signs and symptoms: tiredness, dyspnea, low output signs, and others described above.

Pregnant women with CVD at risk for potential complications (described in Table 12) should preferably be accompanied by a multidisciplinary team consisting of maternal-fetal medicine, cardiology, cardiovascular surgery, anesthesiology, and neonatology professionals and treated at a tertiary care center.⁸⁰

In Brazil, rheumatic disease is the most common heart disease in pregnant women, affecting mainly the mitral and aortic valves.²⁴ Other heart diseases have a low prevalence in this population, and their heterogeneous presentation means that guidelines must be individualized.^{24,25,52}

Physical activity for those with valve diseases will depend on the affected valve and degree of impairment. Valve

Table 11 – Cardiac Disease in Pregnancy risk index

Predictors of Cardiovascular Events	Score
Previous cardiac event (heart failure, transient ischemic attack, infarction before pregnancy or arrhythmia)	1
Baseline NYHA functional class >II or cyanosis	1
Left-sided obstructive heart disease (mitral valve area <2 cm ² , aortic valve <1.5 cm ² or peak gradient of outflow tract >30 mmHg)	1
Reduced systolic ventricular function (ejection fraction <40%)	1

Adapted from Martins et al.⁷⁹ NYHA: New York Heart Association.

Table 12 – Main complications of cardiovascular disease during pregnancy

Cardiovascular Condition	Potential Complications
Arterial hypertension	- Preeclampsia; HELLP syndrome*
Mitral stenosis	- Tachyarrhythmias with low output, pulmonary edema
Mitral insufficiency	- Arrhythmia, pulmonary edema
Aortic stenosis	- Low cardiac output with preload drop
Aortic insufficiency	- Generally well tolerated - Congestive heart failure
Pulmonary stenosis Pulmonary insufficiency	- Usually well tolerated, - Pulmonary edema if right heart failure
Tricuspid stenosis	- Well tolerated
Tricuspid insufficiency	- Well tolerated
Cardiomyopathy	- Arrhythmia; Congestive heart failure; pulmonary edema
Aortic aneurysm	- Aortic dissection, rupture

*Adapted from Adam et al.⁸⁰ *HELLP: hemolysis, elevated liver enzymes and low platelets.*

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stenosis, particularly on the left side, leads to a higher risk of maternal complications than valve regurgitation, in which CO, vasodilation and tachycardia due to pregnancy are not well tolerated.⁸¹ Cavity size, ventricular function, pulmonary BP, association with other heart diseases, atrial fibrillation, heart failure, thromboembolism and previous endocarditis should also be analyzed, which are considered prognostic factors. According to the valvular heart disease risk classification for pregnancy (Table 13), which the Department of Women's Cardiology used in its position statement,²⁴ it is recommended that intermediate- and high-risk patients should not be allowed to exercise due to the severity of the heart disease and the consequent risk for mother and fetus.

In mild valve lesions, when unfavorable factors are absent and functional capacity is within the appropriate age range, light-intensity exercise is suggested. It is acceptable to maintain moderate-intensity exercise only in pregnant women who have mild valve regurgitation without hemodynamic repercussions, as in mitral and aortic insufficiencies, especially for patients who have previously exercised.

It is important to monitor symptoms, echocardiographic findings and the peculiarities of each gestational period. In the third trimester, due to the physiological cardiovascular and respiratory changes and the weight gain, exercise should be reevaluated due to the risk of premature birth and delayed intrauterine growth. It must be remembered that although that physical exercise is important for the mother, it may be harmful to the fetus.

2.6. Precautions for Exercise during Pregnancy and Stopping Criteria

It is essential to maintain a healthy lifestyle during pregnancy, including measures such as maintaining adequate nutrition and rest, staying physically active, avoiding alcohol consumption, unnecessary medications, and active or passive smoking.

Pregnant women should be aware of certain exercise-related issues to avoid complications that are more evident in

certain periods of pregnancy. Attention to diet is important: the caloric expenditure of the exercise must be estimated and balanced with adequate intake, and the signs and symptoms of hypoglycemia must be monitored. Exercising in hot and humid environments must be avoided, especially during the first trimester. Adequate hydration must be maintained, including isotonic fluids before and after exercise.

Beginning at the 10th week, special attention should be paid to stretching and sudden changes in exercise performance, when relaxin levels and the risk of injuries increase.¹⁹ Supine exercises can result in decreased venous return and hypotension in 10% to 20% of all pregnant women, causing lipothymia or syncope, especially after the 20th week. There is insufficient evidence to prove or disprove the safety of this type of exercise.⁸² If these symptoms occur, the exercises should be performed in lateral decubitus or standing. Abdominal exercises should also be avoided due to the increased risk of abdominal diastasis.

There is no specific period for stopping exercise during pregnancy. Mild-intensity exercises should be encouraged at the end of the third trimester and the patient should be advised about the signs of labor³⁷, since there is a natural decrease in physical activity during this stage. Exercise should be stopped and a specialist consulted if symptoms of discomfort appear, such as shortness of breath that does not resolve with rest, severe headaches, regular and painful uterine contractions, vaginal bleeding, continuous loss of amniotic fluid, faintness or persistent dizziness, chest pain, palpitations, visual disturbances, persistent nausea and vomiting, muscle weakness that affects balance, etc.³

2.7. Exercise Recommendations and Adaptations during the Coronavirus Pandemic

The Ministry of Health included pregnant and puerperal women in the highest risk group for unfavorable outcomes in COVID-19. There is no evidence that pregnancy increases susceptibility to infection with SARS-CoV-2/COVID 19.⁸³ In a systematic review of 18 articles published from February

Table 13 – Classification of the risk of heart valve disease during pregnancy

High Risk	Intermediate Risk	Acceptable Risk
Severe mitral stenosis	Biological prosthesis with moderate dysfunction	Discreet valve disease
Severe aortic stenosis	Severe pulmonary stenosis	BP without dysfunction
Stenotic/calcified biological prosthesis	Metallic prosthesis	Valvulopathy + normal LVEF
Malfunctioning metallic prosthesis	Mitral metallic prosthesis > metallic prosthesis aorta risk	Valvulopathy without unfavorable factors
Valvulopathy + PAP ≥50 mmHg	Aortic insufficiency + aortic diseases	
Aortic insufficiency + aortic diseases	Marfan syndrome (Daorta between 40 and 45 mm)	
Marfan Syndrome (Daorta >45 mm)	Bicuspid aortic valve (Daorta between 45 and 50 mm)	
Bicuspid aortic valve (Daorta >50 mm)	Need for anticoagulants	
Valvulopathy + LVEF <35%		

Adapted from Avila et al.²⁴ Daorta: diameter of the ascending aorta; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure. Valve area ≤1 cm² is considered severe aortic or mitral stenosis.

12 to April 4 2020, of 108 pregnant women infected with SARS-CoV-2, 68% had fever, 34% cough, and 12% dyspnea.⁸⁴

Physiological adaptations to pregnancy can aggravate some COVID-19 symptoms. Diaphragm displacement, decreased total lung capacity and chest compliance contribute to a worse outcome in patients with COVID-19 pneumonia, including hypoxia and fetal impairment. In addition to respiratory changes during pregnancy, cardiovascular and hematological changes should also be pointed out, such as increased HR, lower systemic vascular resistance and a hypercoagulable state. These factors have greater implications for pregnant women with heart disease who are infected with COVID-19.⁸⁵

Thus, pregnant women should take extra precautions when exercising during the pandemic. Home exercise routines are recommended to reduce the risk of contamination. Mild- to moderate-intensity exercise is generally safe in a healthy pregnant woman and, as a general rule, certainly helps modulate emotional stress in addition to all the above mentioned health benefits. For pregnant women, the general guidelines for home exercise consist of a place with adequate space, ventilation and temperature, light clothing and tennis shoes, as well as adequate diet and hydration. Some exercises can be performed with common household materials.

For previously active pregnant women, exercise routines are easier to maintain, since they already understand how to perform the exercises, and understand perceived exertion and the warning symptoms for cessation. For sedentary women, the importance of exercise should be explained at the first consultation and mild-intensity exercises should be prescribed initially.

Home exercise, especially for sedentary pregnant women or those with comorbidities, should be supervised whenever possible by an exercise professional or physical therapist, which during the pandemic can include distance classes and telemonitoring, as deemed appropriate. According to the professional's determination (always based on the relative benefits and safety), the first assessment could be in person, provided that measures of asepsis are followed.^{86,87}

Considering that the quarantine is being relaxed heterogeneously in Brazil, with some public spaces reopened, when exercising outdoors, pregnant women should seek out open places with reduced circulation of people to lower the risk of contamination. There is a consensus that masks should be worn outside the home in addition to social distancing, especially when walking on city streets or in residential compounds. A recent Dutch study suggested a distance of 4 to 5 m should be maintained between people who are walking, 10 m between people who are running or cycling slowly, and 20 m between those cycling quickly.⁸⁸

In apartment building gyms, hours should be reserved for residents of the same apartment and the equipment should be cleaned with 70% alcohol prior to use. Currently, gyms in many cities are open with limited hours and follow recommended security protocols.

Pregnant women who have been affected by COVID-19 should only return to regular physical activity after medical and ECG reevaluation, due to the possibility of myocardial injury and arrhythmias secondary to infection.⁸⁹ In those with a more severe

clinical evolution, an obstetrician should perform a thorough maternal-fetal assessment, a cardiologist should assess any cardiovascular complications, and complementary exams, such as transthoracic echocardiography, dynamic electrocardiography (eg, Holter monitoring), etc., should be performed.

3. Postpartum Exercise

When a woman exercises during pregnancy, there is a higher likelihood that she will continue to do so during the postpartum period, which has both short- and long-term benefits on quality of life. Women habitually reduce exercise after childbirth, due to the difficulties involved in this period. A sedentary lifestyle contributes to overweight and obesity and affects the development of other comorbidities, such as DM and CVD.⁹⁰ Approximately 25% of women retain >4 kg in gained weight 1 year after delivery.⁹¹ Although exercise in the postpartum period is important for weight reduction, adjuvant therapies should also be considered. Some systematic reviews have shown that interventions involving a dietary component had a greater effect on weight loss. More intensive dietary interventions and more structured activity programs (eg, that incorporate HR monitoring) have been associated with greater weight loss.⁹²⁻⁹⁴

Obstetricians should emphasize the importance of exercise during this stage, including the cardiorespiratory benefits, fatigue reduction, improved sleep quality, and reduced risk of depression.⁹⁵⁻⁹⁶ It should be pointed out that postpartum depression is a prevalent condition, affecting approximately 10 to 15% of women in the first year after birth.⁹⁷ Women who exercise during this period report a greater sense of well-being and improved quality of life.^{98,99}

The postpartum exercise routine should gradually return to normal as soon as it is safe, which depends on the type of delivery (vaginal or cesarean) and whether there were surgical complications. It is recommended that exercise begin again approximately 6 weeks after cesarean delivery and 4 weeks after vaginal delivery. Progression should be slower if there is discomfort or other relevant factors, such as anemia or wound infection. Patients who exercised regularly prior to delivery should reduce the intensity in the first few months postpartum and progress gradually.^{95,99}

Breastfeeding women can perform mild- to moderate-intensity aerobic exercise without damaging milk production or the growth of the child. Ideally, exercise should be performed after breastfeeding to avoid the discomfort of engorged breasts and should include adequate support. Women at this stage must maintain adequate hydration, even with satisfactory diuresis volume, as well as ensure that caloric intake is at least 75% of what is consumed in exercise; weight loss should be limited to 450 g per week. The caloric expenditure of breastfeeding is estimated at approximately 600 kcal/day.^{100,101} High-intensity exercise can be associated with increased lactic acid in breast milk, which changes the taste of milk. If the mother notices that the baby is rejecting breast milk, she should reduce her exercise level.¹⁰²

Resistance exercises are allowed, but care should be taken not to involve trunk flexion (traditional abdominal exercises), due to the risk of increased diastasis in the rectus abdominis

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muscles. Pilates, a suitable option for training deep abdominal muscles and the pelvic floor, can help return the woman's body to its pre-gestational state. Compromised pelvic muscles can contribute to urinary and fecal incontinence, as well as sexual dysfunction. Pelvic muscle training should be initiated during pregnancy. Jumping exercises should be avoided in the postpartum period due to the fragility of the pelvic floor.¹⁰³

Exercise provides benefits during pregnancy, the puerperium period, and the long term. Women who continue to exercise are less likely to retain the excess weight acquired during pregnancy, develop depression, or develop metabolic and cardiovascular complications.¹⁰⁴ All health professionals who monitor pregnant women should encourage safe exercise.

3.1. Particularities of the Postpartum Period for Patients with Heart Disease

The postpartum period involves important characteristics, especially for women with heart disease, since, in the immediate postpartum period, a significant change in blood volume occurs, which can lead to clinical decompensation. After the expulsive period of labor, there is a sudden increase in venous return, which is due to autotransfusion of the uterine plexus, decompression of inferior vena cava flow and reduced capacity in the venous system. In addition, peripheral vascular resistance is increased by sustained contraction of the uterus, which occludes vessels in the maternal surface of the placenta. The continuous autotransfusion that occurs 24 to 72 h after delivery involves a high risk of pulmonary congestion for women with heart disease.¹⁰⁵

In general, changes in maternal blood volume during labor, the expulsive period and the puerperium involve the following phases: (1) hemoconcentration during labor, which varies with the degree of uterine activity and maternal dehydration; (2) reduced blood volume, which occurs during and immediately after delivery in proportion to the amount of blood lost; (3) an immediate and transient increase in blood volume, which occurs after placental discharge and is attributed to the influx of fluid into the intravascular space due to uterine emptying; (4) a slight increase in blood volume between the second and third postpartum days secondary to a transient increase in

aldosterone secretion; (5) a reduction in plasma volume one week after delivery (the maternal stroke volume may show a slight drop in this period, but normalizes in the short term).¹⁰⁵

As is well known, exercise and a healthy postpartum diet promote weight loss, which can improve or prevent future obesity-related risks, such as DM and systemic arterial hypertension.^{64,106} However, there are no robust data in the literature about postpartum exercise in patients with heart disease or complications during pregnancy. Therefore, exercise prescription follows the guidelines for specific heart diseases, being adapted to minimize risk and maternal injuries and maximize benefits.^{24,52}

The most frequent cardiac complications for women with heart disease during the intrapartum and puerperium include preeclampsia, heart failure, acute pulmonary edema, arrhythmias, thromboembolism, and aortic dissection. Obstetric complications mainly include bleeding and infections.²⁴ For vaginal deliveries, the degree of perineal trauma should be assessed. After cesarean delivery, other outcomes should be analyzed, such as cardiorespiratory disorders, thromboembolism, pain and the need for analgesia, abnormal wound healing, neuropathy and incontinence.¹⁰⁷ Exercise should not be prescribed in the postpartum period until cardiac disease or clinical and surgical complications are controlled and a risk-benefit assessment of exercise is performed, a minimum of 4 weeks after vaginal delivery and 4 to 6 weeks after cesarean section. As soon as it is clinically safe, the patient should begin walking and return to normal pre-pregnancy physical activity, which can reduce the comorbidities associated with a sedentary post-surgical lifestyle.¹⁰⁸⁻¹¹⁰

Physical activity should be resumed at the obstetrician's discretion. When there are cardiovascular diseases and/or complications, joint assessment with a cardiologist becomes important.^{111,112} Due to a lack of data on physical exercise in heart disease patients during the postpartum period, most of the guidelines consist of extrapolations from cardiovascular rehabilitation guidelines. Therefore, more studies are needed to provide individualized and accurate care for this specific population.

References

1. Liddle SD, Pennick V. Interventions for preventing and treating low-back and pelvic pain during pregnancy. *Cochrane Database Syst Rev*. 2015 30; 2015(9): CD001139.
2. Brown HL, Warner JJ, Gianos E et al; on behalf of the American Heart Association and the American College of Obstetricians and Gynecologists. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation*. 2018; 137(24):e843–52.
3. Mottola MF, Davenport MH, Ruchat SM et al. 2019 Canadian Guideline for Physical Activity Throughout Pregnancy. *Br J Sports Med*. 2018; 52(21):1339–46.
4. Santini C, Imakawa TDS, Moisés EC. Physical Activity during Pregnancy: Recommendations and Assessment Tools: Atividade física durante a gestação: recomendações e ferramentas de avaliação. *Rev Bras Ginecol Obstet*. 2017 Aug; 39(8):424–32.
5. Wang C, Zhu W, Wei Y et al. Exercise intervention during pregnancy can be used to manage weight gain and improve pregnancy outcomes in women with gestational diabetes mellitus. *BMC Pregnancy Child birth*. 2015; 15(1):255.
6. Davenport MH, Ruchat SM, Poitras VJ et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Br J Sports Med*. 2018; 52(21):1367–75.
7. Charkamyan F, Hosseinkhani A, Neisani SL et al. Reducing the adverse maternal and fetal outcomes in IVF women by exercise interventions during pregnancy. *Res Q Exerc Sport*. 2019; 90(4):589–99.
8. Nascimento SL, Surita FG, Cecatti JG. Physical exercise during pregnancy: a systematic review. *Curr Opin Obstet Gynecol*. 2012 Dec; 24(6):387–94.

9. Hegaard HK, Pedersen BK, Nielsen BB et al. Leisure time physical activity during pregnancy and impact on gestational diabetes mellitus, pre-eclampsia, preterm delivery and birth weight: a review. *Acta Obstet Gynecol Scand.* 2007; 86(11):1290-6.
10. Perales M, Valenzuela P, Barakat R et al. Gestational Exercise and Maternal and Child Health: Effects until Delivery and at Post-Natal Follow-up. *J Clin Med.* 2020; 9(2):379
11. Newton ER, May L. Adaptation of Maternal-fetal physiology to exercise in pregnancy: The Basis of Guidelines for Physical Activity in Pregnancy. *Clin Med Insights Womens Health.* 2017; 10:1179562X17693224.
12. Davenport MH, Yoo C, Mottola MF et al. Effects of prenatal exercise on incidence of congenital anomalies and hyperthermia: a systematic review and meta-analysis. *Br J Sports Med.* 2019; 53(2):116-23.
13. Brouwers MC, Kho ME, Browman GP et al. AGREE II: Advancing guideline development, reporting, and evaluation in health care. *Prev Med.* 2010; 51(5):421-4.
14. Duvekot JJ, Cheriex EC, Pieters FA et al. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol.* 1993; 169(6):1382-92.
15. Warnes CA. Pregnancy and heart disease. In: Mann DL, Zipes DP, Libby P et al. Braunwald's heart disease. A textbook of cardiovascular medicine. 10th ed. Philadelphia, Pennsylvania: Elsevier. 2015; 1755-6.
16. Mehta LS, Warnes CA, Bradley E et al. Cardiovascular considerations in caring for pregnant patients: a Scientific Statement From the American Heart Association. *Circulation.* 2020; 141(23):e884-903.
17. Price BB, Amini SB KKE. Exercise in pregnancy: effect on fitness and obstetric outcomes-a randomized trial. *Med Sci c; Sport Exerc.* 2012; 44(12):2263-9.
18. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med.* 2011; 32(1):1-13.
19. Bø K, Artal R, Barakat R et al. Exercise and pregnancy in recreational and elite athletes: 2016 evidence summary from the IOC expert group meeting, Lausanne. Part 1-exercise in women planning pregnancy and those who are pregnant. *Br J Sports Med.* 2016; 50(10):571-89.
20. Gati S, Papadakis M, Papamichael ND et al. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. *Circulation.* 2014; 130(6):475-83.
21. Brown HL, Warner JJ, Gianos E et al. Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration with Obstetricians and Gynecologists: A Presidential Advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. *Circulation.* 2018; 137(24):e843-52.
22. Canadian Society for Exercise Physiology. PARmed-X for Pregnancy. Available at <http://www.csep.ca/cmfiles/publications/parq/parmed-xpreg>. [Cited in 2015 Dec 21]. Available from: <http://csep.ca/cmfiles/publications/parmed-xpreg.pdf>.
23. Force US, Curry SJ, Krist AH et al. Screening for Cardiovascular Disease Risk With. Electrocardiography: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2018; 319(22):2308-14.
24. Avila WS, Alexandre ER, Castro ML et al. Posicionamento da Sociedade Brasileira de Cardiologia para Gravidez e Planejamento Familiar na Mulher Portadora de Cardiopatia – 2020. *Arq Bras Cardiol.* 2020; 114(5):849-942.
25. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J et al. ESC Scientific Document Group, 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2018; 39(34):3165-241.
26. Santos IA, Stein R, Fuchs SC et al. Aerobic exercise and submaximal functional capacity in overweight pregnant woman: a randomized trial. *Obstet Gynecol.* 2005 Aug; 106(2):243-9.
27. Avery, ND, Wolfe LA, Amara GA et al. Effects of human pregnancy on cardiac autonomic function above and below the ventilatory threshold. *J Appl Physiol* (1985); 2001; 90(1):321-8.
28. Pivarnik JM, Stein AD, Rivera JM. Effect of pregnancy on heart rate/oxygen consumption calibration curves. *Med Sci Sports Exerc.* 2002; 34(5):750-5.
29. Du H, Newton PJ, Salamonson Y et al. A review of the six-minute walk test: its implication as a self-administered assessment tool. *Eur J Cardiovasc Nurs.* 2009; 8(1):2-8.
30. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test [published correction appears in *Am J Respir Crit Care Med.* 2016 May 15; 193(10):1185]. *Am J Respir Crit Care Med.* 2002; 166(1):111-7.
31. Subias P, Lesniak-Sobelga A, Irtzya O et al. Global cardiac risk assessment in the registry of pregnancy and cardiac disease: Results of a registry from the European Society of. *Cardiology. Eur J Heart Fail.* 2016; 18(5):523-33.
32. Pijuan-Domenech A, Galian L, Goya M et al. Cardiac complications during pregnancy are better predicted with the modified who risk score. *Int J Cardiol.* 2015; 195:149-54.
33. Balci A, Sollie-Szarynska KM, van der Bijl AG et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart.* 2014; 100(17):1373-81.
34. Drenthen W, Boersma E, Balci A et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J.* 2010; 31(17):2124-32.
35. Ruys TP, Roos-Hesselink JW, Hall R et al. Heart failure in pregnant women with cardiac disease: Data from the ropac. *Heart.* 2014; 100(3):231-8.
36. Pescatello, L, Arena R, Riebe D et al. ACSM's guidelines for exercise testing and prescription. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.
37. Nascimento SL, Godoy AC, Surita FG et al. Recomendações para a prática de exercício físico na gravidez: uma revisão crítica da literatura [Recommendations for physical exercise practice during pregnancy: A critical review]. *Rev Bras Ginecol Obstet.* 2014; 36(9):423-31.
38. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* 1982; 14(5):377-81.
39. Zavorsky GS, Longo LD. Exercise guidelines in pregnancy: new perspectives. *Sports Med.* 2011; 41(5):345-60.
40. Connor PJ, Poudevigne MS, Cress ME et al. Safety and efficacy of supervised strength training adopted in pregnancy. *J Phys Act Health.* 2011; 8(3):309-20.
41. Davenport MH, Nagpal TS, Mottola MF et al. Prenatal exercise (including but not limited to pelvic floor muscle training) and urinary incontinence during and following pregnancy: a systematic review and meta-analysis. *Br J Sports Med.* 2018; 52(21):1397-404.
42. Evenson KR, Barakat R, Brown WJ et al. Guidelines for Physical Activity during Pregnancy: Comparisons from Around the World. *Am J Lifestyle Med.* 2014; 8(2):102-21.
43. Hartmann S, Ochsenein-Kolble N, Rake A et al. Aqua fit during pregnancy: maternal and fetal hemodynamic responses during rest, immersion and exercise. *Geburtshilfe Frauenheilkunde.* 2001; 61:977-82.
44. McMurray RG, Katz VL, Berry MJ et al. The effect of pregnancy on metabolic responses during rest, immersion, and aerobic exercise in the water. *Am J Obstet Gynecol.* 1988; 158(3Pt1):481-6.
45. Garcia MK, Rizzo L, Yazbek-Júnior P et al. Cardiorespiratory performance of coronary artery disease patients on land versus underwater treadmill tests: A comparative study. *Clinics (São Paulo).* 2017; 72(11):667-74.
46. Murray RG, Katz VL, Berry MJ et al. Cardiovascular responses of pregnant women during aerobic exercise in water: a longitudinal study. *Int J Sports ed.* 1988; 9(6):443-7.
47. Ravanelli N, Casasola W, English T et al. Heat stress and fetal risk. Environmental limits for exercise and passive heat stress during pregnancy: A systematic review with best evidence synthesis. *Br J Sports Med.* 2019; 53(13):799-805.

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48. Gundle L, Atkinson A. Pregnancy, cold water swimming and cortisol: The effect of cold water swimming on obstetric outcomes. *Med Hypotheses*. 2020; 144:109977.
49. Camporesi EM. Diving and pregnancy. *Semin Perinatol*. 1996; 20(4):292-302.
50. Harrison CL, Brown WJ, Hayman M et al. The Role of Physical activity in pre-conception, pregnancy and postpartum health. *Semin Reprod Med*. 2016; 34(2):e28-e37.
51. Aune D, Sausgstad OD, Henriksen T et al. Physical Activity and the Risk of Preeclampsia A Systematic Review and Meta-Analysis. *Epidemiology*. 2014; 25(3):331-4.
52. Carvalho T, Milani M, Ferraz AS et al. Sociedade Brasileira de Cardiologia. Diretriz Brasileira de Reabilitação Cardiovascular – 2020. *Arq Bras Cardiol*. 2020; 114(5):943-87.
53. Witvrouwen I, Mannaerts D, Van Berendoncks AM et al. The effect of exercise training during pregnancy to improve maternal vascular health: Focus on Gestational Hypertensive Disorders. *Front Physiol*. 2020; 11:450.
54. Brown J, Ceysens G, Boulvain M. Exercise for pregnant women with gestational diabetes for improving maternal and fetal outcomes. *Cochrane Database Syst Rev*. 2017; 6(6):CD012202
55. Metzger BE, Gabbe SG, Persson B et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010; 33(3):676-82.
56. Duarte G, Oliveira R, Batista R et al. Prescrição de exercício para gestantes com diabetes melito gestacional: revisão de literatura. *Fisioterapia e Pesquisa*. 2007; 14(3):76-81.
57. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes. 2019-2020. *Gestão Biênio 2018-2019*. São Paulo: Clannad Editora Científica; 2020.
58. Peters TM, Brazeau AS. Exercise in Pregnant Women with Diabetes. *Curr Diab Rep*. 2019; 19(9):80.
59. Padayachee C, Coombes JS. Exercise guidelines for gestational diabetes mellitus. *World J Diabetes*. 2015; 6(8):1033-44.
60. American Diabetes Association. Management of diabetes in pregnancy: standards of medical care in diabetes-2020. *Diabetes Care*. 2020; 43(Suppl 1):S183-92.
61. Bolinder J, Antuna R, Geelhoed-Duijvestijn P et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet*. 2016 Nov 5; 388(10057):2254-63.
62. Dimitra S, Taousani E, Goulis Dg et al. Guidelines for exercise during normal pregnancy and gestational diabetes: a review of international recommendations. *Hormones (Athens)*. 2018; 17(4):521-9.
63. Stuebe AM, Oken E, Gillman MW. Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. *Am J Obstet Gynecol*. 2009; 201(1):58-1-58.
64. Du MC, Ouyang YQ, Nie XF et al. Effects of physical exercise during pregnancy on maternal and infant outcomes in overweight and obese pregnant women: A meta-analysis. *Birth*. 2019; 46(2):211-21.
65. Melo ME. Ganho de peso na gestação. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica – ABESO [Internet]. [Citado em 2017 mar 28] Disponível em: Disponível: <https://abeso.org.br/wpcontent/uploads/2019/12/5521b01341a2c.pdf>.
66. Halloran DR, Cheng YW, Wall TC et al. Effect of maternal weight on postterm delivery. *J Perinatol*. 2012; 32(2):85-90.
67. Thangaratinam S, Rogozijnska E, Jolly K et al. Interventions to reduce or prevent obesity in pregnant women a systematic review. *Health Technol Assess*. 2012; 16(31):iii-191.
68. Buschur E, Kim C. Guidelines and interventions for obesity during pregnancy. *Int J Gynaecol Obstet*. 2012; 119(1):6-10.
69. Nogueira AI, Carreiro MP. Obesidade e gravidez. *Rev Med Minas Gerais*. 2013; 23(1):88-98.
70. Sundgot-Borgen J, Sundgot-Borgen C, Myklebust G et al. Elite athletes get pregnant, have healthy babies and return to sport early postpartum. *BMJ Open Sport Exerc Med*. 2019; 21;5(1):e000652.
71. Garnaes KK, Morkved S, Salvesen O et al. Exercise Training and Weight Gain in Obese Pregnant Women: A Randomized Controlled Trial (ETIP Trial). *PLoS Med*. 2016; 13(7):e1002079.
72. Wolfe LA, Weissgerber TL. Clinical physiology of exercise in pregnancy: A literature review. *J Obstet Gynaecol Can*. 2003; 25(6):473-83.
73. Pivarnik JM, Ayres NA, Mauer MB et al. Effects of maternal aerobic fitness on cardiorespiratory responses to exercise. *Med Sci Sports Exerc*. 1993; 25(9):993-8.
74. <https://time.com/4757244/female-athletes-competing-winning-while-pregnant> [Internet]. Available from: <https://time.com/4757244/female-athletes-competing-winning-while-pregnant>
75. Radcliffe P. Pregnancy, motherhood and marathons: BBC Sports-Athletics [Internet]. [Citado em 2015 07 junho]. Disponível em: <https://www.bbc.com/sport/athletics/32996740>.
76. Kardel KR. Effects of intense training during and after pregnancy in top-level athletes. *Scand J Med Sci Sports*. 2005; 15(2):79-86.
77. Szymanski LM, Satin AJ. Strenuous exercise during pregnancy: Is there a limit? *Am J Obstet Gynecol*. 2012 Sep; 207(3):179.e1-179.e6.
78. Jastrow N, Meyer P, Khairy P et al. Prediction of complications in pregnant women with cardiac diseases referred to a tertiary center. *Int J Cardiol*. 2011;151(2):209-13.
79. Martins LC, Freire CM, Capuruçu CA et al. Predição de risco de complicações cardiovasculares em gestantes portadoras de cardiopatia. *Arq Bras Cardiol*. 2016; 106(4):289-96.
80. Adam K. Pregnancy in women with cardiovascular diseases. *Methodist Debakey Cardiovasc J*. 2017; 13(4):209-15.
81. Lesegno BV, Nelson-Piercy C. Advances in the management of cardiovascular disease during pregnancy. *Future Cardiol*. 2018; 14(4):269-72.
82. Mottola MF, Nagpal TS, Bgeginski R et al. Is supine exercise associated with adverse maternal and fetal outcomes? A systematic review. *Br J Sports Med*. 2019 Jan; 53(2):82-9.
83. Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Departamento de Atenção Hospitalar, Domiciliar e de Urgência. Protocolo de manejo clínico da Covid-19 na atenção especializada. [Citado em 2020 Mar 23] Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/manejo_clinico_covid19_atencao_especializada.pdf.
84. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand*. 2020 Jul; 99(7):823-9.
85. Avila WS, Carvalho RC. COVID-19: um novo desafio para a cardiopatia na gravidez. *Arq Bras Cardiol*. 2020; 115(1):1-4.
86. Conselho Federal de Fisioterapia e Terapia Ocupacional. Resolução COFFITO, Nº 516, de 20 de março de 2020. Teleconsulta, Telemonitoramento e Teleconsultoria. – Acórdão nº 392 Diário Oficial da União, em 12/06/20.
87. Conselho Federal de Educação Física. Entidades de Fiscalização do Exercício das Profissões Liberais/Conselho Regional de Educação Física da 4ª Região. Resolução Nº 123, de 15 de Abril de 2020. Diário Oficial da União de 23/04/2020.
88. Jurgen T. Belgian-Dutch Study: Why in times of COVID-19 you should not walk/run/bike close behind each other. Medium [Internet]. [Citado em 2020 Jun 29]; Disponível em: <https://medium.com/@jurgenthoele/belgian-dutch-study-why-in-times-of-covid-19-you-can-not-walk-run-bike-close-to-each-other-a5df19c77d08>

89. Long B, Brady WJ, Koyfman A et al. Cardiovascular complications in COVID-19. *Am J Emerg Med.* 2020 Jul; 38(7):1504-7.
90. Cuesta-Vargas AI. Ejercicio físico durante el embarazo, ganancia ponderal y retención de peso posparto [Physical exercise during gestational weight gain and postpartum weight retention]. *Nutr Hosp.* 2019; 36(4):751-2.
91. McKinley MC, Allen-Walker V, McGirr C et al. Weight loss after pregnancy: challenges and opportunities. *Nutr Res Rev.* 2018; 31(2):225-38.
92. Nascimento SL, Pudwell J, Surita FG et al. The effect of physical exercise strategies on weight loss in postpartum women: a systematic review and meta-analysis. *Int J Obes. (Lond).* 2014; 38(5):626-35.
93. Amorim Adegboye AR, Linne YM. Diet or exercise, or both, for weight reduction in women after childbirth. *Cochrane Database Syst Rev.* 2013; (7):CD005627.
94. Lim S, O'Reilly S, Behrens H et al. Effective strategies for weight loss in postpartum women: a systematic review and meta-analysis. *Obes Rev.* 2015; 16(11):972-87.
95. Dipietro L, Evenson KR, Bloodgood B et al. Benefits of Physical Activity during Pregnancy and Postpartum: An Umbrella Review. *Med Sci Sports Exerc.* 2019; 51(6):1292-302.
96. ACOG Committee Opinion No. 650: Physical Activity and Exercise During Pregnancy and the Postpartum Period. *Obstet Gynecol.* 2015; 126(6):e135-42.
97. O'Hara MW, Swain AM. Rates and risk of postpartum depression – A meta-analysis. *Int Rev Psychiatry.* 1996; 8(1):37-54.
98. Yang CL, Chen CH. Effectiveness of aerobic gymnastic exercise on stress, fatigue, and sleep quality during postpartum: A pilot randomized controlled trial. *Int J Nurs Stud.* 2018; 77:1-7.
99. Bahadoran P, Abbasi F, Yousefi AR et al. Evaluating the effect of exercise on the postpartum quality of life. *Iran J Nurs Midwifery Res.* 2008; 12(1):17-20.
100. Davies GA, Wolfe LA, Mottola MF et al. Society of Obstetricians and gynecologists of Canada, SOGC Clinical Practice Obstetrics Committee. Joint SOGC/CSEP clinical practice guideline: exercise in pregnancy and the postpartum period. *Can J Appl Physiol.* 2003; 28(3):330-41.
101. Butte NF, King JC. Energy requirements during pregnancy and lactation. *Public Health Nutr.* 2005; 8(7A):1010-27.
102. Bane SM. Postpartum exercise and lactation. *Clin Obstet Gynecol.* 2015; 58(4):885-92.
103. Woodley SJ, Boyle R, Cody JD et al. Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. *Cochrane Database Syst Rev.* 2017; 12(12):CD007471.
104. Evenson KR, Mottola MF, Artal R. Review of Recent Physical Activity Guidelines During Pregnancy to Facilitate Advice by Health Care Providers. *Obstet Gynecol Surv.* 2019; 74(8):481-9.
105. Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. *Cardiol Clin.* 2012;30(3):317-29.
106. Gavard JA, Artal R. Effect of exercise on pregnancy outcome. *Clin Obstet Gynecol.* 2008; 51(2):467-80.
107. Evenson KR, Mottola MF, Owe KM et al. Summary of international guidelines for physical activity after pregnancy. *Obstet Gynecol Surv.* 2014; 69(7):407-14.
108. Mueller MG, Lewicky-Gaupp C, Collins SA et al. Activity Restriction Recommendations and Outcomes After Reconstructive Pelvic Surgery: A Randomized Controlled Trial. *Obstet Gynecol.* 2017; 129(4):608-14.
109. Nygaard IE, Hamad NM, Shaw JM. Activity restrictions after gynecologic surgery: is there evidence? *Int Urogynecol J.* 2013; 24(5):719-24.
110. Minig L, Trimble EL, Sarsotti C et al. Building the evidence base for postoperative and postpartum advice. *Obstet Gynecol.* 2009; 114(4):892-900.
111. Mujika I, Padilla S. Detraining: loss of training-induced physiological and performance adaptations. Part I: short term insufficient training stimulus. *Sports Med.* 2000; 30(2):79-87.
112. Ceydeli A, Rucinski J, Wise L. Finding the best abdominal closure: an evidence-based review of the literature. *Curr Surg.* 2005; 62(2):220-5

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Brazilian Society of Cardiology Guidelines on Unstable Angina and Acute Myocardial Infarction without ST-Segment Elevation – 2021

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Note: These guidelines are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Brazilian Society of Cardiology Guidelines on Unstable Angina and Acute Myocardial Infarction without ST-Segment Elevation – 2021

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these update, 2020.

Expert	Type of relationship with industry
Alexandre de Matos Soeiro	Nothing to be declared
Alexandre Jorge de Andrade Negri	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AMIB: Instructor of postgraduate courses.
Andre Franci	Nothing to be declared
Ari Timerman	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Sanofi e Daiichi Sankyo: Aulas sobre Síndromes Coronárias Agudas. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Sanofi: Travel to Congress.
Brivaldo Markman Filho	Nothing to be declared
Bruno Ferraz de Oliveira Gomes	Nothing to be declared
Bruno Mendonça Baccaro	Nothing to be declared
Carlos Eduardo Lucena Montenegro	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Servier: Vastarel/Procoralan; Novartis: Entresto; Merk: Concor; Astrazeneca. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Amyloidosis; Servier: CAD/HF; Novartis: HF.
Carlos Eduardo Rochitte	Nothing to be declared
Carlos José Dornas Gonçalves Barbosa	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Daiichi Sankyo: Effient; Servier: Brilinta. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Xarelto; Daiichi Sankyo: Lixiana.

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João Luiz Petriz	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Daiichi Sankyo e Servier: Cardiology.
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José A. Marin-Neto	Nothing to be declared

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José Carlos Nicolau	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Amgen: Lipid-lowering; Bayer: Anticoagulant; Daiichi Sankyo: Antiplatelet, anticoagulant; Novartis: SRA inhibitor, lipid-lowering; Sanofi: Anticoagulant, lipid-lowering, antiplatelet; Servier: antiplatelet. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Astrazeneca: Antiplatelet, hypoglycemic; Bayer: Anticoagulant; Esperion: Lipid-lowering; CSL Behring: lipid-lowering; Dalcort: HDL increase; Jansen: Anticoagulant; Novartis: SARS inhibitor; Novo Nordisk: Hypoglycemic; Sanofi: Anticoagulant, lipid-lowering; Vifor: Iron Deficiency. C - Personal research funding paid by the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Roche: Laboratory kits for platelet aggregability assessment. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Sanofi: Anticoagulant, antiplatelet, lipid-lowering; Bayer: Anticoagulant; Servier: Antiplatelet.
José Maria Peixoto	Nothing to be declared
Juliana Ascensão de Souza	Nothing to be declared
Leonardo Sara da Silva	Nothing to be declared
Leopoldo Soares Piegas	Nothing to be declared
Lilia Nigro Maia	Nothing to be declared
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Marcelo Bueno da Silva Rivas	Nothing to be declared
Marcelo Franken	Nothing to be declared
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Paulo Rogério Soares	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Astrazeneca: Dapaglifozina; Servier: Ticagrelor; Bayer: Rivaroxabana.
Pedro Alves Lemos Neto	Nothing to be declared
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Rafael Rebêlo C. Cavalcanti	Nothing to be declared
Remo Holanda de Mendonça Furtado	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Astra Zeneca: Dapagliflozin (Diabetes, Heart Failure); Servier: Ticagrelor; Bayer: Rivaroxabana. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Rivaroxabana (Covid); Astra Zeneca: Dapagliflozina (Covid), Dapagliflozina (HF); Pfizer: Tofacitinib (Covid), Apixabana (AF); EMS, Aché, Servier, Health Canada, GSK, Servier.
Renato Abdala Karam Kalil	Nothing to be declared

Renato Delascio Lopes	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Anticoagulante; Boehringer Ingelheim: Anticoagulação e Diabetes; Pfizer: Anticoagulação; Bristol-Myers Squibb; Daiichi Sankyo; Glaxo Smith Kline; Medtronic; Merck; Portola; Sanofi. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Apixaban; Bayer: Rivaroxaban; Novartis: Sacubitril, Valsartan. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Rivaroxabana; Pfizer: Apixabana.
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Roberto Luiz Marino	Financial declaration B - Research funding under your direct/personal responsibility (directed to the department or institution) from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - CSL Behring: Myocardial Infarction.
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Walmor Lemke	Nothing to be declared
William Azem Chalela	Nothing to be declared
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Brazilian Society of Cardiology Guidelines on Unstable Angina and Acute Myocardial Infarction without ST-Segment Elevation – 2021

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	Viviana Lemke	Sandra Nives dos Reis Saraiva Falcão
	Wilson Mathias Júnior	

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Definitions of Recommendations and Evidence

Recommendations

Class I: Conclusive evidence, or, failing that, general consensus that the procedure is safe and useful/effective.

Class II: Conflicting evidence and/or divergence of opinion about the procedure's safety and usefulness/effectiveness.

Class IIa: Evidence/opinion is in favor of the procedure. Most approve of it.

Class IIb: The procedure's safety and utility/effectiveness is less well established, opinion is not predominantly in favor of it.

Class III: Evidence and/or consensus that the procedure is not useful/effective and, in some cases, is harmful.

Evidence

Level A: Data obtained from multiple large randomized studies, concordant and/or robust meta-analysis of randomized clinical studies.

Level B: Data obtained from less robust meta-analysis, from a single randomized study or from non-randomized (observational) studies.

Level C: Data obtained from expert consensus.

Changes in recommendations

Changes in recommendations - Biochemical Markers			
2014 Guideline	2020 Guideline		
Biomarkers of myocardial necrosis should be measured in all patients suspected of having non-ST-elevation acute coronary syndromes (NSTEMI-ACS). The markers should be measured at admission and repeated at least once 6 to 9 hours (preferably 9 to 12 hours) after symptom onset if the first dosage is normal or slightly elevated.	I	C	I B
Creatine kinase-MB (CK-MB) mass and troponins are the biochemical markers of choice.	I	A	IIb B
For patients who arrive early at the emergency department (6 h prior to symptom onset), myoglobin and highly sensitive troponin may be considered in addition to a later marker (CK-MB or troponin).	IIb	B	Troponins are the biomarkers of choice in patients with suspected AMI. I A
			Myoglobin can be used to detect myocardial necrosis in patients with suspected NSTEMI-ACS. III

Changes in recommendations - Exercise test			
2014 Guideline	2020 Guideline		
Low-risk patients (clinical and electrocardiogram [ECG]) with normal biochemical markers should be referred for exercise testing (ET) after 9 h of observation, ideally by 12 h, on an outpatient basis.	I	B	I B
			Low-risk patients (clinical and electrocardiogram [ECG]) with normal biomarkers should be referred for ET after 9 to 12 h of observation. These exams can be performed in the chest pain unit as a discharge criterion.

Changes in recommendations - Nuclear cardiology			
2014 Guideline	2020 Guideline		
Stress-rest myocardial perfusion scintigraphy (MPS) is an alternative for patients unable to perform ET.	I	C	I B
Patients with chest pain can be evaluated by rest MPS to determine whether the origin of the pain is ischemic or non-ischemic	IIa	A	IIa A
			Patients with chest pain but without ischemic ECG changes can be evaluated by myocardial perfusion scintigraphy at rest to determine whether the origin of the pain is ischemic or not.

Changes in recommendations - Analgesia and sedation				
2014 Guideline		2020 Guideline		
Administer morphine sulfate to intermediate- and high-risk patients.	I C	Administer morphine sulfate to patients with continuous pain despite optimized anti-ischemic therapy	IIb	B
Administer benzodiazepines to high-risk patients.	I C	Administer benzodiazepines to patients with signs and symptoms of persistent anxiety.	IIb	C
Administer benzodiazepines to intermediate-risk patients.	IIa C			
Changes in recommendations - Nitrates				
2014 Guideline		2020 Guideline		
Nitrates can be used in intermediate- and high-risk patients.	I C	Sublingual nitrates can be used to relieve angina.	I	C
		Intravenous nitrates can be used to control persistent angina, high blood pressure or signs of congestion.	I	C
Changes in recommendations - Beta-blockers				
2014 Guideline		2020 Guideline		
Administer oral beta-blockers to intermediate- and high-risk patients.	I B	Administer oral beta-blockers in the first 24 hours to patients without contraindications (signs of heart failure (HF), signs of low cardiac output, increased risk of cardiogenic shock or other contraindications to beta-blockers).	IIa	B
Changes in recommendations - Use of antiplatelet devices in the Emergency Department				
2014 Guideline		2020 Guideline		
Thienopyridines should be used in patients contraindicated to acetylsalicylic acid (ASA).	I B	In patients allergic to ASA, initial monotherapy with a P2Y ₁₂ inhibitor (preferentially ticagrelor or prasugrel) is indicated.	I	C
Changes in recommendations - Glycoprotein IIb/IIIa Inhibitors				
2014 Guideline		2020 Guideline		
Glycoprotein (GP) IIb/IIIa inhibitors should be used in patients with recurrent ischemic symptoms despite double oral platelet antiaggregation and anticoagulation.	IIa C	In the conservative strategy, adjunct tirofiban can be used in patients with recurrent ischemic symptoms despite treatment with double oral platelet antiaggregation and anticoagulation.	IIb	C
Changes in recommendations - Anticoagulants				
2014 Guideline		2020 Guideline		
Unfractionated heparin (UFH) can be used in all patients.	I A	UFH is preferential in patients with severe renal dysfunction (< 15 mL/min) and obese patients (weighing > 150 kg).	IIa	B
Low-molecular-weight heparins (LMWH) can be used in all patients.	I A	Enoxaparin can be used in patients without severe renal dysfunction (creatinine clearance < 15 mL/min/1.73 m²), until revascularization, for 8 days, or until hospital discharge, 1 mg/kg every 12 h (0.75 mg/kg, every 12 h, if ≥ 75 years old; use 1 mg/kg every 24 h if creatinine clearance is between 15 and 30 mL/min/1.73 m², with a maximum dose of 150 mg.	I	A
New recommendations				
History and physical examination				
Patients with suspected NSTEMI-ACS and persistent pain, dyspnea, palpitations or syncope should be referred to the emergency department, ideally monitored in an ambulance.			I	C
Patients with suspected NSTEMI-ACS with less severe findings (ie, without persistent pain, dyspnea, palpitations or syncope) should be instructed to seek out an emergency department that can perform ECG and troponin measurement.			IIb	C
Electrocardiogram				
ECG should be repeated if symptoms recur.			I	C
V3R-V4R and V7-V9 lead ECGs should be performed on patients with a non-diagnostic 12-lead ECG who remain symptomatic.			I	C

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Biochemical markers

When troponin is available, no other marker should be requested for diagnostic purposes.

I B

Coronary computed tomography angiography

Investigate acute chest pain with the triple rule-out technique.

IIb B

Diagnostic routine and hospitalization criteria

The initial screening should be based on clinical history, physical examination, 12-lead ECG in up to 10 min, and troponin level.

I A

HEART scores should be used to stratify risk and assist in hospital discharge decisions.

I B

Patients with HEART scores ≤ 3 associated with negative troponin results, ECG without ischemic change, and no history of coronary artery disease (CAD) can be released from the emergency department for outpatient reassessment.

I B

Hospital screening can be performed by qualified nurses for early recognition of high-risk patients.

IIa B

EDACS and ADAPT scores for clinical risk stratification can be used as alternatives to the HEART score.

IIa B

The HEART score can be used to determine early release for patients treated in an ambulance.

IIb C

Early invasive strategy

An invasive strategy is recommended for patients with NSTEMI-ACS and refractory angina and/or hemodynamic and/or electrical instability (without serious comorbidities or contraindications for these procedures).

I A

Glycemic control

It is recommended to measure the glycemic levels of all patients with suspected AMI at admission; the blood glucose of diabetic patients and those with hyperglycemia during hospitalization should be monitored.

I C

Glycemic control with intermittent insulin use protocols should be carefully considered in patients with glycemic levels > 180 mg/dL to avoid episodes of hypoglycemia.

IIa C

In patients at increased risk of hypoglycemia, such as older adults, nephropaths, and patients with residual effects from oral and/or fasting hypoglycemic agents, glycemic control should be adjusted to allow slightly higher blood glucose levels, thus preventing hypoglycemia.

IIa C

Beta-blockers

Administer beta-blockers intravenously in patients with risk factors for cardiogenic shock.

III

Initial antiplatelet therapy

Do not perform pretreatment with a P2Y₁₂ inhibitor in unstable and/or high-risk patients indicated for immediate invasive strategy; it is recommended instead for the catheterization room after the coronary anatomy has been determined and percutaneous coronary intervention (PCI) has been scheduled.

I B

P2Y₁₂ inhibitors should not be routinely used as a pretreatment in patients indicated for early invasive strategy (< 24 h).

I B

In patients with a very high risk of bleeding or who need long-term oral anticoagulation, clopidogrel (loading dose) can be used regardless of an initial conservative or invasive strategy.

IIa C

Pretreatment with prasugrel is not recommended.

III

Anticoagulants

Fondaparinux 2.5 mg subcutaneously once a day can be used for 8 days or until hospital discharge as an alternative to enoxaparin, especially in patients with a high risk of bleeding.

I B

Monitor anti-factor Xa in patients with creatinine clearance between 15 and 30 mL/min and in obese patients (100 to 150 kg) who are using enoxaparin.

IIa B

Enoxaparin is preferential to UFH in patients with creatinine clearance ≥ 15 mL/min (1.73 m^2), unless myocardial revascularization surgery is scheduled in the next 24 h.

IIa B

UFH is preferential in the emergency department or hemodynamics unit in very high-risk patients with immediate catheterization scheduled (< 2 h).

IIa C

Enoxaparin can be used in patients with creatinine clearance < 15 mL/min and weight > 150 kg.

III

Fondaparinux can be used in patients with creatinine clearance < 20 mL/min.

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Part 1 – Emergency Assessment and Management

1. Introduction

Acute chest pain is responsible for more than 5% of all emergency department visits and up to 10% of non-trauma related visits. The incidence of chest pain varies between 9 and 19 per 1,000 people/year seen in emergency departments and is involved in up to 40% of hospitalizations. Although most of these patients are discharged with a diagnosis of unspecified or non-cardiac chest pain, about 25% are diagnosed with acute coronary syndrome (ACS).^{1,2}

The subgroup of patients whose electrocardiography (ECG) results show no ST-segment elevation but whose symptoms or complementary exam results are compatible with a coronary etiology are classified as having non-ST-elevation acute coronary syndromes (NSTEMI), the subject of the present guideline. NSTEMI can cause significant morbidity and mortality if not promptly and appropriately treated. Since delaying appropriate treatment can result in serious adverse events, it is important to verify the presence of NSTEMI by assessing clinical data and complementary exams.³

2. Definitions

Chest pain is the main symptom in patients with ACS. ECG must be performed and interpreted within the first 10 minutes of medical contact in patients suspected of ACS, and the results may differentiate patients into two groups:

- ST-elevation ACS: Patients with acute chest pain and persistent ST-segment elevation or new or presumably new left bundle branch block, which is a condition generally related to coronary occlusion and the need for immediate reperfusion.
- NSTEMI: Patients with acute chest pain without persistent ST-segment elevation, whether associated or not with other ECG changes suggestive of some type of myocardial ischemia, including a broad spectrum of severity: transient ST-segment elevation, transient or persistent ST-segment depression, T-wave inversion, other nonspecific T-wave changes (flat or pseudonormalization),

and even normal ECG results. This group includes patients with unstable angina (UA), ie, with no changes in myocardial necrosis markers and those with non-ST-segment elevation myocardial infarction (NSTEMI) when there is an increase in myocardial necrosis markers.

A NSTEMI diagnosis is confirmed when there is an acute myocardial injury, which is confirmed by an increase in troponin levels, and the injury is suspected to be caused by ischemia. Based on its pathophysiology and clinical context, acute myocardial infarction (AMI) is classified into several subtypes (Tables 1.1 and 1.2). Increased troponin levels can be secondary to myocardial ischemia, but they can also occur in other clinical situations (Table 1.3).

Situations in which there is an increase in myocardial necrosis markers but ischemia is not detected in the clinical picture, ECG or imaging tests should be defined as acute myocardial injury, not AMI. They can be secondary to cardiac causes (such as cardiovascular procedures, myocarditis, arrhythmias, or decompensated HF) or extracardiac causes (such as shock, severe anemia, sepsis and hypoxia).⁴

Myocardial injury is often related to a worse prognosis. It is necessary to differentiate between ischemic and nonischemic causes to avoid unnecessary invasive interventions and direct treatment toward other possible etiologies (Table 1.3).

Figure 1.1 summarizes the interpretation of elevated troponin in coronary injury and ischemia scenarios.

2.1. Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA)

Cases of AMI without obstructive coronary artery disease (CAD) are classified as myocardial infarction with nonobstructive coronary arteries (MINOCA). Approximately two-thirds of patients with MINOCA have a clinical presentation of NSTEMI.⁵

According to a document prepared by a European Society of Cardiology working group⁶ and the Fourth Universal Definition of Myocardial Infarction,⁴ the diagnostic criteria for MINOCA are: AMI, angiographic documentation without obstructive CAD (atheromatosis with <50% stenosis or normal coronary arteries) or a clinically evident non-coronary cause for acute presentation.

Table 1.1 – Myocardial injury and infarction¹

Definition of myocardial injury
The term myocardial injury should be used in patients with cardiac troponin values >99th percentile of the upper reference limit. The injury is considered acute if there is dynamic behavior (rising and/or falling from baseline). Persistently high troponin values are considered chronic myocardial injury.
Definition of acute myocardial infarction (AMI types 1, 2 and 3)
AMI implies an acute myocardial injury in a clinical context of myocardial ischemia:
• Symptoms suggestive of acute myocardial ischemia
• New ischemic change in ECG
• New pathological Q-wave in ECG
• Imaging results showing a change in contractility or loss of viable myocardium consistent with ischemic etiology
• Intracoronary thrombus identified by angiography or necropsy (type 1 only)

Table 1.2 – Classification of acute myocardial infarction according to triggering factors

Classification (types)	Description
1	Spontaneous AMI related to myocardial ischemia secondary to a coronary event, such as rupture or erosion of coronary atherosclerotic plaque
2	AMI secondary to ischemia due to a myocardial oxygen supply/demand imbalance that is not directly related to coronary atherothrombosis
3	Sudden death with symptoms suggestive of ischemia accompanied by new ischemic changes in ECG or ventricular fibrillation before biomarkers are collected, if they are elevated, or in AMI confirmed by necropsy
4a	AMI associated with PCI ≤ 48 h, which is defined as a troponin increase >5 times the 99th percentile of the upper reference limit or 20% over already elevated baseline levels, associated with one of the following findings: • New ischemic change in ECG • New pathological Q-wave in ECG • Imaging results of a new change in contractility or loss of viable myocardium in a pattern consistent with myocardial ischemia • Angiographic findings of complications related to coronary flow limitations (dissection, epicardial vessel occlusion, loss of collateral circulation and distal embolization)
4b	AMI associated with stent thrombosis confirmed by angiography or necropsy
4c	AMI related to intrastent or post-angioplasty restenosis without other lesions or intracoronary thrombi that can explain it
5	AMI associated with myocardial revascularization surgery ≤ 48 h, defined by a >10 -fold increase in the 99th percentile of the upper reference limit or 20% over already elevated baseline levels, associated with one of the following findings: • New pathological Q-wave in ECG • Imaging results of a new change in contractility or loss of viable myocardium in a pattern consistent with ischemic etiology • Angiographic results showing the occlusion of a new graft or native coronary artery

Source: adapted from Thygesen K et al.⁴ AMI: acute myocardial infarction; ECG: electrocardiogram; PCI: percutaneous coronary intervention.

Different pathophysiological mechanisms can cause MINOCA:

- Dysfunction of epicardial coronary arteries (eg, atherosclerotic plaque rupture, ulceration, cracking, erosion or coronary dissection).
- Imbalance between oxygen supply and consumption (eg, coronary spasm and coronary embolism).
- Coronary endothelial dysfunction (eg, microvascular disease).

MINOCA prognosis varies greatly, depending on the underlying mechanisms and associated risk factors, such as age and female gender. Some studies indicate that MINOCA has lower hospital mortality than AMI with obstructive coronary artery disease and similar 1-year mortality to AMI with univascular obstruction. However, when analyzing patients with NSTEMI in the AUCITY study, the MINOCA subgroup had the highest 1-year mortality (4.7% vs. 3.6%), which was linked to an increase in non-cardiac deaths.⁷⁻⁹

The large group of patients presenting with elevated troponin but no coronary obstruction or clinical signs of infarction is classified as TINOCA (troponin-positive nonobstructive coronary arteries), which includes those with ischemic injury (MINOCA) and the other described etiologies of nonischemic myocardial injury (eg, myocarditis or Takotsubo syndrome; see Figure 1.2).

2.2. Unstable Angina

UA is defined as myocardial ischemia without myocardial necrosis, ie, with negative biomarkers. During the initial management of ACS, it is often difficult to differentiate UA from NSTEMI on clinical criteria alone (i.e., before

levels of myocardial necrosis biomarkers are available), and both conditions should be treated similarly at this stage. Increased troponin sensitivity decreases the percentage of patients diagnosed with UA and increases the percentage of patients with NSTEMI. The prognosis of patients with UA ranges from relatively low risk to high risk. UA classifications based on clinical presentation and prognostic information facilitate therapeutic management, which will be discussed throughout this document.¹¹⁻¹⁶

3. Epidemiology

AMI is the leading cause of death in Brazil and worldwide.¹⁷ In 2017, according to DATASUS, 7.06% (92,657 patients) of all deaths were caused by AMI, which accounted for 10.2% of hospitalizations in the Brazilian Unified Health System (SUS), was more prevalent in patients over 50 years of age, accounting for 25% of all hospitalizations.¹⁸

In the Brazilian Registry of Acute Coronary Syndromes (BRACE), which evaluated ACS hospitalizations in 72 hospitals, NSTEMI-ACS was responsible for 45.7%, of which about 2/3 involved AMI and 1/3 UA. The study found generally low use of therapies that impact the prognosis of patients with ACS, including important regional differences. It also developed a performance score, which showed that the greater the adherence to proven treatments, the lower the mortality.¹⁹

4. Pathophysiology

The main pathophysiological characteristic of ACS is the instability of atherosclerotic plaque, involving erosion

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Table 1.3 – Causes of myocardial injury

Myocardial injury with an ischemic etiology
• Rupture or erosion of atherosclerotic plaque with thrombosis
• Myocardial injury related to myocardial ischemia due to oxygen supply/consumption imbalance
Reduction in myocardial perfusion:
• Coronary artery spasm
• Coronary microvascular disease
• Coronary embolism
• Coronary dissection
• Sustained bradyarrhythmia
• Hypotension or shock
• Respiratory failure
• Severe anemia
Increase in oxygen consumption:
• Sustained tachyarrhythmia
• Hypertensive crisis
Myocardial injury due to other nonischemic cardiac conditions
• Heart failure/Myocarditis
• Any type of cardiomyopathy
• Takotsubo syndrome
• Myocardial revascularization surgery
• Catheter ablation
• Defibrillation or electrical cardioversion
• Myocardial contusion
• Síndrome de Takotsubo
Myocardial injury due to systemic conditions
• Sepsis or active infectious process
• Chronic kidney disease
• Stroke or subarachnoid hemorrhage
• Pulmonary embolism and pulmonary hypertension
• Infiltrative myocardial disease (eg, amyloidosis, sarcoidosis)
• Chemotherapeutic agents
• Critical patient
• Extreme physical activity

or rupture and subsequent formation of an occlusive or subocclusive thrombus. Such flow limitations, however, can be due to other mechanisms, such as vasospasm, embolism, or coronary dissection. Other factors may be involved in the pathophysiology of ACS by altering the supply and/or consumption of myocardial oxygen, such as anemia, hypertension, tachycardia, hypertrophic cardiomyopathy, aortic stenosis, etc..²⁰

In animals, ischemia has been observed to progress from the subendocardium to the subepicardium. This progression can be delayed when there is efficient

collateral irrigation, reduced oxygen consumption in the myocardium, and intermittent flow (generating ischemic preconditioning). Changes in ventricular function due to the progression of myocardial ischemia initially involve diastolic dysfunction, which may be followed or not by systolic dysfunction. A shorter duration of ischemic injury is associated with a smaller area of myocardial necrosis. Several studies have also suggested that restoring perfusion results in some degree of myocardial injury (reperfusion injury), especially in situations of total coronary occlusion.²¹

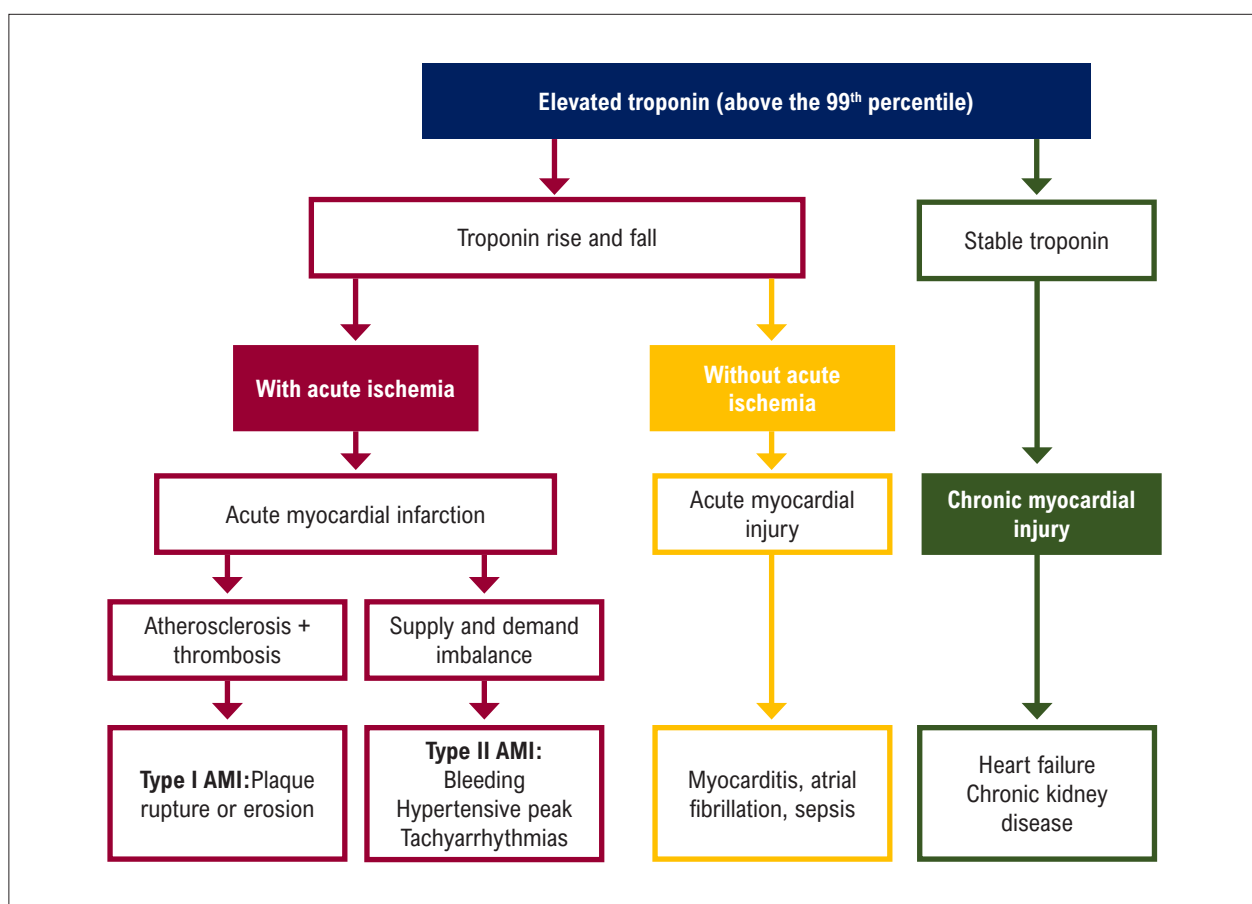


Figure 1.1 – Algorithm for interpreting elevated troponin levels. The troponin “curve” indicates elevation greater than 20%

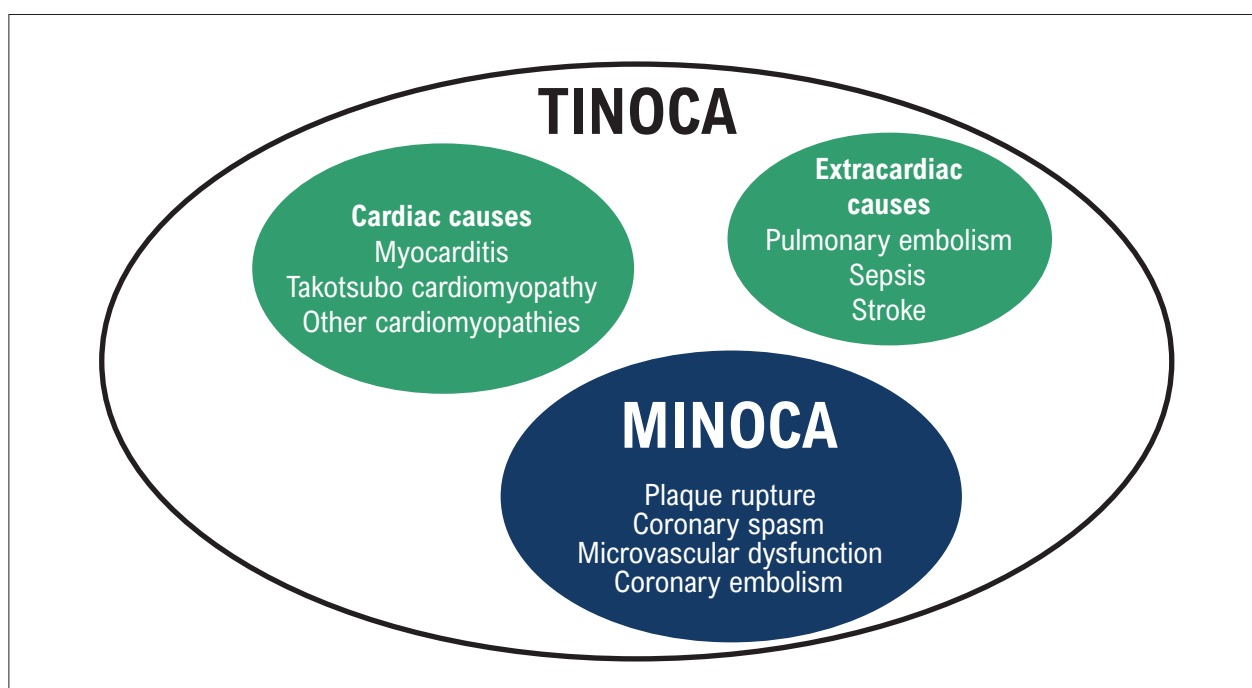


Figure 1.2 – Myocardial infarction with nonobstructive coronary arteries (MINOCA) and troponin-positive nonobstructive coronary arteries (TINOCA): conceptual paradigm. Adapted from Pasupathy et al., 2017.¹⁰

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5. Initial Assessment

5.1. Initial Approach

Patients with suspected ACS and signs of severity (persistent pain, dyspnea, and palpitations due to potentially severe arrhythmias and syncope) should be referred to emergency departments, ideally monitored while in the ambulance. Patients without signs of severity (listed above) should be instructed to seek out an emergency department that can perform ECG and cardiac biomarker measurement, preferably troponin.

Several tools (scores) have been devised for this purpose and, in conjunction with clinical judgment, can help define which patients could benefit from hospitalization, complementary exams, and specific treatment.

5.2. Diagnosis and Prognostic Assessment

5.2.1. History and Clinical Data

5.2.1.1. Characterization of Chest Pain and Angina

The clinical picture of angina can be defined by four main pain characteristics: location, type, duration, and intensification or relief factors.

- Location: usually in the chest, close to the sternum. However, it can affect or radiate from the epigastrium to the mandible, the interscapular region and the arms (more commonly to the left, less commonly to both arms or the right arm).

- Type: the discomfort is usually described as pressure, tightness or weight. Sometimes it involves a feeling of strangulation, compression or burning. It may be accompanied by dyspnea, sweating, nausea, or syncope.

- Duration: the duration of stable anginal pain is generally short (<10 min); episodes of ≥10 min suggest ACS. However, prolonged continuous pain (hours or days) or ephemeral pain (few seconds) is less likely to indicate ACS.

- Intensification or relief factors: one important feature of angina is its relationship with physical exertion. Symptoms classically appear or intensify on exertion. In patients with no history of angina, a reduction in the effort threshold required to trigger angina suggests ACS. ACS discomfort does not usually vary with changes in breathing or position.

The clinical history of patients with NSTEMI-ACS plays an important role in risk stratification. In the presence of angina, patients with NSTEMI-ACS can present in four ways:

- Prolonged resting angina (> 20 min).

- Recent onset angina (class II or III according to Canadian Cardiovascular Society classification): in general, these patients manifest typical symptoms of angina in less than 2 months that begin appearing after minimal exertion.

- Recent worsening of previously stable angina (crescendo angina). Minimal exertion triggers angina, increased pain intensity and/or duration, changes in pain radiation patterns, changes in response to the use of nitrates.

- Post-infarction angina.

Some characteristics, antecedents and comorbidities are related to a higher probability of ACS:

- Advanced age and male sex.

- Risk factors for atherosclerosis: smoking, diabetes mellitus (DM), dyslipidemia, arterial hypertension and chronic renal failure.

- Family history of CAD.

- Previous symptomatic atherosclerosis, such as peripheral arterial obstructive disease, carotid disease, previous coronary disease.

- Chronic inflammatory diseases, such as lupus or rheumatoid arthritis.

ACS patients may present with atypical symptoms, such as isolated epigastric pain, feelings of gastric fullness, lancinating pain, pleuritic pain or dyspnea. Although ACS typically presents in women and older adults (> 75 years) as angina, atypical presentations are also higher in these groups, as well as in patients with DM, renal failure and dementia.

The Coronary Artery Surgery Study proposed a chest pain classification system,²² which is shown in Table 1.4.

5.2.1.2. NSTEMI-ACS in Older Adults

Older adults with ACS generally have a different risk profile from younger adults: they have a higher prevalence of hypertension, DM, previous AMI, angina, peripheral vascular disease, stroke, multivessel disease, and HF. Older adults generally wait longer to seek medical care after symptom onset. In NSTEMI-ACS, instead of pain, patients often have so-called “ischemic-equivalent” symptoms, such as dyspnea, malaise, mental confusion, syncope or pulmonary edema. Older adults have a higher incidence of complications in NSTEMI-ACS, which implies the need for more intensive treatment. However, especially in adults over 75 years of age, the most appropriate therapy, ie, beta-blockers, acetylsalicylic acid (ASA), anticoagulants and lipid-lowering agents, is not used. Of the 3,318 patients with NSTEMI-ACS included in the TIMI III study,²³ 828 were over 75 years old. These individuals received anti-ischemic therapy and underwent cardiac catheterization at a lower percentage than younger patients. Although they had

Table 1.4 – Coronary Artery Surgery Study angina classification system

Definitely anginal pain	Retrosternal pain due to exertion, radiating to the shoulder, neck or left arm and attenuated by rest or nitrates in <10 min
Probably anginal pain	Most of the characteristics of definite angina pain
Probably not anginal pain	Atypical pain that does not meet the criteria for anginal pain
Definitely not anginal pain	Pain uncorrelated with physical activity (suggestive of non-cardiac origin) that is unmitigated by nitrates

Source: Adapted from the National Heart Lung and Blood Institute's Coronary Artery Surgery Study.²²

more severe and extensive CAD, they less frequently underwent myocardial revascularization procedures and had more adverse events within 6 weeks of onset. According to a national database study, the use of proven efficacious therapies after ACS has increased in the last 15 years, both among the oldest old (age > 80 years) and in younger adults (< 50 years), and this increase has been associated with improved survival in both groups.²⁴

5.2.1.3. History

5.2.1.3.1. Patients Undergoing Myocardial Revascularization Procedures: Percutaneous Coronary Intervention and/or Myocardial Revascularization Surgery

The recurrence of angina after coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) can indicate acute complications, new injuries, stent thrombosis, or restenosis. Chest pain up to 48 hours after percutaneous intervention suggests acute obstruction, transient coronary spasm, non-occlusive thrombus, branch occlusion or distal embolization. Recurrent chest pain approximately 6 months after conventional stenting or later, after drug-eluting stenting, is most likely related to restenosis. On the other hand, angina onset 1 year after stenting is usually related to a new coronary lesion or stent restenosis due to neoatherosclerosis. After a CABG, the early appearance of pain is usually associated with thrombotic obstruction of the graft. In the first 12 months after CABG, the mechanism is usually fibrous intima hyperplasia; after this period, pain is indicative of a new atherosclerotic lesion and/or non-thrombotic graft degeneration. The TIMI III registry compared the incidence of death or nonfatal infarction among NSTEMI-ACS patients with or without previous CABG. Those with previous CABG had higher rates of complications up to 10 days after admission (4.5% vs. 2.8% with or without CABG, respectively) and after 42 days (7.7% vs. 5.1%, respectively), which suggests that this is a higher risk group, mainly due to more extensive atherosclerosis.²⁵

5.2.1.3.2. Risk Factors for Coronary Artery Disease

Some studies have suggested that smokers have a better prognosis, probably due to the fact that they suffer ACS at an earlier age and have less atherosclerotic burden than non-smokers.^{26,27} On the other hand, Antman et al. showed that having three or more risk factors for CAD (systemic arterial hypertension, DM, dyslipidemia, family history and smoking) is an independent marker of a worse prognosis.²⁸

5.2.2. Physical examination

During assessment of individuals with NSTEMI-ACS, a physical examination can help identify individuals at higher risk (those with signs of severe ventricular dysfunction or mechanical complications) and help in the differential diagnosis of chest pain unrelated to ACS.

As a rule, a normal or slightly modified physical examination is insufficient to stratify patient risk, since even patients with multivessel or left main coronary lesions can appear normal upon physical examination.²⁹⁻³¹ However, when changes are found in a physical examination, they can be important for categorizing patients as high risk.

Some findings that indicate a poor prognosis include systolic murmur in the mitral focus tachycardia, tachypnea, hypotension, sweating, weak pulse, third heart sound, and pulmonary rales.

Changes in physical examination results allow differential diagnosis between ACS and other causes of chest pain:

- **Cardiac:** pericarditis (pericardial friction), cardiac tamponade (paradoxical pulse), aortic stenosis (aortic systolic murmur), and hypertrophic cardiomyopathy (ejection systolic murmur in the parasternal area that increases with the Valsalva maneuver).

- **Non-cardiac:** aortic dissection (pulse and pressure divergence between the arms and a diastolic murmur of aortic insufficiency), pulmonary embolism/pulmonary infarction (pleural friction), pneumothorax (decreased breath sounds and hyperresonance to percussion), and musculoskeletal symptoms (pain on palpation).

History and physical examination - Summary of recommendations and evidence

Patients with suspected NSTEMI-ACS and persistent pain, dyspnea, palpitations or syncope should be referred to emergency departments, ideally monitored in the ambulance.	I	C
Patients suspected of NSTEMI-ACS with less severe findings (i.e., without persistent pain, dyspnea, palpitations or syncope) should be instructed to seek out an emergency department that can perform ECG and troponin measurement.	IIb	C

5.2.3. Electrocardiogram

Twelve-lead ECG is the initial diagnostic tool for patients with suspected ACS. Ideally, it should be performed and interpreted during pre-hospital care or within 10 minutes of hospital admission.

About 1% to 6% of patients with NSTEMI-ACS have normal (non-diagnostic) ECG results at admission. The ECG should be repeated after 15 to 30 minutes, especially in individuals who are still symptomatic. Normal or non-diagnostic ECG results can occur even with left circumflex or right coronary artery occlusion. Thus, additional V3R, V4R, V7, V8, and V9 derivations are recommended to increase the method's sensitivity.

More than 1/3 of patients will have typical ACS changes, such as ST-segment depression, transient ST-segment elevation, and T-wave inversion. Dynamic changes in the ST-segment (depression or elevation) or T-wave inversions during a painful episode that resolve at least partially when the symptoms are relieved are important markers of adverse prognosis, ie, subsequent AMI or death.³² Patients with ST changes in anterior leads often have significant stenosis of the anterior descending coronary artery and are a high-risk group.

ST-segment and T-wave changes are not specific to NSTEMI-ACS and can occur in several conditions, including: ventricular hypertrophy, pericarditis, myocarditis, early repolarization, electrolyte alteration, shock, metabolic dysfunction, and digitalis effect.

The diagnostic accuracy of an abnormal ECG is increased when previous ECG results are available for comparison.

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Transient ST-segment elevation is consistent with Prinzmetal or vasospastic angina. Concomitant ST elevation in the anterior and inferior leads (reflecting extensive ischemia) is associated with an increased risk of sudden death.³³

5.2.3.1. Electrocardiogram Findings and Prognosis

Patients with NSTEMI-ACS are at high risk of ischemic ECG changes (elevated or depressed ST-segment), atrial fibrillation, and ventricular arrhythmias. These changes imply a worse prognosis.³¹ In the GUSTO II trial, certain baseline ECG factors in patients with ACS were prognostic of early mortality:³⁴ left bundle branch block, left ventricular (LV) hypertrophy or pacemaker rhythm (11.6%); ST-segment depression (8%); ST-segment elevation (7.4%); and normal T-wave inversion or normal ECG (1.2%).

Moreover, in 1,416 patients with ACS, the TIMI III Registry ECG Ancillary Study³⁵ found the following ECG presentations: ST-segment deviation > 1 mm (14.3%), left bundle branch block (19%), isolated T-wave inversion (21.9%), or none of these changes (54.9%).

Electrocardiogram - Summary of recommendations and evidence		
All patients with suspected NSTEMI-ACS should undergo ECG. Ideally, an ECG should be performed within 10 minutes of the patient's arrival at the hospital.	I	B
The ECG should be repeated at least once within 6 hours in non-diagnostic cases.	I	C
The ECG should be repeated in case of symptom recurrence.	I	C
The V3R-V4R, and V7-V9 leads should be recorded in patients who remain symptomatic and have a non-diagnostic 12-lead ECG.	I	C

5.2.4. Biomarkers

In patients with ACS, biomarkers are useful for both diagnosis and prognosis. When myocardial cells are injured, their cell membranes lose integrity, intracellular proteins diffuse across the interstitium and into the lymphatic system and capillaries. After a myocardial injury, marker kinetics depend on several factors: intracellular protein degradation, molecule size, regional lymphatic and blood flow, as well as marker clearance rate. Such factors, together with the characteristics of each marker, differentiate each patient's diagnostic AMI performance.³⁶

In patients with symptoms suggestive of ACS but without diagnosed AMI, cardiac biomarkers are useful to confirm the diagnosis. They also provide important prognostic information, since there is a direct association between elevated serum markers and the risk of cardiac events in the short and medium-term.³⁷ The necrosis marker results must be available within 60 minutes of collection. If the clinical analysis laboratory cannot provide this, point-of-care technologies should be considered.³⁸

5.2.4.1. Troponins

Troponins are a complex of myofibrillar regulatory proteins in striated cardiac muscle that include troponin T, troponin I, and troponin C. Troponin C is coexpressed in slow-twitch

skeletal muscle fibers and is not considered as a specific cardiac marker. In recent decades, immunoassay techniques with specific monoclonal antibodies for cardiac troponin T and cardiac troponin I have been developed. Meta-analyses have shown that the sensitivity and specificity of cardiac troponin I for diagnosing AMI was approximately 90% and 97%, respectively. Cardiac troponins remain elevated for a longer time, up to 7 days after AMI. Troponins are the biomarkers of choice for diagnostic evaluation in patients with suspected AMI since their diagnostic accuracy is higher than that of creatine kinase MB (CK-MB) mass and other biomarkers of myocardial injury. Patients with elevated troponins are at increased risk of cardiac events during the first days of hospitalization and are the NSTEMI-ACS subgroup that can most benefit from an invasive strategy.³⁹ Although troponins can accurately identify myocardial injury, they cannot identify the mechanism of injury(ies). The mechanisms can include non-coronary etiologies, such as tachyarrhythmias and myocarditis, or non-cardiac conditions, such as sepsis, pulmonary embolism, and renal failure.⁴⁰ Thus, in cases where the clinical presentation is not typical of ACS, other causes of cardiac injury related to increased troponins should be considered.

Troponins have recognized value when evaluating patients with ischemic ECG changes or with clinical symptoms suggestive of anginal pain. The major limitation of conventional troponins is their low sensitivity in patients whose time to onset is less than 6 hours. With the introduction of highly sensitive troponin assays, it became possible to detect lower troponin levels in a shorter time after ischemic myocardial injury.^{41,42} The unit used to express the values of conventional troponin is ng/mL, and in highly sensitive troponins, the values can be expressed in ng/L, since their detection power is 10 to 100 times greater than conventional troponins.

Highly sensitive troponins are significantly more sensitive than conventional troponins in ACS diagnosis, improving the diagnostic power for AMI by 61% if collected less than 3 hours after onset and 100% if collected 6 hours after onset.⁴³ Due to the highly sensitive troponin assay's increased sensitivity and diagnostic accuracy for AMI, accelerated diagnosis algorithms have been proposed. Thus, the time to diagnosis can be shortened, which means less time in the emergency department and lower costs.⁴⁴⁻⁴⁶ It is recommended that the investigation algorithm be used within 3 hours (see routine diagnostic flowchart and hospitalization criteria).

5.2.4.2. Creatine Kinase: Isozymes and Isoforms

Before troponins emerged as more accurate biomarkers in AMI diagnosis, CK-MB was the most common biomarker in chest pain protocols. Ideally, CK-MB should be measured by immunoassay for plasma concentration (CK-MB mass) rather than activity. This change in measurement patterns is due, in part, to studies that demonstrated that CK-MB mass has greater sensitivity and specificity for AMI.⁴⁷ CK-MB subforms have emerged as early markers (< 6 hours) of myocardial injury and early inference of AMI severity, according to data from a necropsy study that demonstrated a better correlation between CK-MB mass and AMI size.⁴⁸ However, the main limitation of CK-MB mass is damage to other non-cardiac

tissues (false positives), especially after injuries to smooth or skeletal muscle. In about 4% of patients, false-positive results can occur, with positive CK-MB and negative troponin.⁴⁹ In cases where CK-MB is elevated and troponin is normal, both within their kinetic windows, clinical decisions should be based on the troponin results.

Biochemical markers - Summary of recommendations and evidence		
Troponins are the biomarkers of choice for diagnosing patients with suspected AMI.	I	A
When highly sensitive troponin assays are available, no other marker should be requested for routine AMI diagnosis.	I	B
Biochemical biomarkers of myocardial necrosis should be measured in all patients with suspected NSTEMI-ACS. When highly sensitive troponin assays are available, serum levels should be measured on admission and, ideally, reassessed in 1 h or up to 2 h. If unavailable, conventional troponin measurement should be performed at admission and repeated at least once, 3 to 6 hours later, if the initial results are normal or slightly elevated.	I	B
CK-MB mass levels can be used if troponin assays are unavailable.	IIb	B
Myoglobin can be used to detect myocardial necrosis in patients with suspected NSTEMI-ACS.	II	

5.2.5. Non-Invasive Imaging in the Emergency Department

5.2.5.1. Functional Assessment

Non-invasive exams play an essential role in the diagnosis (especially in patients with normal ECG and biomarker results) and risk stratification of patients with suspected ACS. The choice for each patient – whether ET, myocardial perfusion scintigraphy, cardiac resonance, or coronary computed tomography angiography – will depend on the objectives and clinical questions to be answered.⁵⁰

5.2.5.2. Exercise Testing in the Emergency Department

In the emergency department, patients whose chest pain is identified as low or intermediate risk can undergo ET. Normal results indicate a low risk of cardiovascular events, allowing for earlier and safer hospital discharge.⁵⁰ National and international guidelines recommend ET as the first choice for risk stratification in patients who can exercise since it is a low-cost procedure, is widely available, and has a low frequency of complications.⁵¹ However, patients with moderate- to high-risk ACS, acute aortic diseases, pulmonary thromboembolism, myocarditis, or pericarditis must be ruled out since these conditions are absolute contraindications. The testing protocol should be determined according to the patient's clinical condition, with the most recommended being a modified Naughton or Bruce ramp test.

ET indications in ACS (to characterize low risk after initial clinical stratification) include:

- Baseline ECG and necrosis biomarkers without changes.
- Absence of symptoms (chest pain or dyspnea).

- Hemodynamic stability and adequate conditions for physical exertion.

If the ET results are normal and the patient has shown adequate functional capacity, other procedures may not be necessary due to the test's high negative predictive value.⁵¹

Exercise testing - Summary of recommendations and evidence		
Low-risk patients (according to clinical and ECG results) with normal biomarkers should be referred for ET after 9 to 12 hours of observation. In chest pain unit routines, these exams can be performed as a discharge criterion.	I	B
If an ET cannot be performed or the ECG is uninterpretable (left bundle branch block, artificial pacemaker, atrial fibrillation, LV overload, etc.), the patient can undergo ischemia tests associated with non-invasive imaging.	I	B

5.2.5.3. Echocardiography

Echocardiography is a useful complementary method for evaluating chest pain in emergencies.⁵²⁻⁵⁴ This non-invasive exam provides quick diagnostic information.⁵⁵⁻⁵⁹ When performed during an episode of chest pain, a lack of abnormal ventricular segmental contraction indicates a nonischemic cause. Although echocardiography cannot determine whether the segmental change is recent or pre-existing, the presence of segmental contraction abnormalities reinforces the probability of CAD being indicative of infarction, ischemia, or both. However, it can also appear in cases of myocarditis.⁶⁰⁻⁶²

Other no less important etiologies of chest pain (e.g., aortic dissection, aortic stenosis, hypertrophic cardiomyopathy, and pericardial disease) can also be assessed with echocardiography. Significant coronary heart disease is commonly found in patients with UA. These patients are generally identified by clinical history, and reversible ECG changes can be detected with pain episodes. When the patient's history and ECG are atypical, documenting a segmental contraction abnormality with echocardiography during or immediately after a pain episode strongly suggests the diagnosis.⁶³ Echocardiography also determines the presence and extent of ventricular dysfunction and the presence and severity of valve abnormalities.

Other parameters are also important in determining prognosis in addition to the LV ejection fraction (LVEF) and segmental motility. Ersbøll et al. prospectively studied patients with infarction and LVEF > 40% within 48 hours of admission. All patients underwent ECG with semi-automated global longitudinal strain (GLS) assessment. Of the 849 patients, 57 (6.7%) had severe cardiac events, and GLS > -14% was associated with a 3-fold increase in the risk of severe events.⁶³

5.2.5.4. Stress Echocardiography

Stress echocardiography is being increasingly used in emergency departments and soon after hospitalization.⁶⁴ One study analyzed 108 patients who were observed for 4 hours with serial biomarkers and ECG and underwent stress ET or dobutamine stress ECG. Ten patients had positive stress ET results, and 8 had positive stress ECG results. The exams were consistent in 4 patients. All patients whose stress ECG results

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showed no evidence of ischemia were cardiac event-free at the end of 12 months of follow-up, as were 97% of the patients with negative stress ET results.⁶⁵

A Brazilian study evaluated 95 patients with low- and moderate-risk UA with echocardiography under dobutamine stress, most of whom were assessed in the first 72 hours of hospitalization. For the clinical outcomes (death, AMI, new hospitalization due to UA and myocardial revascularization procedures), the exam proved to be safe and had an excellent negative predictive value (96%), allowing early discharge without the need for other tests.⁶⁶ Using perfusion techniques to perform stress echocardiography can increase diagnostic sensitivity; their applications are discussed in Part 2 of this Guideline.

Because it is an accessible, fast, low-cost, and non-invasive test, echocardiography can provide additional prognostic information about the previously mentioned parameters by assessing global and regional ventricular function and identifying associated valvulopathy. It can be routinely used in the investigation of these patients. Its disadvantages are its limited acoustic window in some patients and reduced sensitivity to dobutamine stress in patients on beta-blockers.

Echocardiography - Summary of recommendations and evidence		
Transthoracic echocardiography must be performed for a differential diagnosis when there is clinical suspicion of aortic disease, pericardial disease, pulmonary embolism, or heart valve disease.	I	C
Emergency echocardiography should be performed when there are complications resulting from NSTEMI-ACS, such as interventricular communication and mitral regurgitation.	I	C
Stress echocardiography can be used for functional stratification in patients without recurrent chest pain or ECG evidence of ischemia and/or troponin elevation.	I	B
In patients with chest pain, resting echocardiography can identify changes compatible with ischemic etiology.	IIa	C

5.2.5.5. Nuclear Cardiology

Several studies have suggested that low-risk results for resting myocardial scintigraphy performed in the emergency department indicate a very low risk of subsequent cardiac events. On the other hand, there is a much greater probability that patients with high-risk myocardial perfusion scintigraphy results will develop AMI, be revascularized (surgery or angioplasty), or have coronary lesions a coronary angiogram.⁶⁷⁻⁶⁹ The ERASE trial evaluated care strategies for ACS patients with normal or non-diagnostic ECG, finding admission rates of 54% for patients who underwent MPS and 63% for all others, which suggests that an initial strategy involving resting scintigraphy is an acceptable risk stratifier.⁷⁰

International guidelines recommend rest myocardial perfusion imaging during acute chest pain to stratify risk in patients with suspected ACS who have non-diagnostic ECG results.⁷¹⁻⁷³

Radiotracer injection:

The main applications of MPS in the first hours after the patient's hospital admission include:

- Injection of the radiotracer (sestamibi/MIBI or technetium-99m-labeled tetrofosmin, or 99mTc-sestamibi, and 99mTc-tetrofosmin) at rest during a chest pain episode in patients with normal or nonspecific ECG, aiming at a rapid, definitive diagnosis.

- Injection of the radiotracer at rest in patients without chest pain, normal or nonspecific ECG, and symptom cessation less than 6 hours, but preferably within the previous 2 hours. Wackers et al. found that when the injection was performed in the first 6 hours of pain in ACS patients, the incidence of perfusion abnormalities was 84%, which decreased to 19% when the radiotracer was intravenously administered between 12 and 18 hours after the last pain episode.⁷⁴

Overall, radiotracers can be used to obtain resting perfusion images for acute chest pain assessment without formal contraindications, and most patients well tolerate them. MPS with physical or pharmacological stress in low- or intermediate-risk ACS patients is recommended after stabilizing the acute condition and is usually performed during hospitalization. Stable clinical and hemodynamic conditions are paramount in both situations. The limitations of this method are its availability and cost.

Nuclear cardiology - Summary of recommendations and evidence		
MPS at rest during acute chest pain to stratify risk in patients with suspected ACS who have non-diagnostic ECG results	I	A
MPS can be used for functional stratification in patients without recurrent chest pain, without ECG evidence of ischemia and/or elevated troponin levels	I	B
Patients with chest pain and no ECG evidence of ischemic changes can be assessed with MPS at rest to determine whether the pain has an ischemic origin	IIa	A

5.2.5.6. Anatomical Assessment: Coronary Computed Tomography Angiography

In recent years, coronary computed tomography angiography (CCTA) has been increasingly used to assess patients with suspected obstructive coronary disease. It has been demonstrated that the method is more accurate in diagnosing luminal stenosis than invasive coronary angiography, especially its high negative predictive value.⁷⁵⁻⁷⁷ Several studies in different clinical situations have also shown the prognostic value of CCTA regarding the presence and extent of obstructive and non-obstructive CAD, which can help with decision-making.^{78,79}

Three large multicenter randomized controlled trials have evaluated CCTA for chest pain in emergency departments, including a total of more than 3,000 patients. The multicenter CT-STAT study randomized 699 patients with low-risk chest pain to stratification with CCTA or rest-stress myocardial scintigraphy.⁸⁰ The CCTA strategy reduced diagnosis time by 54% and hospitalization costs by 38%, with no difference in the rate of adverse events between the two methods. The ACRIN-PA study primarily aimed at assessing the safety of CCTA for evaluating patients with low- and intermediate-risk chest pain compared to the traditional approach.⁸¹

None of the patients with negative CCTA had the primary outcome (cardiac death or infarction) in the first 30 days after admission. Also, patients in the CCTA group had a higher rate of discharge from emergency departments (49.6% vs. 22.7%) and fewer days of hospitalization (18 hours vs. 24.8 hours, $p < 0.001$), with no significant differences in the incidence of coronary angiography or revascularization in the first 30 days after admission. Finally, the ROMICAT II study evaluated the emergency department length of stay and hospital costs in similar groups of patients.⁸² It included 1000 patients with an average age of 54 years (46% female). The length of hospital stay was significantly shorter in patients stratified by CCTA than the traditionally-assessed group (23.2 ± 37 hours vs. 30.8 ± 28 hours; $p = 0.0002$). The time until an ACS diagnosis was also shorter in the CCTA group (17.2 ± 24.6 hours vs. 27.2 ± 19.5 hours; $p < 0.0001$). There were no significant safety differences between the groups. In the CCTA group, there was a substantial increase in patients discharged directly from the emergency department (46.7% vs. 12.4%; $p = 0.001$), but significantly more diagnostic tests were used in this group (97% vs. 82%, $p < 0.001$). Despite the higher cost associated with CCTA and a tendency toward more catheterizations and revascularizations, the overall costs were similar between the two groups ($p = 0.65$).

A subsequently published meta-analysis confirmed that using CCTA to assess patients with acute chest pain is associated with reduced cost and length of hospital stay, with an apparent increase in invasive angiographies and myocardial revascularizations compared to traditional approaches.⁸³

5.2.5.6.1. Triple Rule-out

CCTA can be used in the emergency department to visualize the coronary arteries and obtain information about the aorta and pulmonary arteries, allowing assessment for acute aortic syndromes, pulmonary thromboembolism, or other thoracic changes that may be differential diagnoses of ACS (pneumonia and trauma).^{84,85} Through specific acquisition protocols, all of this information can be obtained in a single exam. This approach is called the triple rule-out, but it should only be used in specific situations where clinical evaluation cannot direct the diagnosis.⁸⁶

In summary, CCTA is a safe and efficient strategy for evaluating patients with acute low- and intermediate-risk chest pain in emergency departments, reducing the time until correct diagnosis and length of hospital stay.⁸⁷ The method's disadvantages include the use of ionizing radiation, its high cost, the need for iodinated contrast media, its limited availability in Brazil, and the fact that it cannot be used in patients with heart rates above 80 beats per minute or who cannot use beta-blockers.

Coronary computed tomography angiography - Summary of recommendations and evidence		
In patients with acute chest pain and a low to intermediate probability of CAD, non-diagnostic ECG, and negative markers of myocardial necrosis.	I	A
Acute chest pain can be investigated with the triple rule-out technique.	IIb	B

5.3. Risk Stratification

5.3.1. Risk Stratification of Ischemic Cardiovascular Events

Using the TIMI IIB database, Antman et al. found the following independent markers of worse prognosis in patients with NSTEMI-ACS ("TIMI group risk score"): age ≥ 65 years, elevated biochemical markers, ST-segment depression ≥ 0.5 mm, ASA use in the 7 days prior to symptom onset, three or more traditional risk factors for CAD (hypertension, hypercholesterolemia, DM, smoking, or family history), known CAD, and recent severe angina (< 24 hours).²⁸ With one point for each item, a score of 0 to 2 is classified as low risk, 3 to 4 as intermediate risk, and 5 to 7 as high risk. This risk score has been validated in other NSTEMI-ACS studies. An association has been found between each marker and a higher incidence of events (death, reinfarction, and recurrent ischemia requiring revascularization) and higher risk scores. (Figure 1.3).

Due to its good discriminatory power, the Global Registry of Acute Coronary Events (GRACE) risk score allows more accurate stratification at both hospital admission and discharge (Figure 1.4). However, it is complex, requiring a personal computer or digital device to calculate the risk.⁸⁸ The original GRACE score provides an estimate of in-hospital death or AMI and death 6 months after discharge. The score was later validated for risk estimation at 1 and 3 years. Eight prognostic variables of hospital mortality have been identified for this score, and the total score for a given patient is the sum of each variable:

- 1 – Age in years - ranging from 0 (< 30) to 100 points (> 90).
- 2 – Heart rate (bpm) - ranging from 0 (< 50) to 46 points (> 200).
- 3 – Systolic blood pressure (mmHg) - ranging from 0 (> 200) to 58 points (< 80).
- 4 – Creatinine levels (mg/dL) - ranging from 1 (< 0.40) to 28 points (> 4.0).
- 5 – Heart failure (Killip class) - ranging from 0 (class I) to 59 points (class IV).
- 6 – Cardiac arrest at admission - ranging from 0 (no) to 39 points (yes).
- 7 – ST-segment deviation - ranging from 0 (no) to 28 points (yes).
- 8 – Increased levels of cardiac injury biomarkers - ranging from 0 points (no) to 14 points (yes).

The incidence of hospital death is $\leq 1\%$ for low-risk patients (total scores ≤ 108), between 1% and 3% for intermediate-risk scores (between 109 and 140), and over 3% for high-risk patients (> 140).⁸⁹ A new version of the GRACE score (GRACE 2.0), developed using the same predictor variables for treatment outcome, has expanded the risk estimates for in-hospital death to 6 months, 1 year, and 3 years risk of death or AMI to 1 year.⁹⁰ Table 1.5 shows the risk stratification based on clinical, ECG, and laboratory variables.

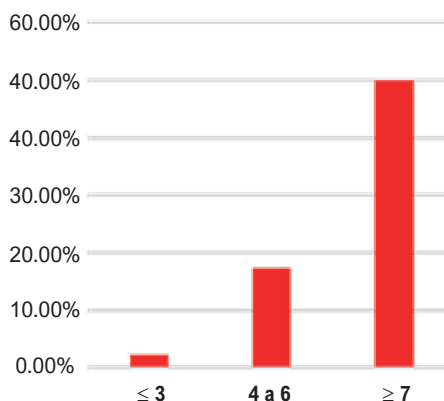
The HEART score (discussed in item 5.4) assesses the risk of a major cardiac event (infarction, revascularization, or death) 6 weeks after initial presentation in patients with chest pain.

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HEART score

History	2 = highly suspicious 1 = moderately suspicious 0 = little/no suspicion
ECG	2 = significant ST-segment depression 1 = nonspecific repolarization abnormalities 0 = normal
Years (age)	2 = ≥ 65 years 1 = ≥ 45 years and <65 years 0 = < 45 years
Risk (factors*)	2 = ≥3 or a history of atherosclerotic disease 1 = 1 or 2 0 = none
Troponin	2 = ≥3x the upper limit 1 = 1 - 3x the upper limit 0 = ≤ upper limit

Major cardiovascular events in 6 weeks



Low risk = HEART score ≤ 3

*hypercholesterolemia, diabetes, hypertension, obesity (BMI >30 kg/m²), smoking (current or having stopped for 3 months), family history of early CAD.

ADAPT score

Troponin		Risk group	Risk of major cardiovascular events in 30 days
Electrocardiogram	Normal troponin, normal ECG and TIMI 0	Low	0 – 0.3%
	Normal troponin, normal ECG and TIMI 1	Intermediate	0.8%
TIMI risk score	Elevated troponin, altered ECG and TIMI >1	High	15.3%

EDACS score

Age	18-45	2	Sex	Female	0	Pain radiates to arm, shoulder, neck or jaw	No	0
	46-50	4		Male	6		Yes	5
	51-55	6	Known CAD or ≥3 risk factors*	No	0	Pain elicited by palpation	No	0
	56-60	8		Yes	4		Yes	-6
	61-65	10	Diaphoresis	No	0	Low risk: EDACS <16, ECG without ischemia, and 2 negative troponins (0-2h)		
	66-70	12		Yes	3			
	71-75	14	Pain occurs or worsens with inspiration	No	0			
	76-80	16		Yes	-4			
	81-85	18						
	≥86	20						

*dyslipidemia, diabetes, hypertension, current smoking, family history of early CAD. Risk factors apply to patients aged 18-50 years.

Figura 1.3 – Clinical risk stratification scores for chest pain.

Risk stratification				
GRACE score (Hospital mortality)				
		Risk	Points	Hospital death (%)
Age (years)	— 0-100	Low	1-108	<1
Heart rate	— 0-46			
Systolic BP (mmHg)	— 58-0	Intermediate	109-140	1-3
Creatinine (mg/dL)	— 1-28			
HF (Killip)	— 0-59	High	>140	>3
Cardiac arrest at admission	□ 39			
ST deviation	□ 28			
↑ Necrosis biomarkers	□ 14			
1 – 372				

Figure 1.4 – GRACE risk score. Source: adapted from Granger et al.⁸⁹ BP: blood pressure; ICC: intraclass correlation coefficient; PCR: polymerase chain reaction

Table 1.5 – Risk stratification for death or infarction in patients with acute ischemic syndrome without ST-segment elevation⁹¹

	High	Moderate	Low
Prognostic Variable	At least one of the following characteristics must be present	No high-risk features, but any of the following	No intermediate or high risk characteristics, but any of the following
History	Symptom worsening in the last 48 hours. Age > 75 years	Age = 70 to 75 years, previous infarction, cerebrovascular or peripheral disease, DM, revascularization surgery, previous ASA therapy	
Precordial pain	Prolonged pain (>20 min), at rest.	Resting angina >20 min resolved, with a moderate-to-high probability of CAD Angina at rest ≤20 min, with spontaneous relief or through nitrates	New episode of CCS class III or IV angina in the last 2 weeks without prolonged pain at rest, but with moderate or high probability of CAD
Physical exam	Pulmonary edema, worsening or appearance of mitral murmur or regurgitation, S ₃ , new rales, hypotension, bradycardia or tachycardia		
Electrocardiogram	ST-segment depression >0.5 mm (associated or not with angina), dynamic ST change, new or presumably new complete branch block, sustained ventricular tachycardia	T-wave inversion >2 mm; pathological Q waves.	Normal or unchanged during the pain episode
Serum markers of ischemia*	Markedly high	High	Normal

* High cardiac troponin I, cardiac troponin T, or creatine kinase-MB (preferentially mass): above the 99th percentile; slight elevation: above the detection level and below the 99th percentile. ASA: acetylsalicylic acid; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society.

5.3.2. Bleeding Risk Stratification

Bleeding is associated with an adverse prognosis in NSTEMI-ACS, and every effort should be made to reduce it. Certain variables may help classify patients at different risk levels for major bleeding during hospitalization. Bleeding risk scores have been developed based on cohort studies and ACS clinical studies. The CRUSADE score (www.crusadebleedingscore.org)

was developed from a cohort of 71,277 patients and subsequently validated in a cohort of 17,857 patients⁹² (Table 1.6). In a Brazilian population, it predicted not only bleeding but in-hospital mortality (area under the ROC curve = 0.753, $p < 0.001$).⁹³ The rate of major bleeding gradually increased as the bleeding risk score increased. By incorporating admission and treatment variables, this score's accuracy for

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Table 1.6 – CRUSADE bleeding risk score (reference b) | Algorithm
used to determine the CRUSADE risk score for major in-hospital bleeding

Prognostic factor	Score
Baseline hematocrit (%)	
< 31	9
31-33.9	7
34-36.9	3
37-39.9	2
> 40	0
Creatinine clearance (mL/min)	
< 15	39
16-30	35
31-60	28
61-90	17
91-120	7
> 120	0
Heart rate (bpm)	
< 70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
> 120	11
Sex	
Male	0
Female	8
Heart failure signs at presentation	
No	0
Yes	7
Previous vascular disease	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure (mmHg)	
< 90	10
91-100	8
101-120	5
121-180	1
181-200	3
> 200	5

estimating bleeding risk is relatively high. Although age is not listed among the prognostic factors in this score, it is included in the creatinine clearance calculations.

Another score was derived from the ACUTY and HORIZONS studies. Six independent variables (female sex, advanced age, elevated serum creatinine, elevated white blood cell count, anemia, ACS with or without ST elevation) and one treatment-related variable (heparin and GP IIb/IIIa inhibitor use instead of bivalirudin alone) were identified (Table 1.7). This score identified patients at increased risk of bleeding (unrelated to CABG) and mortality after 1 year.⁹⁴

Both scores were derived from cohorts in which femoral access was predominantly or exclusively used. Their prognostic value may be reduced regarding radial access.⁹⁵

Finally, the authors point out that no score (either for ischemic events or for hemorrhagic events) should replace clinical evaluation. Rather, they are merely tools to help doctors in their decision-making process.

Risk stratification - Summary of recommendations and evidence

All patients should be stratified as having a high, intermediate or low risk of major cardiac events. Classification by more than one method is recommended, and the worst case scenario must be considered in treatment decisions.

I B

All patients must be stratified as high, intermediate or low risk of bleeding.

I B

5.4. Emergency Diagnostic Flowchart and Hospitalization Criteria

It is essential to develop a diagnosis flowchart for patients with chest pain, determining the criteria for early discharge and hospitalization. This can identify low-risk patients to be investigated in an outpatient setting, as well as more serious cardiac conditions that require hospitalization.

Emergency department chest pain screening is based on a brief clinical history, physical examination, 12-lead ECG within 10 minutes of arrival, and biomarker measurement. This assessment protocol is mainly aimed at early identification of high-risk patients who require hospitalization or urgent transfer for hemodynamic monitoring.

To avoid premature discharge, these patients should remain monitored in an environment where an accelerated diagnostic protocol can be used. This protocol involves serial ECG and highly sensitive troponin measurement upon arrival at the emergency department and 3 hours later. In addition to this protocol, risk scores that include demographic data, symptoms, ECG findings and biomarkers are important tools for assessing chest pain patients in the emergency department. The most commonly-used scores (HEART, ADAPT, and EDACS)⁹⁶⁻⁹⁸ are summarized in Figure 1.3.

Greenslade et al. compared the effectiveness of these scores in relation to premature discharge from the emergency department, finding that all scores were effective and had very high sensitivity.⁹⁹

The HEART score was developed using conventional troponin as a biomarker. However, retrospective studies that used highly sensitive troponin found results similar to those of

Table 1.7 – Bleeding risk score proposed by Mehran et al.⁹⁴ Algorithm used to determine the risk of major in-hospital bleeding

	Sum
Sex	Male, Female 0, +8
Age (years)	<50, 50-69, 60-69, 70-79, ≥80 0, +3, +6, +9, +12
Serum creatinine (mg/dL)	<1.0, 1.0, 1.2, 1.4, 1.6, 1.8, ≥2.0 0, +2, +3, +5, +6, +8, +10
Total leukocytes (10 ⁹ /mL)	<10, 10, 12, 14, 16, 18, ≥20 0, +2, +3, +5, +6, +8, +10
Anemia	No, Yes 0, +6
ACS Presentation	STEMI, NSTEMI, unstable angina +6, +2, 0
Antithrombotic medications	Heparin + GP IIb/IIIa inhibitor, bivalirudin 0, -5
Total score	

NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction

validation studies.^{100,101} No studies have validated this tool for care outside the hospital. However, an ongoing study (ARTICA) aims to validate this score for pre-hospital care.¹⁰²

A HEART score from 0 to 3 identifies 35% to 46% of patients at low risk, showing high sensitivity and negative predictive value, while patients with a score of 7 to 10 are at high risk, with an event rate > 50% in 6 weeks.¹⁰³⁻¹⁰⁶ The HEART score could better distinguish low-risk patients for major cardiac events than the GRACE and TIMI scores, with a lower loss rate and greater accuracy for initial risk stratification in the emergency department.^{107,108}

The growing joint use of clinical data, ECG, highly sensitive troponin, and the systematized use of scores has amplified the effectiveness of diagnostic assessment protocols and the risk stratification of chest pain in the emergency department, which promotes safe early discharge and reduction of additional exams within 30 days.¹⁰⁹

A randomized study that compared emergency care HEART scores with chest pain found a high negative predictive value for major cardiovascular events in the first year, with no differences observed regarding hospitalization or readmission to the emergency department.¹¹⁰

Thus, the impact of additional routine imaging exams on low-risk patients has been reconsidered because, despite the reduced diagnosis time, current evidence has shown that these additional tests have no verified benefit regarding the occurrence of AMI or relevant clinical events.¹¹¹

5.5. Nurses and the Chest Pain Protocol

When performed by qualified nurses, hospital screening improves the identification of high-risk patients and reduces door-to-ECG time.¹¹² It has been shown that, in rural hospitals, emergency nurses have a high level of accuracy, which reduces waiting time and length of stay without compromising patient safety.¹¹³ Thus, nurses should be actively encouraged to participate in the screening of patients with chest pain, and

the multidisciplinary team should receive continuing training about patients with chest pain.

A flowchart for emergency department treatment of patients with chest pain is shown in Figure 1.5.

Rotina diagnóstica e critérios de internação – Sumário de recomendações e evidências		
A triagem inicial deve ser realizada com base em história clínica, exame físico, ECG de 12 derivações em até 10min e troponina.	I	A
O escore HEART deve ser utilizado para estratificação de risco e auxílio na decisão de alta hospitalar precoce.	I	B
Pacientes com escore HEART ≤ 3 associado à troponina em tempo hábil negativa, ECG sem alteração isquêmica e ausência de antecedentes de DAC podem ser liberados do serviço de emergência com segurança para reavaliação ambulatorial.	I	B
Triagem hospitalar realizada por enfermeiros habilitados, visando ao reconhecimento precoce de pacientes sob maior risco.	IIa	B
Uso de escore EDACS e ADAPT para estratificação de risco clínico como opção ao escore HEART.	IIa	B
Utilização do escore HEART visando à liberação precoce em pacientes atendidos por ambulância.	IIb	C

6. Emergency Procedures After Risk Stratification

6.1. Indications for Early Invasive Strategy

An invasive strategy is indicated for patients with a very high risk of death (Table 1.8). This patient profile is not widely represented in randomized studies. Coronary intervention within 2 hours is indicated for these patients. When interventional cardiology service is not available, these patients should ideally be transferred to other centers.

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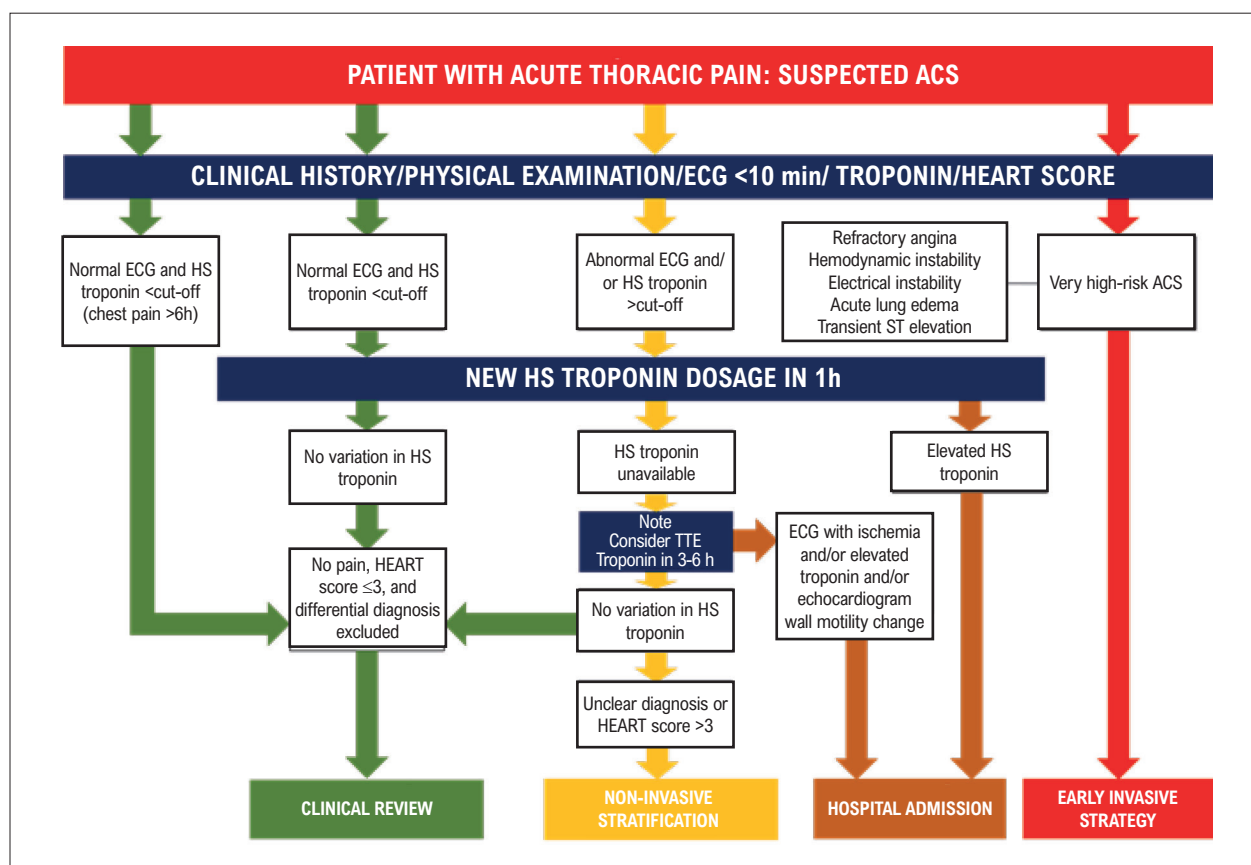


Figure 1.5 – Flowchart of routine diagnosis of the patient with acute chest pain in the Emergency Department. HS: highly sensitive; TTE : transthoracic echocardiogram.

Tabela 1.8 – Indications for an invasive strategy

Hemodynamic instability or cardiogenic shock
Chest pain refractory to drug treatment
Malignant arrhythmias or cardiorespiratory arrest
Mechanical complications of infarction
Acute HF
Recurrent ST-T segment changes with intermittent ST-segment elevation

Early invasive strategy - Summary of recommendations and evidence

An early invasive strategy is indicated for patients with NSTEMI-ACS and refractory angina or hemodynamic or electrical instability (without severe comorbidities or contraindications for these procedures).

I A

6.2. Initial Treatment (Emergency Department/Ambulance)

6.2.1. Supplemental Oxygen

Hypoxemia and myocardial ischemia can occur due to changes in the ventilation-perfusion ratio secondary to pulmonary arteriovenous shunting (due to an increase in LV end-diastolic pressure) and interstitial and/or pulmonary alveolar

edema. Hypoxemia worsens myocardial ischemia, increasing myocardial injury. O₂ saturation (SaO₂) should be measured using digital oximetry in pre-hospital and/or ambulance care for early diagnosis of hypoxemia.

Supplemental oxygen therapy is indicated for patients with AMI who present hypoxia with SaO₂ <90% or clinical signs of respiratory distress.¹¹⁴ However, in a randomized study of more than 6000 patients, oxygen therapy in patients with suspected ACS and SaO₂ ≥90% was not associated with reduced mortality or other cardiovascular outcomes in 1 year of follow-up.¹¹⁵

Oxygen therapy should not eliminate hypoxic respiratory stimulation when there is a chronic obstructive pulmonary disease or other causes of hypercapnia. Patients with pulmonary congestion, cyanosis, arterial hypoxemia, or

respiratory failure should receive oxygen supplementation and be carefully monitored with serial blood gas analysis. Non-invasive ventilatory support should be used in certain cases with signs of respiratory failure, persistent pulmonary congestion, and hypoxemia. Treatment should progress to invasive ventilation in the event of circulatory shock, non-invasive ventilatory support failure, and in unstable patients indicated for urgent myocardial revascularization (PCI or CABG). The unnecessary administration of oxygen for a prolonged period can cause systemic vasoconstriction and can even be harmful.

Oxygen therapy - Summary of recommendations and evidence		
Oxygen therapy (2 to 4 L/min) should be performed for intermediate- and high-risk patients with SaO ₂ <90% and clinical signs of respiratory distress.	I	C

6.2.2. Analgesia and Sedation

The precordial pain and anxiety usually present in ACS lead to hyperactivity of the sympathetic nervous system. This hyperadrenergic state, in addition to increasing myocardial oxygen consumption, predisposes patients to atrial and ventricular tachyarrhythmias. Initial antianginal therapy with beta-blockers and nitrates should be performed as long as there are no contraindications, such as cardiogenic shock and/or hypotension. Morphine sulfate may be used in refractory cases or when there is a contraindication to nitrates or beta-blockers. The therapy should be administered intravenously, at a dose of 2 to 4 mg (diluted) every 5 minutes, up to a maximum of 25 mg. The low dosage is to avoid adverse effects such as hypotension and respiratory depression. Morphine derivatives should be avoided, except in cases of hypersensitivity, for which meperidine sulfate can be used in fractional doses of 20 to 50 mg intravenously.

Despite its efficacy in controlling angina, there is evidence that morphine reduces the antiplatelet effect of P2Y₁₂ inhibitors, such as clopidogrel,¹¹⁶ and more potent antiplatelet drugs, such as prasugrel and ticagrelor.^{117,118}

Regarding clinical events, a subanalysis of the CRUSADE¹¹⁹ registry and, more recently, a meta-analysis that included almost 70,000 patients found that early routine use of morphine may be associated with increased in-hospital mortality and major cardiovascular events.¹²⁰ In a *post-hoc* analysis of the EARLY-ACS trial, it was found that morphine was associated with a greater risk of early ischemic events when used concomitantly with clopidogrel pretreatment. However, in the group of patients who did not receive clopidogrel before catheterization, morphine did not worsen the clinical outcome.¹²¹

Although the routine use of anxiolytics has become common practice in Brazil, it often seems excessive and should be reserved for special situations. A randomized, double-blind clinical trial with 131 male AMI patients found that the degree of anxiety, blood pressure, heart rate, and precordial discomfort did not differ between diazepam and placebo groups.¹²² Diazepine derivatives have been the most commonly used drug in this indication.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used (except ASA) to control pain in AMI patients since they increase the risk of major cardiovascular events. NSAID use should be suspended in patients who used them prior to hospitalization due to the worsening cardiovascular prognosis associated with elevated blood pressure, the risk of acute kidney injury, and blood hyperviscosity.¹²³

Analgesia and sedation - Summary of recommendations and evidence		
Administer morphine sulfate in patients who have continuous pain despite optimized anti-ischemic therapy.	IIb	B
Administer benzodiazepines to patients with signs and symptoms of anxiety.	IIb	C
NSAIDs should not be administered (with the exception of ASA) in patients with suspected AMI.	III	

6.2.3. Glycemic Control

More than 30% of AMI patients have DM or are unaware of their diagnosis. These individuals have higher bleeding rates and a worse 30-day prognosis than patients with normal blood glucose levels.¹²⁴⁻¹²⁷ Thus, glycemic control protocols should be used for AMI patients with significant hyperglycemia (> 180 mg/dL). This therapy aims to reduce blood glucose levels and avoid hypoglycemic episodes (< 70 mg/dL), which can cause several harmful effects, including the expansion of the AMI area. In patients at higher risk of hypoglycemia, such as older adults, those with chronic kidney disease, and those with residual effects from oral and/or fasting hypoglycemic agents, glycemic control should be adjusted to tolerate slightly higher blood glucose levels and thus prevent hypoglycemia.

Glycemic control - Summary of recommendations and evidence		
The blood glucose levels of all patients with suspected ACS at admission should be measured, and the blood glucose of diabetic patients or those who present hyperglycemia during hospitalization should be monitored.	I	C
Glycemic control with intermittent insulin protocols should be considered carefully in patients with glycemic levels > 180 mg/dL to avoid episodes of hypoglycemia.	IIa	C
In patients at higher risk of hypoglycemia, such as older adults, those with kidney disease, and those with residual effects from oral and/or fasting hypoglycemic agents, glycemic control should be adjusted to tolerate slightly higher blood glucose levels and thus prevent hypoglycemia.	IIa	C

6.2.4. Anti-ischemic Therapy

The goal of anti-ischemic therapy is to reduce oxygen consumption (by decreasing the heart rate, blood pressure, and myocardial contractility) or to increase oxygen supply (by administering oxygen or promoting vasodilation).

6.2.4.1. Nitrates

The therapeutic benefits of nitrates are related to their effects on peripheral and coronary circulation. Their

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vasodilator effect, which decreases venous return to the heart and LV end-diastolic volume, reduces oxygen consumption by the myocardium. Additionally, they have vasodilatory effects on coronary arteries (whether normal or atherosclerotic) and redirect intracoronary flow, with increased collateral circulation and platelet aggregation inhibition. In addition to their symptomatic effects, nitrates reduce pulmonary congestion, mainly by lowering systemic venous return.

No controlled clinical studies have tested nitrates' effects on clinical outcomes and mortality in NSTEMI-ACS, although their use is universally accepted. UA studies that have evaluated them have been small and observational.¹²⁸⁻¹³² Nitrates are associated with the improvement of both anginal and congestive symptoms, although they have no impact on mortality, infarction, or the need for revascularization.

Treatment is initiated in the emergency department, with sublingual administration (nitroglycerin, mononitrate, or isosorbide dinitrate). If rapid pain relief does not occur, these patients may benefit from intravenous administration (nitroglycerin and isosorbide mononitrate are available in Brazil).

Nitrates are contraindicated in the presence of significant arterial hypotension (systolic blood pressure [SBP] < 100 mmHg), the use of sildenafil in the last 24 hours, or the use of tadalafil in the previous 48 hours. A common side effect is a headache. The sublingual use of nitroglycerin (0.4 mg tablet), isosorbide dinitrate (5 mg tablet), or isosorbide mononitrate (5 mg tablet) should not exceed three tablets, administered at 5-min intervals. Intravenous nitroglycerin is used at a dose of 10 µg/min in increments of 10 µg every 5 min until symptoms improve, blood pressure is reduced (the drop in SBP should not exceed 30% or reach < 110 mmHg), or the heart rate increases (> 10% of baseline). Tolerance to the hemodynamic effects of this medication can be expected after the first 24 hours of use. Intravenous treatment should continue 24 to 48 hours after the last angina attack and should be suspended gradually.

Nitrates - Summary of recommendations and evidence

Sublingual nitrates can be used to relieve angina.	I	C
Intravenous nitrates can be used to control persistent angina, high blood pressure, or signs of congestion.	I	C

6.2.4.2. Beta-blockers

As with nitrates, few controlled clinical trials have been conducted on beta-blockers in UA. Evidence for their beneficial effects is based on their mechanism of action, the results of small controlled clinical trials, and the extrapolation of results from studies on stable angina and STEMI. Beta-blockers competitively inhibit the effects of circulating catecholamines. In UA, their benefits are related to their action on beta-1 receptors. They decrease heart rate, blood pressure, and myocardial contractility, causing reduced myocardial oxygen consumption. Despite the lack of large-scale randomized trials evaluating their

action on hard clinical outcomes, such as mortality in patients with NSTEMI-ACS, these drugs, together with nitrates, are considered agents of the first choice for ACS treatment the emergency department in patients without contraindications. Only a few small studies have compared beta-blockers with placebo in UA.¹³³⁻¹³⁵ Although no mortality-reducing effect was found, a meta-analysis of five small studies¹³⁶ on beta-blocker therapy in 4,700 UA patients showed a 13% reduction in the relative risk of progression to AMI. A Brazilian study in patients with NSTEMI-ACS found a significant association between oral beta-blocker therapy in the first 24 hours of hospitalization and lower in-hospital mortality, regardless of LV dysfunction.¹³⁷

Despite involving patients with STEMI, the COMMIT trial¹³⁸ suggested that the routine use of a high intravenous dose of beta-blocker followed by oral administration could increase the incidence of cardiogenic shock, mainly when used in the first 24 to 48 hours or in patients with LV dysfunction or risk factors for cardiogenic shock (age over 70 years, heart rate > 110 bpm/min or systolic pressure < 120 mmHg). Although no randomized clinical trial specifically for a population with NSTEMI-ACS has been conducted, a database study with more than 20,000 patients found results similar to the COMMIT study.¹³⁹

Thus, the routine use of oral beta-blockers is recommended in patients without contraindications (Part 2 of this Guideline provides further details). If the patient has persistent ischemic pain and/or tachycardia (non-compensatory), the intravenous formulation can be used. Various therapeutic regimens can be used depending on the selected beta-blocker. There is no evidence that one beta-blocker is superior to others. Beta-blockers (carvedilol, bisoprolol, and metoprolol succinate) are highly recommended for patients who develop ventricular dysfunction (LVEF < 40%) without pulmonary congestion.

The following is a dosage list for metoprolol and atenolol, the most commonly used beta-blockers in Brazil:

Metoprolol: Intravenous – 5 mg (1 to 2 min) every 5 min until a maximum dose of 15 mg is reached.

Oral - 50 to 100 mg every 12 hours, beginning 15 min after the last intravenous dose.

Atenolol: Intravenous – 5 mg (1 to 2 min) every 5 min until a maximum dose of 10 mg is reached.

Oral - 25 to 50 mg every 12 hours, beginning 15 min after the last intravenous dose.

During intravenous administration, careful monitoring of heart rate, blood pressure, ECG, and pulmonary auscultation should be performed.

Beta-blockers should not be used during acute intoxication in patients with symptoms of vasospasm due to cocaine use. In patients with asthma or chronic obstructive pulmonary disease, beta-blockers are contraindicated only in the presence of bronchospasm; in such cases, beta-1 selective beta-blockers are recommended.

Beta-blockers - Summary of recommendations and evidence	
Administer oral beta-blockers in the first 24 hours to patients without contraindications (signs of HF, low output symptoms, increased risk of cardiogenic shock, or other contraindications to beta-blockers).	IIa B
Administer intravenous beta-blockers in intermediate- and high-risk patients with persistent ischemia, tachycardia, and hypertension provided that they do not show clinical/radiological signs of HF.	IIb B
Administer intravenous beta-blockers to patients with risk factors for cardiogenic shock.	III A

6.2.5. Initial Antithrombotic Therapy (Ambulance/Emergency Department)

6.2.5.1. Oral Antiplatelet Therapy

The phenomenon of coronary atherosclerotic plaque instability, a recognized mechanism of ACS, results from rupture or erosion, with subsequent platelet activation and thrombosis.¹⁴⁰

This concept has guided advances in antiplatelet therapy and the current idea of dual therapy with ASA and P2Y₁₂ inhibitors in patients with ACS, determining which should receive invasive strategy and the initially proposed clinical treatment.¹⁴¹

The characteristics of and scientific evidence for antiplatelet drugs are described in detail in Part 2. However, a critical decision in the emergency department is for the time for beginning P2Y₁₂ inhibitors, particularly in patients undergoing early invasive strategy with cardiac catheterization and PCI. The term "pre-treatment" generally refers to administering P2Y₁₂ inhibitors before determining the coronary anatomy, either in the ambulance or the emergency department.

6.2.5.1.1. The Basics of Pretreatment with P2Y12 Inhibitors

The goal of pre-treatment with a second potent antiplatelet agent in NSTEMI-ACS is to achieve effective platelet inhibition and prevent further aggregation, which would prepare the patient for invasive strategy, potentially reducing the extent of thrombosis, as well as the risk of recurrent AMI and PCI-related complications, such as stent thrombosis and periprocedural infarction.¹⁴²

In contrast, pre-treatment involves an increased risk of bleeding, associated or not with coronary artery bypass surgery. This factor is associated with a relevant increase in morbidity and mortality in ACS.¹⁴³⁻¹⁴⁵

One important issue is determining the minimum time required for clinically useful action, knowing that even the most potent oral antiplatelet agents need at least 30 to 60 minutes for effective platelet inhibition, thus providing "appropriate pretreatment" before catheterization and PCI.¹⁴⁶⁻¹⁴⁹

Following pretreatment with P2Y₁₂ inhibitors, a second antiplatelet agent was used in the CURE (clopidogrel)^{150,151}

and PLATO (ticagrelor) trials;^{152,153} in the TRITON trial, prasugrel was only administered after the coronary anatomy had been determined.¹⁵⁴

6.2.5.1.2. Comparative Studies on Pretreatment vs. Second Antiplatelet Use in the Catheterization Unit

The ARMYDA-5 PRELOAD trial assessed clopidogrel pretreatment in NSTEMI-ACS (n = 409) and stable angina patients and found no reduction in adverse cardiovascular events in either group.¹⁵⁵

The CREDO trial was designed to assess the benefits of pretreatment with clopidogrel and ASA in patients undergoing PCI. In this controlled trial, 2116 patients (39% with ACS and 61% with stable CAD) received 300 mg of clopidogrel (n = 1053) or placebo (n = 1063) 3 to 24 hours before PCI. The average time between the loading dose of clopidogrel and PCI was 9.8 hours, with 51% and 49% of the patients receiving the loading dose 3 to 6 hours and 6 to 24 hours before PCI, respectively. No significant reduction was found in the combined outcome (death, infarction, or urgent revascularization of the target vessel) in 28 days. However, when analyzed according to treatment time (3 to 6 hours, 6 to 12 hours, or 12 to 24 hours before PCI), a significant interaction was observed: clopidogrel pretreatment < 6 hours before PCI had no effect, but treatment 6 to 12 hours and 12 to 24 hours before PCI resulted in 35.5% and 40.1% relative reductions in the combined final outcome, respectively. These findings support the hypothesis that clopidogrel requires more time to act when used as a pretreatment.¹⁵⁶

The ACCOAST clinical trial (n = 4,033) was a randomized, multicenter controlled study that compared administration of 60 mg of prasugrel in the catheterization room at the time of PCI versus pretreatment with 30 mg of prasugrel and a second 30 mg dose during coronary angiography within 2 to 48 hours after randomization.¹⁵⁷ The primary composite endpoint was death from cardiovascular causes, AMI, stroke, urgent revascularization, or rescue therapy with GP IIb/IIIa inhibitors by the seventh day. PCI was performed in 69% of the patients, a mean of 4.3 hours after the initial loading dose. Only 9% of the patients had a GRACE score > 140. The incidence of the primary endpoint at seven at 30 days did not differ significantly between the pretreatment and placebo groups (10.0% vs. 9.8%, hazard ratio [HR] 1.02, 95% CI 0.84-1.25, p = 0.81). A higher rate of major bleeding (related or not to CABG) was found in the pretreatment group (HR, 1.90; 95% CI, 1.19-3.02; p = 0.006). The rates of major bleeding (TIMI) or life-threatening bleeding unrelated to CABG were 3 and 6 times higher in the pretreatment and placebo groups, respectively. Half of all episodes were related to urgent revascularization surgery, and half of the major bleeding events unrelated to CABG were caused by vascular bleeding at the access site.

The DUBIUS randomized clinical trial evaluated 1,449 NSTEMI-ACS patients whose coronary angiography was scheduled within 72 hours, comparing pretreatment

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with ticagrelor versus. a second antiplatelet agent, either prasugrel or ticagrelor (randomization 1:1), administered in the hemodynamics unit in patients indicated for PCI.¹⁵⁸ The population had a moderate ischemic risk profile (mean GRACE score = 122) and did not have a high hemorrhagic risk (mean CRUSADE score = 22). Pre-specified interim futility analysis guided early interruption of the study. After 30 days, the primary outcome, i.e., death due to vascular causes, non-fatal infarction or non-fatal stroke, and hemorrhagic phenomena (Bleeding Academic Research Consortium [BARC] types 3, 4, and 5), did not differ significantly between the groups (2.9% and 3.3%, respectively, for no pretreatment vs. pretreatment). This finding was consistent in the subgroup that underwent PCI (72% of the population); the meantime until PCI was 23.3 hours, which was notably longer than the ACCOAST study (4 hours). The findings, however, were similar to those who underwent coronary angiography after 24 hours. An original strategy of this study was that the non-pretreatment group still received ticagrelor, although a drug comparison could not be performed. Despite the analysis limitations due to early interruption, pretreatment in NSTEMI-ACS with invasive handling showed no benefits, although the results indicate that an individualized choice of drugs is possible in the hemodynamics unit.

6.2.5.1.3. Pretreatment Data in Meta-analysis

A meta-analysis that included 16 studies, including 61,517 patients with ACS with or without ST-segment elevation, found a significantly lower incidence of major adverse cardiac events in the subgroup with NSTEMI-ACS allocated to pretreatment with clopidogrel (OR = 0.83; 95% CI 0.71- 0.96, $p = 0.01$), and no increase in major bleeding in patients who underwent PCI within 48 hours.¹⁵⁹

Another meta-analysis of 23 studies and 60,907 patients aimed to compare the efficacy and safety of P2Y₁₂ inhibitors (clopidogrel, ticagrelor, and prasugrel) administered at two different periods compared to PCI: early (< 2 hours pre-PCI) vs. late (> 2 hours pre-PCI or post-PCI). In studies that included patients with NSTEMI-ACS pretreatment with ticagrelor or prasugrel showed no benefit, but prasugrel increased the risk of bleeding in this population.¹⁶⁰

As previously explained, the routine use of a second oral antiplatelet agent in the initial treatment of NSTEMI-ACS has shown no clear benefits, especially for invasive strategies in emergencies, where the drug can be determined in the catheterization room. However, pretreatment can be considered in patients without a critical hemorrhagic risk, with moderate or high ischemic risk, when a coronary angiography has been scheduled, or during initial conservative treatment in full anti-ischemic therapy.

The challenge of balancing ischemic and bleeding risks requires a personalized approach to the use and type of second antiplatelet. The patient's clinical characteristics, the availability of coronary angiography, efficacy and safety data, and the pharmacodynamic properties of P2Y₁₂

inhibitors available in Brazil must be considered. However, it should be pointed out that prasugrel is contraindicated for pretreatment when the coronary anatomy has not yet been determined. Although any P2Y₁₂ inhibitor can be used in the catheterization room, in the absence of contraindications, prasugrel or ticagrelor are preferred due to their rapid onset and greater antithrombotic efficacy. Clopidogrel can be used when there is a very high hemorrhagic risk (Figure 1.6).

Initial antiplatelet therapy - Summary of recommendations and evidence		
In all patients without contraindications, ASA should be used in the emergency department as early as possible at an initial dose of 150 to 300 mg (in patients who have not previously used it) and a maintenance dose of 75 to 100 mg.	I	A
A P2Y ₁₂ inhibitor is recommended in addition to ASA, except when contraindicated or when there is an increased risk of bleeding.	I	A
Pretreatment with a P2Y ₁₂ inhibitor is recommended in unstable and/or high-risk patients indicated for immediate invasive strategy; it is recommended for use in the catheterization room when coronary anatomy has been determined, and PCI has been scheduled.	I	B
There is no routine indication for P2Y ₁₂ inhibitors as a pretreatment in patients indicated for early invasive strategy (< 24 h).	I	B
In patients with no history of previous stroke or transient ischemic attack (TIA), prasugrel (loading dose) should be used in the hemodynamics unit only after angiography and if the coronary intervention has been scheduled	I	B
Ticagrelor (loading dose) should be used regardless of the initial strategy (conservative or invasive).	I	B
Clopidogrel (loading dose) should be used regardless of the initial strategy (conservative or invasive) when ticagrelor or prasugrel is unavailable or contraindicated.	I	B
In patients allergic to ASA, initial monotherapy with a P2Y ₁₂ inhibitor (preferentially ticagrelor or prasugrel) is recommended.	I	C
Clopidogrel (loading dose) should be used regardless of the initial strategy (conservative or invasive) in patients at very high risk of bleeding or who need long-term oral anticoagulation.	IIa	C
Prasugrel can be used in the pretreatment	III	

6.2.5.2. Glycoprotein IIb/IIIa Inhibitors

Activation of platelet surface receptors, called GP IIb/IIIa, is the final mechanism of platelet aggregation. It results from a morphological alteration in the receptor, which increases its affinity to bind to fibrinogen, a protein that acts as a bridge between two platelets. These drugs have been used in clinical situations that have great potential for platelet activation, such as complex PCIs and thrombotic complications, e.g., no-reflow after angioplasty.

Abciximab is a monoclonal antibody that acts as a non-competitive and irreversible GP IIb/IIIa inhibitor. It has a short plasma half-life of 5 to 10 minutes, and its biological half-life is 6 to 12 hours after injection of an isolated bolus. These therapeutic doses block 80% to 90%

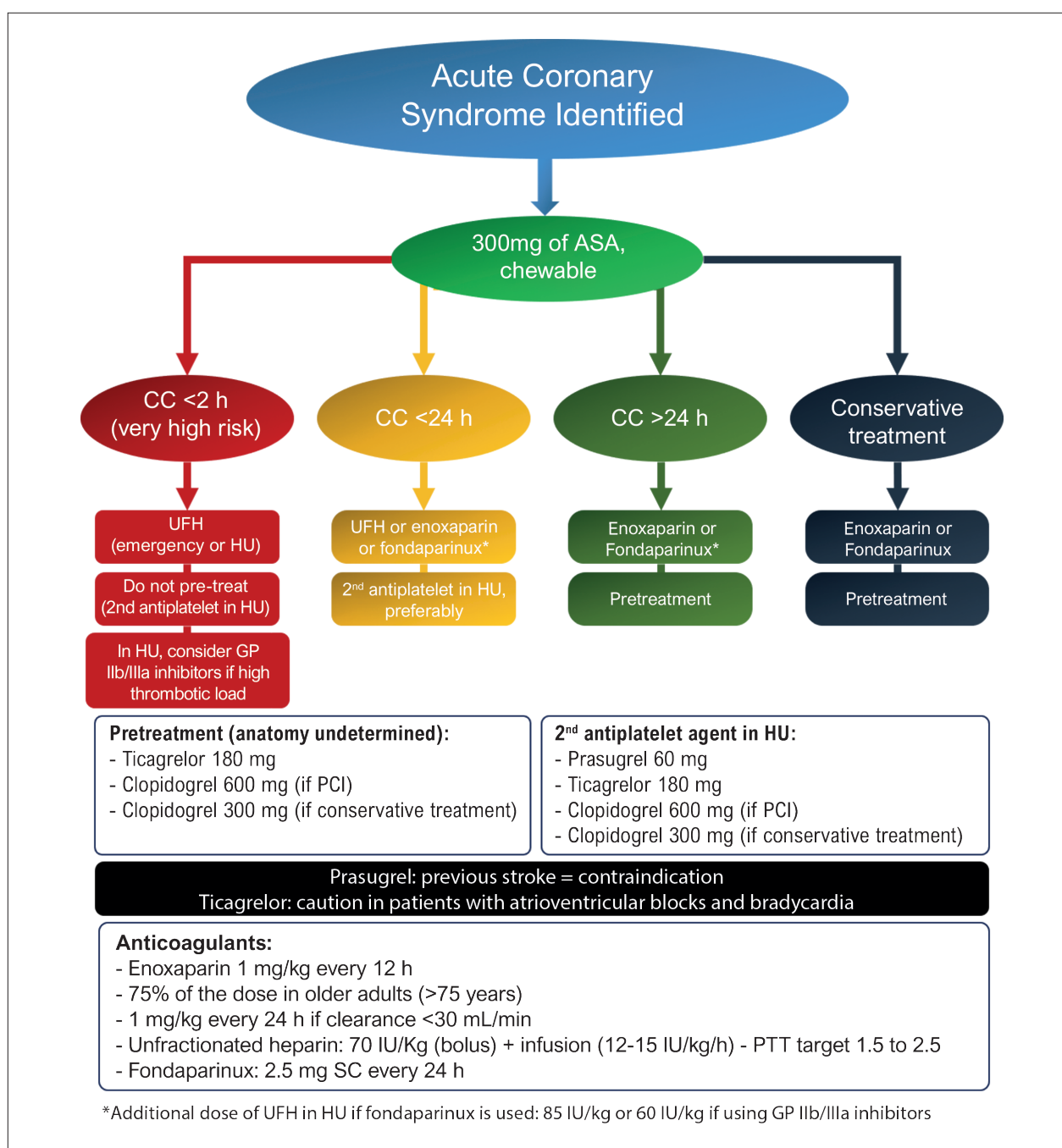


Figura 1.6 – Initial antithrombotic therapy in non-ST-elevation acute coronary syndromes. CC: cardiac catheterization; HU: hemodynamics unit; SC: subcutaneously; UHF: unfractionated heparina.

of surface receptors. Fifty percent of these receptors still remain blocked one week after use. The recommended dose is 0.25 mg/kg in a bolus, followed by 0.25 µg/kg for 12 hours.

Tirofiban, a synthetic derivative, is a non-peptide, small molecule GP IIb/IIIa inhibitor whose molecular structure includes the RGD sequence (arginine-glycine-aspartate), an integrin recognition site present in adhesive proteins

of fibrinogen, von Willebrand factor, vitronectin, etc. Tirofiban also acts competitively at GP IIb/IIIa receptors, preventing them from binding to fibrinogen. The recommended dose is 0.4 µg/kg/min for 30 min, followed by a maintenance dose of 0.11 µg/kg/min for 12 to 24 hours after the procedure (maximum 96 hours). If the first administration is in the catheterization room, it should begin at a dose of 1010 µg/kg, administered in a bolus in 3 minutes, followed by 0.15 µg/kg/min.

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The efficacy of abciximab and tirofiban is comparable when a large bolus of tirofiban (25 µg/kg) is injected. However, abciximab is superior to tirofiban when used with a normal bolus of 10g/kg.^{161,162}

Generally speaking, GP IIb/IIIa inhibitors tend to increase bleeding risk, and thrombocytopenia, although rare, is a non-negligible complication.

In patients with NSTEMI-ACS who undergo essentially "conservative" strategies (i.e., without early intervention), the use of GP IIb/IIIa inhibitors is based on studies in which, in addition to heparinization, platelet activation was systematically antagonized only by ASA.¹⁶³⁻¹⁷⁰ A meta-analysis of > 30,000 patients found a 9% reduction in the relative risk of death or infarction at 30 days of follow-up ($p = 0.015$) with beta-blockers,¹⁶⁹ although the benefits were restricted to higher-risk patients, mainly with elevated troponin and/or depressed ST-segment and/or undergoing PCI (24% at 30 days of follow-up).

Several studies have tested the role of GP IIb/IIIa inhibitors in patients undergoing PCI.¹⁷¹⁻¹⁷⁷ The results of these studies are more homogeneous, invariably demonstrating benefits, although there is a significant increase in bleeding. It should be noted that these studies did not involve routine use of thienopyridine upon patient arrival at the hospital. A meta-analysis of studies that analyzed the role of GP IIb/IIIa inhibitors in ACS patients with or without ST elevation found, in addition to significant decreases in death and (re) infarction ($p < 0.0001$), a 21% decrease (95% CI: 0.64-0.67) in the relative risk of death at six months of follow-up.¹⁷⁸

The ISAR-REACT-2 trial involved 2,022 patients with NSTEMI-ACS who received dual antiplatelet therapy (DAPT) with ASA + clopidogrel, adding abciximab was compared to placebo. Abciximab was associated with a lower incidence of the composite outcome, including death, AMI, and urgent revascularization (risk ratio [RR] 0.75; CI 0.58-0.97; $p = 0.03$), and no significant increase in serious or non-serious hemorrhagic outcomes. It should be pointed out that abciximab only benefitted individuals with troponin elevation.¹⁷⁹

The ACUTY-Timing trial included 9207 patients with NSTEMI-ACS (98% with pre-angiography ASA and 65% with pre-angiography P2Y₁₂ inhibitor) and investigated the best time to administer GP IIb/IIIa inhibitors, randomizing patients to the routine early tirofiban or eptifibatide in the emergency room before coronariography versus the selective use at the cath lab when PCI is about to be performed. It was found that the routine use of GP IIb/IIIa inhibitors did not reduce ischemic outcomes, and the incidence of significant bleeding increased significantly (RR = 0.80, $p < 0.001$).¹⁸⁰

Similar results were found in the EARLY-ACS study, in which 9,492 patients with NSTEMI-ACS were randomized to platelet anti-aggregation with eptifibatide before catheterization vs. selected use before angioplasty (based on angiographic aspects). Again, the routine use of GP IIb/IIIa inhibitors did not reduce ischemic complications and increased the incidence of bleeding, as well as the need for transfusions.¹⁸¹

Based on this body of evidence, the use of GP IIb/IIIa inhibitors as a third antiplatelet agent should be reserved for patients who do not have a high risk of hemorrhaging but are at high ischemic/thrombotic risk according to clinical and angiographic criteria.

6.2.5.3. Anticoagulants

Anticoagulant therapy should be administered as quickly as possible to all patients with NSTEMI-ACS since the use of these compounds reduces the incidence of AMI and death when used within hours of diagnosis.¹⁸²

The choice and timing of the anticoagulant are determined by the treatment strategy (invasive or conservative), the severity of the clinical presentation, and the particularities of each hospital department. In patients with an initial conservative treatment, enoxaparin or fondaparinux is preferential. The recommended doses are shown in Table 1.9. Enoxaparin should not be administered to patients with creatinine clearance < 15 mL/min, and fondaparinux should not be administered

Table 1.9 – Anticoagulant dosage according to renal function

Medication	Recommendation		
	Normal renal function or stage 1-3 CRF (creatinine clearance ≥ 30 mL/min/1.73 m ²)	Stage 4 CRF (creatinine clearance between 15 and 29 mL/min/1.73 m ²)	Stage 5 CRF (creatinine clearance < 15 mL/min/1.73 m ²)
Unfractionated heparin	Before coronary angiography: 60 to 70 IU/kg IV bolus (max. 5000 IU) and infusion (12 to 15 IU/kg/h) with PTT target 1.5-2.5 × control During coronary angiography: 70 to 100 IU/kg IV in non-anticoagulated patients or 50 to 70 IU/kg if concomitant use with GP IIb/IIIa inhibitors	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg SC every 12 h >75 years: 75% of the dose	1 mg/kg every 24 h	Not recommended
Fondaparinux	2.5 mg SC every 24 h	Not recommended if clearance < 20 mL/min/1.73 m ²	Not recommended

CRF: chronic renal failure; IV: intravenously; PTT: Partial thromboplastin time; SC: subcutaneously.

to patients with creatinine clearance < 20 mL/min. For patients whose clearance is between 15 and 30 mL/min and in obese patients (BMI > 30 kg/m² or weight > 100 kg), the enoxaparin usage guidelines recommended anti-factor Xa monitoring to minimize the risk of excessive doses and severe bleeding.¹⁸³⁻¹⁸⁵

In morbidly obese patients, pharmacodynamic studies and observational data identified a frequent need for dose adjustment according to anti-factor Xa level to achieve the therapeutic goal (BMI > 40 kg/m²), which suggests the usefulness of monitoring when available.^{186,187}

However, in the CRUSADE registry, which assessed obese patients with ACS, a standard dose of enoxaparin (1 mg/kg/weight) in patients > 150 kg was associated with a greater risk of bleeding than in a subgroup of patients between 120 and 150 kg. (11.4% vs. 5.6%, $p < 0.001$). UFH is an alternative for these patients.^{188,189}

Enoxaparin, fondaparinux, and UFH are options for invasive strategy. Despite the fact that enoxaparin and UFH had similar efficacy in the SINERGY study, for very high-risk patients who require immediate catheterization, using UFH in the emergency department or, preferably, in the catheterization room can prevent crossing over from enoxaparin to UFH and the greater hemorrhagic risk that results from this practice.¹⁹⁰

For other patients, the choice should be guided by the patient's ischemic and hemorrhagic risk and the department's own experience.

Enoxaparin is preferred to UFH because systematic review data from randomized trials across the ACS spectrum show that enoxaparin is more effective than UFH at preventing the composite outcome of all-cause mortality or severe bleeding in patients with NSTEMI-ACS who undergo PCI.¹⁹¹⁻¹⁹³

Fondaparinux is a safe option for non-invasive treatment. If catheterization is subsequently indicated, UFH is recommended during the procedure due to the risk of catheter thrombosis.^{194,195}

Patients who have previously used direct-acting oral anticoagulants (DOAC) in ACS should be handled with caution to avoid increasing the risk of hemorrhage. There is no evidence that early parenteral anticoagulation or PCI can be performed. In urgent situations, PCI should be performed regardless of when the last dose of DOAC was administered. The procedure should be postponed in patients with lower ischemic risk. In patients with normal renal function (creatinine clearance > 50 mL/min), the effect of DOAC is reduced 24 hours after the last dose. In patients with renal dysfunction, this period is 48 hours. Thus, the patient can undergo PCI with less risk of bleeding. Parenteral anticoagulation is indicated in patients who undergo emergency PCI regardless of when the last dose of DOAC was administered.¹⁹⁶

For hemodynamic/PCI examinations, it has been shown that the radial approach is the most effective strategy to reduce bleeding, resulting in reduced mortality in patients with ACS.¹⁹⁷

Anticoagulants - Summary of recommendations and evidence

UFH should be used in patients with severe renal dysfunction (clearance < 15 mL/min).	I	A
Enoxaparin should be used until revascularization (for eight days or until hospital discharge).	I	A
Fondaparinux can be used for eight days or until hospital discharge as an alternative to enoxaparin, especially in patients at high bleeding risk.	I	B
In patients using fondaparinux, administer UFH 85 IU/kg intravenously at the time of PCI or 60 IU/kg in those receiving GP IIb/IIIa inhibitors.	I	B
UFH should be used in patients weighing > 150 kg.	IIa	B
Enoxaparin is preferable to UFH in patients with a clearance $\geq$ of 15 mL/min/1.73 m ² , unless myocardial revascularization surgery is planned within 24 h.	IIa	B
UFH is preferred in emergency patients who require hemodynamic study.	IIa	C
Heparin cross-over (UFH and enoxaparin).	III	
Enoxaparin can be used in patients with creatinine clearance < 15 mL/min and weight > 150 kg.	III	
Fondaparinux can be used in patients with creatinine clearance < 20 mL/min.	III	
Fondaparinux can be used alone in PCI.	III	

Part 2 – Treatment During Hospitalization

1. Hospitalization and Coronary Care Unit Discharge

Patients with intermediate- and high-risk NSTEMI-ACS should remain hospitalized in a coronary care unit whenever possible until the definitive treatment is implemented. After the PCI is completed, the patient must return to the coronary care unit and remain for 12 to 24 hours if there are no complications. Post-PCI complications are serious outcomes, such as occlusion of the target vessel, the need for emergency revascularization surgery or a new unscheduled PCI, recurrent angina, and death. When a CABG procedure is indicated, patients should remain hospitalized (ICU or Coronary Unit) until surgery is performed. When intravenous drug treatment is indicated, patients should remain in the coronary care unit until they are stable and can be discharged and prescribed oral medications.

2. Nitrates

No controlled clinical trials have tested the effects of nitrates on clinical outcomes and mortality in UA, although their use is universally accepted; only small and observational studies have investigated them.^{128-130,198} Borzak et al. evaluated the effects of pre and in-hospital antianginal medication (calcium antagonists, beta-blockers, and nitrates) on clinical outcomes, mortality, and non-fatal myocardial infarction in 410 patients. No benefits were found. Multivariate analysis also showed no correlation with the incidence of death, nonfatal infarction, or recurrent angina.¹⁹⁹

Guidelines

Hospital nitrates - Summary of recommendations and evidence		
Nitrates should be used in intermediate- and high-risk patients who remain symptomatic or to control blood pressure.	I	C
Use associated with arterial hypotension, right ventricular infarction. Use of the phosphodiesterase inhibitors sildenafil and vardenafil within 24 h and tadalafil within 48 h (20 mg dose).	III	A

3. Beta-blockers

Clinical experience with beta-blockers is limited to small controlled clinical studies whose results are extrapolated to patients with UA and STE-ACS. Despite the lack of large-scale randomized studies, beta-blockers, such as nitrates, are widely used. Further details about this drug class are provided in Part 1.

4. Calcium Channel Antagonists

Calcium channel antagonists are a heterogeneous class of drugs, some of which act as negative regulators of chronotropism and coronary vasodilators. Their anti-ischemic action occurs by reducing calcium influx through the cell membrane, which reduces myocardial contractility, vascular tone, atrioventricular (AV) conduction, and sinus node activity.

These agents differ in terms of their ability to produce arterial vasodilation, reduce myocardial contractility, and delay AV conduction. Their beneficial effects in NSTEMI-ACS are due to a combination of decreased myocardial oxygen consumption, afterload, myocardial contractility, and heart rate, in addition to increased oxygen supply to the myocardium due to coronary vasodilation. Coronary vasodilation among different agents is similar. Dihydropyridines cause greater peripheral arterial vasodilation and tend to produce reflex tachycardia (more evident with short-acting nifedipine); verapamil and diltiazem tend to cause bradycardia by reducing chronotropism and dromotropism, which can lead to atrioventricular block (most evident with verapamil). These drugs should generally be avoided in patients with impaired LV function and/or changes in atrioventricular conduction. Water retention is another side effect that usually appears only after prolonged use.

Calcium channel antagonists are as effective as beta-blockers for controlling symptoms.^{200,201} However, they do not reduce the incidence of refractory angina, infarction, or death; on the contrary, a meta-analysis suggests that they increase the incidence of these complications.²⁰² So far, only first-generation representatives have been assessed in UA. Although these deleterious results were observed in all tested classes of calcium antagonists^{135,136,203}, conclusive data on dihydropyridines do not exist. On the other hand, in patients with NSTEMI, there is evidence that diltiazem and verapamil (which are not associated with induced tachycardia) may have a protective effect.^{204,205} These agents can be used to control refractory ischemic symptoms in patients already using nitrates and beta-blockers in appropriate doses or in

patients who cannot tolerate these drugs (especially in cases of contraindication), or even in cases of variant angina of Prinzmetal. However, the routine use of calcium channel antagonists is not recommended, and fast-acting nifedipine is particularly contraindicated.

Calcium channel antagonists - Summary of recommendations and evidence		
Use in intermediate- and high-risk patients. Non-dihydropyridine derivatives can be used in patients contraindicated to beta-blockers and without LV dysfunction.	I	B
Use in patients with variant angina of Prinzmetal.	I	B
Long-acting dihydropyridines can be used in patients with refractory ischemia and without ventricular dysfunction who are taking appropriate doses of nitrates and beta-blockers.	IIa	B
Dihydropyridine derivatives (rapid onset) can be used in high-risk patients who are taking appropriate doses of beta-blockers.	IIb	B
Dihydropyridine derivatives (rapid onset) can be used in patients who are not taking appropriate doses of beta-blockers.	III	B

5. Antiplatelet Drugs

5.1. Acetylsalicylic acid

ASA is the antiplatelet drug of choice and should always be prescribed, except in cases of intolerance or adverse events.²⁰⁶⁻²⁰⁹ Its importance in NSTEMI-ACS treatment is based on studies published in the 1980s,^{210,211} which, for the most part, had relatively small samples and a low outcome incidence. However, in general, they found that ASA clearly reduced non-fatal AMI and mortality in the short and medium terms.

The recommended dosage for ASA is 150 to 300 mg for the loading dose, followed by 75 to 100 mg daily for the maintenance dose. In one of its arms, the CURRENT OASIS-7 trial tested a high maintenance dose of ASA in patients with ACS (about 70% of patients without ST elevation). There was no difference between the normal (75 to 100 mg per day) and high maintenance doses (300 to 325 mg/day) for serious cardiovascular events (mortality, non-fatal AMI, or stroke, $p = 0.61$). There was also no difference regarding the occurrence of severe bleeding ($p = 0.90$).²¹²

5.2. P2Y₁₂ Inhibitors

Thienopyridine derivatives (clopidogrel and prasugrel) are platelet-activating antagonistic drugs mediated by adenosine diphosphate (ADP). They irreversibly inhibit P2Y₁₂ platelet receptors, reduce the level of circulating fibrinogen, and partially block GP IIb/IIIa receptors, impeding binding to fibrinogen and von Willebrand factor. In addition to ticagrelor (derived from cyclopentyltriazolopyrimidine, a non-thienopyridine agent), a reversible inhibitor of ADP-induced platelet aggregation, these are the three platelet receptor P2Y₁₂ inhibitors currently available in Brazil and should preferably be used in association with ASA.

5.2.1. Clopidogrel

CURE, the first large clinical trial to test the role of clopidogrel in addition to ASA in NSTEMI-ACS, followed more than 12,000 patients for 3 to 12 months (average of 9 months). At the end of follow-up, there was a 20% reduction (RR 0.80; 95% CI 0.72-0.89; $p = 0.00005$) in the incidence of events (cardiovascular death, AMI or stroke) in the clopidogrel group + ASA vs. the placebo + ASA group, at the expense of increased bleeding incidence in the clopidogrel + ASA group (RR 1.38, $p = 0.001$).²¹³ The beneficial effects of DAPT occurred in patients of all risk levels. Other CURE analyses demonstrated that DAPT would benefit both surgical myocardial revascularization patients and patients receiving isolated drug treatment.²¹⁴

Based on ACS studies and a study that focused primarily on PCI²¹⁵, DAPT becomes imperative when NSTEMI-ACS patients are treated with PCI. In the context of ACS, the CURE sub-study (PCI-CURE),¹⁵¹ and the CREDO study have been developed.¹⁵⁶

Due to clopidogrel's limitations regarding metabolism and drug interactions, a double dose was also tested in the CURRENT OASIS-7 trial.²¹⁶ In this study, 25,086 invasive strategy ACS patients (71% without ST elevation) were randomized to receive a double dose of clopidogrel (600 mg loading dose followed by 150 mg daily for 6 days and 75 mg daily after the first week) or the usual dosage (300 mg loading dose followed by 75 mg daily). At the end of 30 days, there was no significant difference in the primary outcome (cardiovascular death, non-fatal AMI, or stroke) between groups (HR 0.94; 4.2% vs. 4.4%, $p = 0.30$). However, the double dose was associated with a significant increase in major bleeding (HR 1.24; 2.5% vs. 2%, $p = 0.01$). In a pre-specified analysis,²¹² considering only patients treated with PCI ($n = 17,263$), there was a 14% reduction in the primary composite outcome at 30 days (HR 0.86; 3.9% vs. 4.5%, $p = 0.039$, number needed to treat = 167), in addition to a significant reduction in definite stent thrombosis (HR 0.54; 0.7% vs. 1.3%, $p = 0.0001$), although there was a higher incidence of severe bleeding (HR 1.41; 1.6% vs. 1.1%, $p = 0.009$, number needed to harm = 200). Considering the high number needed to treat, a cautious assessment of the patient's prior bleeding risk is recommended when determining the dose.

Patients who do not reach the expected level of platelet inhibition with clopidogrel are referred to as having a "poor response" (or "resistance"). This is identified by *in vitro* laboratory tests that quantify the intensity of platelet aggregation mediated by ADP. Poor clopidogrel response has been consistently associated with a higher incidence of thrombotic events, especially in patients undergoing PCI with stenting.²¹⁷⁻²¹⁹ Currently, three main factors are related to poor clopidogrel response: 1) genetic variability, characterized by polymorphisms associated with cytochrome P450 enzymes involved in the hepatic metabolism process, notably CYP2C19;²²⁰ 2) changes in intestinal absorption related to P-GP expression in intestinal epithelial cells;²²¹ 3) concomitant use of other drugs that could interfere with liver metabolism mediated by cytochrome P450 enzymes, such as ketoconazole (which inhibits cytochrome P450 and reduces

the action of clopidogrel) and rifampicin (which stimulates cytochrome P450 and enhances the action of clopidogrel).

Several *in vitro* studies have indicated that platelet inhibition is reduced when proton pump inhibitors are associated with clopidogrel, which could be especially frequent with omeprazole.²²²⁻²²⁵ However, studies analyzing ischemic events showed conflicting results,²²⁶⁻²²⁸ as well as an association between increased ischemic events and the use of clopidogrel + proton pump inhibitors. A subanalysis of the TRITON trial found no association,²²⁹ and a similar subanalysis of the PLATO trial²³⁰ found a greater incidence of ischemic events in both the clopidogrel and ticagrelor groups when taken with proton pump inhibitors. More recently, the TRILOGY trial found that among ACS patients who did not undergo myocardial revascularization, proton pump inhibitors did not affect the antiplatelet response in the prasugrel or clopidogrel groups although they were associated with a lower incidence of infarction in the prasugrel group.²²⁸

COGENT, the only randomized clinical trial that has directly tested such a hypothesis,²³¹ evaluated 3761 patients indicated for DAPT for at least 12 months (clopidogrel + omeprazole group vs. a clopidogrel + placebo group). However, this study was stopped early due to funding issues and an insufficient number of patients for follow-up (i.e., a very small number of events were obtained), which significantly compromised its statistical power. In any case, until the study was interrupted, there was no significant difference in the incidence of ischemic events (4.9% in the clopidogrel + omeprazole group vs. 5.7% in the clopidogrel + placebo group, $p = 0.96$). As expected, a higher incidence of digestive bleeding was observed in the placebo group (2.9% vs. 1.1%, $p < 0.001$). Thus, considerable research suggests that, in principle, using PPIs (mainly omeprazole) in conjunction with clopidogrel should be avoided. Patients at increased risk of gastrointestinal bleeding (history of gastrointestinal bleeding, diagnosed peptic ulcer, *Helicobacter pylori* infection, age ≥ 65 years, and concomitant use of anticoagulants or steroids) may receive H2-receptor blockers (e.g., ranitidine). If a PPI is necessary, pantoprazole is suggested, whose metabolism via cytochrome P450 is less pronounced.

Therefore, clopidogrel is indicated in NSTEMI-ACS when there is a moderate to high risk of new ischemic events. Administration consists of a loading dose of 300 mg and a maintenance dose of 75 mg daily. In patients undergoing PCI and with a low risk of bleeding, a loading dose of 600 mg, with a maintenance dose of 150 mg in the first 7 days and 75 mg/day afterward, can be considered. The drug must be used for 12 months, regardless of the treatment received (clinical, percutaneous, or surgical). When elective surgical revascularization is indicated, clopidogrel should be discontinued at least 5 days before the procedure due to the risk of bleeding. Since there is no evidence that adjusting antiplatelet therapy by assessing platelet aggregability is superior to standard antiplatelet therapy, this strategy should only be used in special situations.²³²⁻²³³ Due to clopidogrel's limitations, new drugs have been developed to obtain faster, more effective, and more consistent platelet aggregation inhibition.

Guidelines

5.2.2. Prasugrel

Prasugrel is a newer generation thienopyridine that fulfills these objectives, due basically to the fact that its metabolism is simpler than clopidogrel, involving only one phase of hepatic metabolism. As a consequence, its active metabolite reaches the plasma peak in just 30 minutes, in addition to having less interaction with medications metabolized by cytochrome P450.²³⁴

The TRITON trial included 13,608 ACS patients who had not recently used thienopyridine and had defined coronary anatomy (in patients with NSTEMI-ACS) and scheduled PCI. Of these patients, 74% presented with NSTEMI-ACS and a moderate or high risk of ischemic/thrombotic complications. Patients who were thrombocytopenic, anemic, or at high risk of bleeding were excluded. The patients were randomized to clopidogrel (300 mg loading and 75 mg daily maintenance) or prasugrel (60 mg loading and 10 mg daily maintenance) after coronary angiography and PCI indication, with a mean follow-up of 14.5 months. The primary efficacy endpoint, cardiovascular death, (re)infarction, and stroke, was 19% lower in the prasugrel group (RR 0.81; 12.1% vs. 9.9%, $p < 0.001$) than the clopidogrel group. Regarding secondary efficacy outcomes, the prasugrel group had a 24% reduction in AMI (RR 0.76; 9.5% vs. 7.3%, $p < 0.001$), a 34% reduction in urgent revascularization (RR 0.76; 3.7% vs. 2.5%, $p < 0.001$) and a 52% reduction in stent thrombosis (RR 0.48; 2.4% vs. 1.1%, $p < 0.001$).

In the prasugrel group, the safety outcome analysis showed a 32% increase in the incidence of major bleeding (according to the TIMI criterion) unrelated to revascularization surgery (RR 1.32; 1.8% vs. 2.4%, $p = 0.03$) and a 52% increase in life-threatening bleeding (RR 1.52; 0.9% vs. 1.4%, $p = 0.01$), in addition to a significant increase in fatal bleeding (RR 4.1; 0.1% vs. 0.4%, $p < 0.002$).

Overall, prasugrel had lower net benefits than clopidogrel in individuals with previous stroke or TIA (RR 1.54, $p = 0.04$), was neutral in individuals > 75 years of age or weighing < 60 kg and had higher net benefits in individuals < 75 years of age and weighing > 60 kg without previous stroke or TIA, (RR 0.8; $p < 0.001$).¹⁵⁴

Applying the new AMI classification to the TRITON-TIMI results, Morrow et al. demonstrated that prasugrel was more effective than clopidogrel for reducing various types of infarction.²³⁵ Study sub-analyses showed favorable results to prasugrel in diabetic patients²³⁶ and in those who underwent myocardial revascularization surgery.²³⁷

Prasugrel was also evaluated in the TRILOGY trial, which included 9326 patients with NSTEMI-ACS and an additional risk factor (minimum age of 60, DM, history of AMI, PCI or myocardial revascularization), who did or did not undergo coronary angiography but were specifically indicated for clinical treatment (without myocardial revascularization after the index event for study entry). The patients were randomized to clopidogrel (300 mg loading dose with a 75 mg daily maintenance dose) or prasugrel (30 mg loading dose with a 10 mg daily maintenance dose if aged < 75 years, or 5 mg daily if aged ≥ 75 years or weighing < 60 kg). The patients were followed up for an average of 17 months, and the medication was used for an average of 15 months.²³⁸

Regarding the primary efficacy endpoint (cardiovascular death, AMI, or stroke), there was no significant difference between the prasugrel and clopidogrel groups ($p = 0.21$). There were also no significant differences between groups regarding the main safety outcomes (severe or life-threatening bleeding by the GUSTO criterion or severe bleeding by the TIMI criterion).

Finally, in the TRILOGY trial, approximately one-third of the patients underwent platelet aggregation analysis and, despite superior platelet aggregation inhibition in the prasugrel group, a significant association between platelet reactivity and ischemic/thrombotic events could not be determined.²³⁸

As with clopidogrel, if indicated, prasugrel should, in principle, be taken for 12 months. Prasugrel should be suspended at least 7 days before elective myocardial revascularization.

5.2.3. Ticagrelor

Ticagrelor also blocks ADP-induced platelet aggregation through P2Y₁₂ inhibition, although it does not belong to the thienopyridine class. Ticagrelor is a cyclopentyltriazolopyrimidine with a half-life of approximately 12 hours and, unlike thienopyridines, its inhibition of P2Y₁₂ receptors is reversible and does not depend on hepatic metabolism to initiate its action. With such characteristics, ticagrelor has a more intense, rapid, and consistent antiplatelet effect than clopidogrel.²³⁹

In the PLATO trial,¹⁵² approximately 18,000 patients admitted for intermediate- and high-risk ACS within 24 hours of symptom onset were randomized to receive ticagrelor (180 mg loading dose followed by a maintenance dose of 90 mg every 12 hours) or clopidogrel (300 mg loading dose followed by a maintenance dose of 75 mg daily). Patients who underwent PCI received an additional dose of 90 mg of ticagrelor and could, at the discretion of the investigator, receive an additional dose of 300 mg of clopidogrel. All patients, except when contraindicated, received ASA, and the study medication was continued for 12 months, regardless of the treatment strategy (PCI, surgical revascularization, or clinical treatment alone). In patients indicated for CABG, clopidogrel was discontinued 5 days before the procedure, while ticagrelor was discontinued 24 to 72 hours prior to surgery. The primary efficacy endpoint was the composite of death from vascular causes, non-fatal AMI or stroke in 12 months, while the primary safety endpoint was severe bleeding according to the study's own criterion. In the total sample, the prevalence of NSTEMI-ACS was approximately 60%, of whom approximately 43% had AMI without ST elevation, and 17% had intermediate- or high-risk UA. The median patient age was 62 years, with 15% older than 75 years. Approximately 64% underwent PCI, and 10% underwent CABG, with the remainder receiving clinical treatment alone. At the end of the study, the ticagrelor group had a significant reduction (16%) in the primary efficacy outcome (RR 0.84; 9.8% vs. 11.7%, $p < 0.001$). In separate analyses of composite outcome components (main secondary goals), there were significant reductions in the incidence of AMI (RR 0.84; 5.8% vs. 6.9%, $p = 0.005$) and death from vascular causes (RR 0.79; 4.0% vs. 5.1%, $p < 0.001$), with no significant differences in stroke

($p = 0.22$). Regarding the primary safety outcome, there was no significant difference in the incidence of severe bleeding according to the study's criterion ($HR = 1.04$; $p = 0.43$) and the TIMI criterion ($HR = 1.03$, $p = 0.57$). Although there was no difference in the incidence of fatal bleeding ($HR = 0.87$; $p = 0.66$) or in the need for transfusions ($HR = 1$; $p = 0.96$), ticagrelor led to a slight but significant overall increase in fatal intracranial bleeding (0.1 vs. 0.01; $p = 0.02$) and major bleeding unrelated to CABG (4.5% vs. 3.8%, $p = 0.03$). There was a higher incidence of other adverse effects in the ticagrelor group. There was a significant increase in the occurrence of dyspnea ($RR 1.84$; 13.8% vs. 7.8%, $p < 0.001$), which, in general, was transient and led to drug cessation in less than 1% of patients. It is debated whether this side effect could be explained by increased plasma adenosine levels.²⁴⁰⁻²⁴² There was also an increase in the incidence of transient bradycardia, with a significant increase in the ventricular pauses > 3 seconds in the first 7 days of medication use (5.8% vs. 3.6%, $p = 0.01$). However, this effect lost significance after 30 days of medication use (2.1% vs. 1.7%, $p = 0.52$).²⁴³ There was no overall difference between the groups regarding the need for pacemaker implantation or the occurrence of syncope or heart block.²⁴³ There was an increase in creatinine (10% vs. 8%) and uric acid levels (14% vs. 7%), which reverted 1 month after the end of treatment.²⁴⁴

The PLATO database provides data on several pre-specified subgroups, including diabetics²⁴⁵ chronic kidney disease,²⁴⁶ previous stroke,²⁴⁷ PPI use,²³⁰ initial invasive or conservative strategy,²⁴⁸ surgical myocardial revascularizations,²⁴⁹ the recurrence of events,²⁵⁰ cost-effectiveness,²⁵¹ etc. In summary, ticagrelor appears to be cost-effective, and the sub-analysis results were very close to those of the original publication, which included the entire population. The drug must be suspended at least 3 days prior to elective myocardial revascularization surgery.

More recently, ISAR-REACT 5, a multicenter, non-blinded randomized trial, compared the use of ticagrelor (180 mg at hospital arrival followed by 90 mg twice a day) vs. prasugrel (60 mg in the hemodynamics unit followed by 10 mg or 5 mg for patients ≥ 75 years of age or < 60 kg, respectively) in 4018 patients with ACS indicated for early invasive treatment (41.1% of AMI with supra and 58.9% of NSTEMI-ACS). The primary outcome (death, AMI, or stroke within 1 year of follow-up) occurred in 184 patients (9.3%) in the ticagrelor group and in 137 patients (6.9%) in the prasugrel group ($HR 1.36$; 95% CI, 1.09 to 1.70; $p = 0.006$). Major bleeding, the safety outcome, was similar in both groups: 5.4% in the ticagrelor group vs. 4.8% in the prasugrel group ($HR 1.12$; 95% CI, 0.83 to 1.51; $p = 0.46$). However, some study limitations should be pointed out: the study was open (not blinded); 90% of the patient contacts were made by telephone (83%) or letter (7%); neither medication was dispensed by the study (patients acquired them on their own); invasive stratification in NSTEMI-ACS was determined very quickly, which is not our practice; in the prasugrel group, the primary outcome occurred less frequently (6.9%) than in the TRITON TIMI 38 trial (9.9%) and well below what was estimated for this group (12.9%) in the sample calculation.²⁵²

5.3. Adjusting Antiplatelet Therapy According to Platelet Aggregation Tests or Genetic Tests

Three randomized clinical studies have sought to demonstrate the clinical impact of antiplatelet therapies in patients with poor

response to clopidogrel. The GRAVITAS trial²³² tested whether a high dose of clopidogrel (600 mg loading dose and 150 mg/day maintenance dose) would prevent cardiovascular events after PCI and drug-eluting stenting better than standard therapy (75 mg/day without a loading dose). Patients were selected according to high platelet reactivity to clopidogrel, which was assessed with the VerifyNow® P2Y₁₂ assay. Of the 5429 patients initially assessed, 2214 (40.8%) had platelet hyperreactivity (via ADP) and were included in the study (40% diagnosed with NSTEMI-ACS). Despite a 22% overall reduction in the number of patients with continued platelet hyperreactivity (P2Y₁₂ reaction unit value ≥ 230), treatment with a high dose of clopidogrel did not reduce the risk of death from cardiovascular causes, non-fatal AMI, or stent thrombosis in 6 months after PCI ($HR 1.01$, 95% CI 0.58 to 1.76, $p = 0.97$). There was also no increase in severe bleeding between groups. In the ARCTIC study,²³³ 2440 patients with scheduled PCI and drug-eluting stent implantation (27% with NSTEMI-ACS) were randomized to two different platelet anti-aggregation strategies: a conventional strategy with ASA and P2Y₁₂ inhibitors used at normal dosages and a monitored strategy in which the doses were adjusted according to the results of platelet aggregability determined through the VerifyNow® aspirin system and P2Y₁₂ assay. Randomization, assessment of platelet reactivity, and intervention, when indicated in the monitored therapy group, were performed prior to the scheduled stent implantation procedure. The incidence of platelet hyperreactivity in clopidogrel patients was 34.5%, and resistance to ASA was observed in 7.6%. In the monitored therapy group, a new platelet function assessment was performed 2 and 4 weeks after stent implantation, and new therapeutic adjustments were made when necessary. In this new assessment, there was a significant reduction (15.6% vs. 34.5% [i.e., approximately 50%], $p < 0.001$) in the number of patients with platelet hyperreactivity at the time of PCI, defined as a P2Y₁₂ reaction unit value ≥ 235 or $\leq 15\%$ platelet inhibition compared to control values. However, the primary outcome (all-cause mortality, AMI, stroke, TIA, emergency coronary revascularization, or stent thrombosis within 1 year) was 34.6% in patients who received monitored therapy and 31.1% in those treated conventionally ($HR 1.13$; 95% CI 0.98 to 1.29; $p = 0.10$). The rate of serious bleeding events also did not differ significantly between groups. In the ANTARTIC trial, older adults (age ≥ 75 years) undergoing PCI after ACS were randomized to a strategy guided by platelet aggregation assays vs. a conventional strategy. All patients were initially treated with prasugrel 5 mg and, in the guided therapy group, the dose could be increased to 10 mg in case of inadequate platelet inhibition (defined as P2Y₁₂ reaction unit ≥ 208) or to 75 mg clopidogrel in case of excessive platelet inhibition (defined as P2Y₁₂ reaction unit ≤ 85). The outcome consisted of cardiovascular death, stroke, infarction, urgent revascularization, stent thrombosis, or clinically relevant bleeding in 12 months ($HR 1.00$, 95% CI 0.78 to 1.29).²⁵³ Thus, antiplatelet therapy guided by aggregability tests should only be used in selected cases.

Regarding genetic tests, the POPular Genetics trial tested therapy guided by cytochrome 2C19 polymorphism testing. In this study, 2488 patients with ACS were randomized to a standard strategy with ticagrelor or prasugrel vs. a personalized strategy in which patients without polymorphisms (which

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leads to a loss of 2C19 function and, thus, have normal clopidogrel metabolism) received clopidogrel instead of the other two antiplatelet agents. The personalized strategy was not inferior to the conventional one for the composite outcome (death, infarction, stroke, stent thrombosis, or major bleeding), and it reduced major bleeding (HR 0.78; 95% CI 0.61 to 0.98 ; $p = 0.04$).²⁵⁴ The TAILOR PCI study included patients undergoing PCI (approximately 80% with ACS and 60% with NSTEMI-ACS) and assessed a therapy strategy guided by genotyping. This strategy was not superior to conventional treatment for reducing the composite outcome of cardiovascular death, infarction, stroke, stent thrombosis, or severe recurrent ischemia (HR 0.66; 95% CI 0.43-1.02; $p = 0.06$) in patients carrying the allele that leads to loss of 2C19 function (approximately 35% of included patients).²⁵⁵ Further studies, including cost-effectiveness analyses, are needed to confirm these results before a final decision is made about the routine use of genotyping.

Antiplatelet therapy - Summary of recommendations and evidence		
ASA (162-300 mg loading dose, 81-100 mg/day maintenance dose) should be used in all patients, except when contraindicated, regardless of the treatment strategy, continuing indefinitely.	I	A
Thienopyridines can be used in patients with ASA intolerance.	I	B
Dual antiplatelet therapy can be used for 12 months after an acute event regardless of the initial strategy (clinical, percutaneous, or surgical) unless contraindicated.	I	A
Clopidogrel (300 mg loading dose, 75 mg/day maintenance dose) should be used in addition to ASA for 12 months in intermediate- or high-risk NSTEMI-ACS patients, in patients with a very high risk of bleeding, with concomitant use of oral anticoagulants, or when prasugrel or ticagrelor is not available.	I	A
Ticagrelor (180 mg loading dose, followed by 90 mg twice/day maintenance dose) should be used in intermediate- or high-risk NSTEMI-ACS patients, regardless of the subsequent treatment strategy (clinical, surgical, or percutaneous), rather than clopidogrel, for 12 months.	I	B
Prasugrel (loading dose 60 mg, followed by 10 mg daily) should be used rather than clopidogrel in intermediate- or high-risk NSTEMI-ACS patients with known coronary anatomy treated with PCI, and without risk factors for bleeding (age ≥ 75 years; with < 60 kg; previous stroke or TIA) for 12 months.	I	B
In addition to ASA, clopidogrel (600 mg loading dose, followed by 150 mg daily for 7 days, and a subsequent dose of 75 mg daily) should be used in patients undergoing PCI who have a high risk of ischemic events and a low risk of bleeding.	IIa	B
Ticagrelor, prasugrel, or clopidogrel use should be resumed after coronary bypass surgery, as soon as it is safe.	IIa	B
Platelet aggregation tests or genetic tests (genotyping) should be used in selected cases.	IIb	B
ASA can be combined with other NSAIDs.	III	C
Prasugrel can be used in patients with a history of TIA or previous stroke or in NSTEMI-ACS patients with unknown cardiac anatomy.	III	B

6. Antithrombotic Therapy

6.1. Unfractionated Heparin

UFH was the first injectable anticoagulant to be synthesized. Heparin is a sulfated polysaccharide with a molecular weight range of 3000 to 30,000 Da (mean 15,000 Da). Its action is due to the inactivation of thrombin and activated factor X (factor Xa) through an antithrombin-dependent mechanism. Heparin binds to antithrombin through a high-affinity pentasaccharide and, to inhibit thrombin, it binds to both antithrombin and the coagulation enzyme. By inactivating thrombin, prevents fibrin formation and inhibits thrombin-induced activation of platelets and factors V and VIII. Its variable pharmacological response occurs through independent binding of heparin antithrombin to plasma proteins and through the proteins released by platelets and endothelial cells, causing heparin resistance. For this reason, it is important to monitor thromboplastin activation time. Due to its short half-life, UFH should be administered in a continuous intravenous infusion to ensure stable levels of anticoagulation.^{256,257}

The evidence for using UFH in NSTEMI treatment comes from randomized studies and meta-analyses. In a meta-analysis of six randomized studies, Eikelboom et al. found that UFH or LMWH reduces major cardiovascular outcomes in ACS.¹⁸² UFH is a widely used anticoagulant in NSTEMI when cardiac catheterization is performed within the first 2 hours of arrival at the hospital, despite consistent evidence of a higher risk of bleeding compared to other antithrombotics.¹⁹¹

The proposed therapeutic regimen for UFH should be adjusted to patient body weight: an initial dose of 60 units/kg should be administered intravenously, followed by an infusion of 12 units/kg/hour. Anticoagulation intensity is adjusted by monitoring thromboplastin activation time. The first blood sample must be collected in the third hour of infusion and, subsequently, every 6 hours until the target range is reached, after which it can be collected every 24 hours. The therapeutic range is narrow, so thromboplastin activation time values should be maintained between 1.5 and 2.0 times the control values in seconds.¹⁹⁸

During PCI, the UFH dose should keep the activated clotting time between 250 and 350 seconds. Dose titration should be guided by body weight. The administration of a bolus of 70-100 IU/kg of UFH is sufficient for adequate anticoagulation. With the concomitant use of GP IIb/IIIa inhibitors, the initial dose should be 60-70 IU/kg.²⁵⁸

The most frequent side effects of UFH are major or minor bleeding, which occurs mainly when the clotting time is above the therapeutic range. UFH can trigger an intense immune reaction, heparin-induced thrombocytopenia, a potentially fatal clinical condition that concomitantly induces bleeding and thrombosis.²⁵⁸

During life-threatening bleeding or when emergency surgery is required, an antidote must be used to neutralize the anticoagulant effect. Protamine sulfate is used to inactivate the effects of UFH. Since the half-life of UFH is approximately 1 to 1.5 hours, the protamine dose should be based on the total UFH dose administered in the previous 2 to 3 hours. Approximately 1 mg neutralizes 100 IU of UFH. A slow

intravenous infusion is recommended to avoid hypotension and bradycardia.²⁵⁸

6.2. Low-Molecular-Weight Heparins

During investigations into the structure of conventional heparin (UFH), it was found that its polysaccharide chains can undergo depolymerization through various physical and chemical processes to obtain heterogeneous compounds with lower molecular weight, which are called generic fractionated or LMWH.^{256,257}

LMWH consist of short polysaccharide chains, which result in a more predictable anticoagulant effect than UFH. LMWH has several potential advantages over UFH:²⁵⁷

- Greater anti-factor Xa activity than factor IIa activity. More effective inhibition of thrombin production.
- Greater inhibition than UFH in the tissue factor pathway.
- Less frequently induce thrombocytopenia.
- Subcutaneous administration due to their great bioavailability.
- Predictable anticoagulation due to less binding to plasma proteins.
- Plasma level monitoring is unnecessary.

Fraxiparin, dalteparin, and enoxaparin are examples of LMWH that have been tested in ACS. Enoxaparin remains the drug of choice in this context due to the larger body of experimental data. Previous studies have shown that fraxiparin and nadroparin are similar to UFH.

Two studies, TIMI IIB, and ESSENCE have compared enoxaparin with UFH for clinical efficacy and safety in patients with UA and NSTEMI. In summary, they showed for the first time that LMWH (in this case, enoxaparin) was superior to UFH and that enoxaparin provides no additional benefits after the hospitalization phase (TIMI IIB). During the outpatient phase, major bleeding occurred in 1.5% of the group treated with placebo and 2.9% in the group treated with enoxaparin ($p = 0.021$).^{259,260} Perhaps, more importantly, a pooled analysis of the two studies showed that the enoxaparin group had significantly fewer “hard” events, i.e., death or (re)infarction, than UFH, with the advantages still evident 1 year after the initial treatment.²⁶¹

The SINERGY study compared enoxaparin to UFH in patients with high-risk NSTEMI-ACS. A total of 10,027 patients were randomized, and the primary outcome was a composite of cardiovascular death, AMI, stroke, and urgent revascularization. In the enoxaparin arm, the event rate was 14.0% (696/4993), while in the UFH arm, it was 14.5% (722/4985) (RR, 0.96; 95% CI, 0.86-1.06). Regarding safety, there was a statistically significant increase in major bleeding with enoxaparin (9.1% vs. 7.6%, $p = 0.008$), (TIMI criteria) and a non-significant increase in severe bleeding (GUSTO criteria) (2.7% vs. 2.2%, $p = 0.08$) and blood transfusions (17.0% vs. 16.0%, $p = 0.16$). The authors' conclusion was that enoxaparin was neither superior to UFH nor inferior to high-risk treatment for NSTEMI-ACS.²⁶² Enoxaparin is a safe and effective alternative to UFH. The advantage of subcutaneous use and the fact that it does not require routine anticoagulation monitoring should be considered in light of the modest excess of major bleeding. Another consideration from an unspecified analysis was that switching classes of anticoagulants during the hospital phase of patients with ACS should be avoided.²⁶²

A 1 mg/kg dose of enoxaparin should be administered subcutaneously twice a day. Beginning at 75 years of age, the dose should be reduced to 0.75 mg/kg twice a day. In patients with an estimated glomerular filtration rate ≤ 30 mL/min/1.73 m², the dose should be reduced by half, and then 1 mg/kg should be administered subcutaneously once a day. When the estimated glomerular filtration rate reaches 15 mL/min/1.73 m², enoxaparin should be avoided. UFH is an alternative for this condition since its metabolism is exclusively hepatic. In patients pretreated with enoxaparin, using additional enoxaparin during PCI is not recommended if the last subcutaneous enoxaparin injection was administered 8 hours before the procedure. An additional 0.3 mg/kg intravenous bolus is recommended if the last subcutaneous dose of enoxaparin was administered ≥ 8 hours before angioplasty.²⁶³

6.3. Fondaparinux

Fondaparinux is a synthetic pentasaccharide that consists of a sequence of sugars (A B C D F) - the smallest sequence capable of directly binding to thrombin. This discovery was a milestone in the pharmacological development of heparins. It provided the tools to understand the biology of this class of drugs and advance its pharmacology. The development of fondaparinux showed that selective and direct inhibition of factor Xa promotes an important antithrombotic effect, which opened the way for new direct oral anticoagulants.²⁶⁴ Synthetic pentasaccharide, which selectively binds to thrombin, leads to factor Xa inhibition. Due to its discreet interaction with plasma components, it has predictable anticoagulant action and little individual variability. It has good bioavailability, which favors subcutaneous administration. It reaches its plasma peak quickly (2 hours) and has a long half-life (17 hours), allowing the use of a single daily dose. Fondaparinux is eliminated exclusively by the kidneys, which requires renal monitoring. When the estimated glomerular filtration rate is < 30 mL/1.73 m², its use should be suspended.²⁶⁵

The OASIS-5 trial tested the efficacy and safety of fondaparinux vs. enoxaparin in patients with NSTEMI-ACS. It was designed to assess whether fondaparinux would continue the anti-ischemic benefits of enoxaparin while reducing bleeding in patients with ACS. A total of 20,078 patients with NSTEMI-ACS who received fondaparinux (2.5 mg/day) or enoxaparin (1 mg/kg twice a day) were randomized for an average exposure of 6 days. The primary composite efficacy outcome was cardiovascular death, AMI, or refractory ischemia on a ninth day, while major bleeding was the primary safety outcome. A combination of these outcomes was considered the net clinical benefit. The patients were followed for up to 6 months, and the composite efficacy outcome was similar in both groups (579 events with fondaparinux [5.8%] vs. 573 with enoxaparin [5.7%]; RR: 1.01 in the fondaparinux group; 95% CI 0.90-1.13; p for non-inferiority = 0.007).¹⁹⁴ Further sub-analyses of the study were published, the most important of which analyzed the 12,715 patients who underwent angiography during hospitalization (6238 treated with PCI). During the course of OASIS 5 (after reports of catheter thrombosis from some centers), the protocol was amended, requiring the hemodynamic catheter to be washed with 200 IU of UFH before the procedure. Among the patients who underwent PCI, the efficacy of fondaparinux was similar to enoxaparin for the primary outcome in 9 days (6.2% vs. 6.3%; RR 1.09; $p = 0.79$), with a lower incidence of severe

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bleeding (10.4% vs. 8.2%; RR = 0.78; p = 0.004). However, there was a higher incidence of catheter thrombosis (0.4% vs. 0.9%), and this complication was associated with higher rates of stroke and AMI.^{266,267}

Antithrombotic therapy - Summary of recommendations and evidence		
UFH can be used routinely.	I	A
LMWH can be used routinely.	I	A
Subcutaneous fondaparinux 2.5 mg can be used once/day for 8 days or until hospital discharge.	I	B
For patients using fondaparinux, administer UFH 85 IU/kg intravenously at the time of PCI, or 60 IU/kg for those receiving GP IIb/IIIa inhibitors.	I	B
Enoxaparin is preferential to UFH unless myocardial revascularization surgery is planned within 24 h.	IIa	A
Consider discontinuing anticoagulation after PCI unless there is an indication to maintain it.	IIa	C
Heparin cross-over (UFH and enoxaparin).	III	B

7. Associating Oral Antiplatelets and Anticoagulants in Special Circumstances

In recent years, four DOACs have been studied regarding atrial fibrillation in patients undergoing angioplasty and have become viable alternatives to warfarin.

Clinical studies that tested DOACs in patients with CAD (chronic and acute) associated with atrial fibrillation found the following results in comparison to triple therapy (ASA + clopidogrel + warfarin):

In the PIONEER AF-PCI trial, 15 mg rivaroxaban (reduced to 10 mg in patients with creatinine clearance between 30-50 mL/min) + P2Y₁₂ inhibitors (clopidogrel/ticagrelor) for 12 months was associated with significantly lower bleeding rates (primary goal), and the efficacy component (cardiovascular death, AMI, and stroke) was similar (secondary outcome).²⁶⁸

In the REDUAL PCI trial, dabigatran 110 mg or 150 mg twice a day + P2Y₁₂ inhibitors (clopidogrel/ticagrelor) for 12 months was associated with significantly lower bleeding rates (primary outcome), with a significant p-value for non-inferiority in both dabigatran groups but a significant p-value for superiority only in the 110 mg dabigatran group; dual therapy (both dabigatran groups) was similar to triple therapy for the composite outcome of thromboembolic events.²⁶⁹

- In the AUGUSTUS trial, apixaban 5 mg twice a day (or 2.5 mg twice a day was used if two of the following three conditions were present: age > 80 years, weight < 60 kg or serum creatinine > 1.5 mg/dl) + P2Y₁₂ inhibitors (clopidogrel) was associated with a lower bleeding rate (primary outcome) and a lower rate of death or hospitalization (secondary outcome), with no significant difference in the incidence of ischemic events. It should be pointed out that ACS patients without PCI were also included in the study.²⁷⁰

- In the ENTRUST AF-PCI trial, edoxaban 60 mg in association with P2Y₁₂ inhibitors (n = 751) was used in one group, while warfarin was combined with DAPT (ASA + P2Y₁₂ inhibitors) was used in the other group, totaling 1,506 patients. The primary outcome was major bleeding, (HR = 0.83; 95% CI 0.65-1.05;

p = 0.0010 for non-inferiority and p = 0.1154 for superiority). There was no significant difference for the secondary outcome (cardiovascular death, stroke, systemic embolism, AMI, or stent thrombosis).²⁷¹

In these studies, about half of the patients had ACS, and clopidogrel was much more frequently used than ticagrelor as a P2Y₁₂ inhibitor. The safety outcome (bleeding) was always the primary objective. Although they had different designs, these studies showed that DOACs were safe compared to warfarin when associated with antiplatelet agents. However, there were no significant differences in ischemic (i.e., secondary) outcomes.²⁷² The total time for triple therapy, either with DOACs or warfarin, and for suspending ASA, should be determined according to the risk of ischemic and hemorrhagic events.²⁷³

8. Hypolipidemic Drugs

Several studies have demonstrated the benefits of cholesterol-lowering therapies in secondary prevention.^{274,275} In high-risk patients, the benefits are independent of baseline LDL-C levels.²⁷⁶ A study by Dondo et al. with more than 389,000 NSTEMI-ACS patients and a mean follow-up of 2.2 years found that non-adherence to statin treatment was one of the most important factors in reduced survival. If the guidelines were applied and followed correctly, i.e., adherence to statin use, coronary angiography when indicated, cardiovascular rehabilitation, and smoking cessation, 28.9% of the associated deaths could be prevented.²⁷⁷

Although lipid targets vary in different guidelines, a more rigorous strategy to reduce LDL levels has recently been recommended. The 2017 Brazilian Guideline on Dyslipidemia and the Prevention of Atherosclerosis recommended LDL levels < 50 mg/dL and non-HDL levels < 80 mg/dL in very high-risk patients.²⁷⁸ When large doses of statins cannot be tolerated, association with ezetimibe is an alternative.²⁷⁹

It is assumed that lipid-lowering therapy should ideally begin during hospitalization, provided there is no contraindication. The SECURE-PCI trial evaluated an 80 mg loading dose of atorvastatin before coronary angiography in 4,191 ACS patients indicated for invasive strategy. The loading dose did not reduce major cardiovascular outcomes in 30 days compared to the placebo (HR 0.88; 95% CI 0.69 to 1.11; p = 0.27), although the subgroup of patients who underwent PCI may have benefitted (HR 0.72; 95% CI 0.54 to 0.96; p = 0.02).²⁸⁰

Hypolipidemic drugs - Summary of recommendations and evidence		
Begin early treatment with a high dose of statin in all patients, regardless of LDL levels, as long as there are no contraindications.	I	A
Associate ezetimibe in patients using the maximum tolerated statin dose if LDL levels do not reach the established goals.	I	A

9. Renin-Angiotensin-Aldosterone System Inhibitors

This group of drugs is very important for treating high blood pressure, HF, and some groups of patients with CAD. There is

no conclusive evidence that the early use of these drugs benefits patients with NSTEMI-ACS, although some studies have suggested that they may be useful in the chronic phase after an acute episode. The HOPE trial²⁸¹ included patients at high risk of cardiovascular events, often with major atherosclerotic arterial disease (usually reaching the coronary region). Regardless of the stage, ramipril (target dose of 10 mg/day) had long-term benefits: in 5 years of follow-up, there was a 26% reduction in the relative risk of death ($p < 0.001$), a 20% reduction in infarction, ($p < 0.001$), and a 32% reduction in stroke ($p < 0.001$). Similar results have also been demonstrated for perindopril in chronic coronary disease patients.²⁸² The benefits are greater in patients with LV dysfunction and previous AMI, including improved cardiac remodeling and LV function and decreased progression to HF.²⁸³

The aim of treatment is to reach the highest tolerable dose of medications: captopril 50 mg every 8 hours (which can later be replaced by ramipril 10 mg/day or enalapril 20 mg/day every 12 hours), losartan 50 mg every 12 hours, or valsartan 320 mg/day.

Regarding aldosterone antagonists, the EPHESUS trial found lower mortality with eplerenone (not available in Brazil) in patients with AMI (with or without ST elevation) and LV dysfunction who showed symptoms of HF or DM (RR 0.85; 95% CI 0.75-0.96; $p = 0.008$). The benefits were already evident in the first 30 days of treatment.^{284,285} The RALES trial had previously found lower mortality in patients with chronic HF and LV ejection fraction (LVEF) $\leq 35\%$.²⁸⁶ Thus, a target dose of 25 mg of spironolactone (an aldosterone antagonist available in Brazil) once a day (which can be increased to 50 mg after 8 weeks of treatment if there are signs of HF progression without hyperkalemia). Aldosterone blockers are contraindicated in patients with significant renal dysfunction ($\text{Cr} > 2.5 \text{ mg/dL}$) or potassium levels $> 5.5 \text{ mEq/L}$. Potassium levels and renal function must be carefully monitored, especially when aldosterone blockers are used concomitantly with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.

Renin-angiotensin-aldosterone system inhibitors - Summary of recommendations and evidence		
Administer angiotensin-converting enzyme (ACE) inhibitors to intermediate- and high-risk patients with LV dysfunction, high blood pressure, or DM.	I	A
Administer angiotensin II receptor blockers to intermediate- and high-risk patients with contraindications to ACE inhibitors.	I	C
Use spironolactone in patients with NSTEMI-ACS, LVEF $\leq 35\%$, HF symptoms, or a history of DM.	I	C
Administer ACE inhibitors to all intermediate- and high-risk patients.	IIb	B

10. Complementary Methods of Risk Stratification

In patients with ACS, risk stratification must be a continuous process, from the initial clinical evaluation to the previously

discussed subsidiary exams to the complementary methods described below.

11. Non-Invasive Tests for Ischemia Diagnosis and Prognostic Assessment

Functional tests are indicated for assessing myocardial ischemia and, in some cases, are essential for decision-making, especially for the diagnosis and prognosis of intermediate- and high-risk patients. Non-invasive prognostic methods are more common in the conservative therapeutic strategy.

11.1. Exercise Testing

During the hospitalization phase, ET is used to determine the residual degree of ischemia and assess cardiac performance. Residual ischemia is estimated by ST-segment changes during exercise or the recovery phase and by anginal pain. Cardiac performance is assessed through blood pressure and double product. Cardiac performance and autonomic response related to heart rate reduction during the recovery phase have shown a better correlation with mortality than other parameters and have a very high value (98% to 100%), although their positive predictive value is modest (approximately 50%), with abnormal ET results being uncommon in patients indicated for this stratified procedure in chest pain units.²⁸⁷⁻²⁸⁹

In multivariate regression analysis, the main independent predictors of event-free survival (death and AMI) in 1 year were the number of leads with depressed ST-segment and the maximum load achieved. Regarding safety, there is a 0.5% incidence of complications (death or AMI) in stabilized patients within 24 hours of ET.²⁹⁰⁻²⁹²

ET is recommended for estimating prognosis and assisting clinical decision-making in intermediate-risk patients 24 to 48 hours after complete clinical stabilization (hemodynamic stability, no active clinical or electrocardiographic ischemia, no new Q waves, no clinical signs of HF, and normal myocardial injury markers), provided the patient is able to exercise.^{51,198}

Thus, ET as an early strategy (< 48 hours) is formally contraindicated in high-risk patients. However, 48 hours after full stabilization of the clinical condition, even during hospitalization, ET may be indicated in patients undergoing coronary angiography, when a functional assessment of a known lesion is required or the risk level must be determined before hospital discharge, as well as to properly guide cardiac rehabilitation programs.^{293,294}

Exercise testing - Summary of recommendations and evidence		
ET can be performed in intermediate-risk patients 24 to 48 h after complete clinical stabilization, provided that there are no active ischemic symptoms, no signs of HF or hemodynamic impairment, resting ECG without ischemia, and normal myocardial necrosis markers.	I	B
ET can be performed in high-risk patients 48 h after clinical stabilization.	IIb	C
ET can be performed in high-risk patients 48 h before clinical stabilization.	III	C

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11.2. Echocardiographic Methods (Ischemia, Viability, Stress, Contrast Microbubbles, Strain, etc.)

11.2.1. Transthoracic Echocardiogram

A new analysis of LV contractile changes may, in fact, help determine the diagnosis and prognosis of ACS.²⁹⁵⁻²⁹⁹ The wall motion score index is the reference parameter for expressing LV segmental function, and its normal value is 1 (the LV is divided into 16 or 17 segments that are classified based on systolic thickening); values between 1 and 1.6 show a mild contractile change, while wall motion score index values > 1.6 indicate greater involvement and worse prognosis. Obviously, a lack of segmental contractility changes in resting transthoracic echocardiogram results does not exclude CAD.³⁰⁰

It is worth remembering that ventricular function assessment by transthoracic echocardiogram during the acute phase of ischemia could be compromised by myocardial stunning. After 2 weeks, marked improvement in ventricular function may occur.³⁰¹

Through new technologies in echocardiography, such as 2D speckle-tracking, it has become possible, by analyzing the global longitudinal strain (GLS) of the LV walls, to obtain an early diagnosis of ischemic changes in patients with troponin changes but no ECG or resting echocardiogram changes (25% to 75% of patients with ACS have normal echocardiogram results).³⁰²

GLS (when < 16.5%) can complement existing diagnostic algorithms and act as an early marker of ischemia.³⁰³ A recent publication proposes that GLS can help determine candidates for invasive strategy.³⁰⁴ Small centers have routinely used GLS in the emergency department, and changes in GLS patterns (< 18%) have been reported even before changes in troponin.³⁰⁵

In special circumstances with a suboptimal acoustic window, a transthoracic echocardiogram should be complemented with microbubble contrast echocardiography to better determine the endocardial borders or evaluate any myocardial perfusion defects.³⁰⁶

Transthoracic echocardiogram - Summary of recommendations and evidence		
Use to assess global and segmental ventricular function.	I	C
Use in a differential diagnosis of alternative causes of chest pain: severe aortic stenosis, hypertrophic cardiomyopathy, pulmonary embolism, aortic dissection, pericarditis, and cardiac tumors.	I	C
Use in chest pain with hemodynamic instability and suspected cardiac origin.	I	C
Use for suspected mechanical complications in myocardial infarction: LV aneurysm, free wall or papillary muscle rupture, interventricular communication, and pericardial effusion.	I	C
Calculate GLS using speckle tracking as an adjunct to existing diagnostic and risk classification algorithms in patients with suspected coronary disease.	IIa	B

11.2.2. Stress Echocardiography

Stress echocardiography can detect transient regional contraction abnormalities, which are indicative of exercise-

induced and pharmacologically-induced ischemia.³⁰⁷ The stress echocardiogram is an independent predictor of cardiovascular death; adding value to other methods, it can prevent cardiac catheterization. It is recommended for risk stratification in chest pain units, especially when the diagnosis cannot be determined through ECG and the ET is submaximal, cannot be performed, or is inconclusive, given that the pain is relieved for at least 24 hours in low- to moderate-risk patients and no ischemic changes or necrosis markers are evident in the ECG.^{307,308}

An improved segmental contraction in dyssynergic areas after initial dobutamine doses (5 to 10 g/kg/min) identifies myocardial viability in regions "stunned" by prior ischemia.³⁰⁷⁻³⁰⁹

Assessment by stress echocardiogram - Summary of recommendations and evidence		
Use in patients with unstable angina or clinically controlled low-risk NSTEMI-ACS* before deciding on an invasive strategy.	IIa	A
Use to assess the functional significance of moderate coronary obstruction on angiography, as long as a result interferes with management.	IIa	C
Use for risk stratification after uncomplicated myocardial infarction.	IIa	A
Use to investigate suspected microvascular disease to determine whether segmental changes occur in conjunction with angina and ECG changes.	IIa	C
Use strain and strain rate parameters derived from speckle tracking as an adjunct tool to the wall motion score index for diagnosis and/or prognosis of acute coronary disease.	IIa	B
Use in high-risk unstable angina or acute myocardial infarction.	III	C

*Without recurrent angina, signs of HF, changes in initial/serial ECG and with normal troponin; typical anginal pain with abnormal ECG or functional test with normal cardiac catheterization.

11.2.3. Echocardiographic Assessment of Myocardial Perfusion

In patients with acute chest pain and non-diagnostic ECG, contrast echocardiography increases sensitivity for ACS diagnosis.³¹⁰ Patients with normal perfusion and myocardial function at rest have a good prognosis, while perfusion defects at rest indicate a high-risk ACS subgroup.^{306,311}

Echocardiographic contrast agents are solutions that contain gas microbubbles with size of red blood cells, whose interface with the liquid medium is highly refractive, which improves the echocardiographic signal of the medium. Myocardial microcirculation can be assessed at the bedside with this method since microbubbles are microvascular markers that behave like red blood cells, i.e., they do not reach areas of microvascular obstruction. Thus, infarcted areas do not show this contrast and are easily detected by echocardiography.³⁰⁶ Through this type of echocardiography, changes in LV segmental contraction and myocardial perfusion are obtained simultaneously and instantly.³¹²

Echocardiographic contrast allows a better definition of the endocardial borders, allowing an adequate assessment of myocardial thickening and global and segmental contractile

functions of the LV at rest and under stress. In addition, contrast agents allow more accurate measurement of ventricular volumes and LVEF, especially in cases of suboptimal images, and have proven useful in determining anatomical changes.^{306,313}

Extensive transient regional perfusion defects during stress are indicative of severe CAD. An improved segmental contraction in dyssynergic areas with perfusion during the initial dobutamine infusion (5 to 10 $\mu\text{g/kg/min}$) identifies myocardial viability in regions "stunned" by prior ischemia.

In summary, in patients with chest pain treated at the emergency department, contrast echocardiography at rest adds diagnostic and prognostic data. Complete filling of the myocardium in contrast (perfusion) within 4 seconds identifies patients with normal motility and perfusion and, therefore, of low risk. Normal perfusion but a segmental change in wall movement indicates a stunned myocardium, while a fixed perfusion defect shows that the entire area is at risk during acute ischemic injury.^{314,315} In patients with AMI, stress echocardiography with myocardial contrast not only identifies the areas of infarction or stunning at rest but can identify ischemic areas at a distance by analyzing the transient changes in myocardial motility and perfusion.

11.2.3.1. Echocardiographic Assessment of Myocardial Perfusion - Summary of Recommendations and Evidence

Assessment of Myocardial perfusion by Echocardiogram - Summary of Recommendations and Evidence		
Use contrast transthoracic echocardiography to improve the Doppler signal in patients with suboptimal imaging or to determine the endocardial borders during stress echocardiography in patients with suboptimal images at rest.	IIa	B
Use stress echocardiogram with microbubbles in intermediate-risk patients with unclear ET results.	IIb	B
Use stress echocardiogram with microbubbles in high-risk patients.	III	C

11.3. Nuclear Cardiology Methods

MPS is fundamental when an ET cannot be performed and when there are difficulties interpreting the exercise ECG. One advantage of MPS is that it is among the most widely used non-invasive techniques for low-risk UA patients. It allows assessment of patients who cannot undergo physical exertion through pharmacological stress and has a better correlation with anatomical data than ET.

MPS and radionuclide ventriculography have great diagnostic and prognostic value in acute and chronic coronary diseases.³¹⁶⁻³¹⁸ One of the main advantages of MPS is that it can be performed early in ACS and has a wide safety margin, using vasodilating agents such as dipyridamole and adenosine. For this application, MPS was found to be superior to other tests. It should also be pointed out that tomographic scintigraphy can be synchronized with ECG (gated SPECT) to assess regional systolic function and measure ventricular ejection fraction with a single exam.³¹⁹ Studies have consistently demonstrated

that patients diagnosed with UA who have normal findings belong to a subgroup with a markedly reduced risk of serious events (about 1% in 1 year), while reversible defects indicate an unfavorable prognosis, with an event rate of approximately 20% in 1 year.³²⁰⁻³²³

Positron emission tomography, a non-invasive technique for assessing obstructive coronary disease, has a very high accuracy for detecting myocardial ischemia and myocardial viability. It has been found useful for diagnostic and prognostic assessment of CAD. It also provides a very accurate assessment of coronary flow reserve by absolute quantification. This information can be useful for assessing infarction in patients without significant coronary obstructions (MINOCA).^{324,325} It is difficult to obtain radiotracers (rubidium and ammonia) in Brazil, although new gamma chamber detectors of cadmium-zinc-tellurium can also quantify flow reserve using technetium tracers.³²⁶

Myocardial perfusion scintigraphy - Summary of recommendations and evidence		
Use MPS in intermediate-risk patients with unclear ET results or who cannot undergo ET.	I	B
Use MPS to identify the presence/extent of ischemia in patients who cannot undergo catheterization or when its results are insufficient to determine treatment.	I	B
Use MPS after catheterization to identify which artery is related to the event (region to be revascularized) and/or for complementary risk stratification.	I	A
Use MPS in patients with ventricular dyssynergic areas when it is necessary to determine the viability of the myocardium to guide treatment.	I	A
Use MPS as the first option for ischemia assessment, even in patients for whom ET is feasible and interpretable.	IIb	B
Use nuclear angiocardiology in intermediate- and high-risk patients to identify right ventricular involvement.	IIa	C
Use MPS in high-risk patients before the first 48 h of stabilization.	III	C

11.4. Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance (CMR) is a very useful method of morphological and functional cardiac assessment, providing important diagnostic and prognostic information about the ischemic disease and nonischemic cardiomyopathies. The test can provide accurate information about morphological aspects of the heart, quantify volumes, mass, and global and regional ventricular function, assess myocardial ischemia (by analyzing the segmental contractility under dobutamine stress without using contrast medium or by stress myocardial perfusion with vasodilators, such as dipyridamole and adenosine, and gadolinium-based contrast), as well as assess myocardial fibrosis/necrosis with the myocardial enhancement technique.³²⁷ All of this information is provided in an integrated manner through a single exam. The method also allows, by combining these and other forms of image acquisition, visualization of the pericardium and the great vessels, as well as flow and valve function analysis.

Several clinical studies and meta-analyses have shown that CMR is a highly accurate method for detecting myocardial

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ischemia, even compared to stress echocardiography,³²⁸ myocardial scintigraphy,^{329,330} and FFR.³³¹

The use of delayed enhancement imaging to assess myocardial viability has also been studied and validated in ACS. This method provides important diagnostic and prognostic information and is considered the gold standard for assessing myocardial viability and detecting infarctions.³³²⁻³³⁶ Uni- and multicenter studies have shown that CMR is an extremely sensitive technique for detecting and localizing infarction, even small subendocardial infarctions,³³⁷⁻³³⁹ which have prognostic importance, perhaps due to their frequent association with critical coronary stenosis and the fact that they may go unnoticed both in clinical evaluation and other diagnostic tests.³⁴⁰⁻³⁴² In addition, the infarcted area, which is measured by CMR, has a great prognostic impact independent of other clinical factors; some studies have found it more important than LVEF itself.^{343,344} When techniques for identifying areas of edema are associated with the measurement of areas of delayed enhancement, the rate of myocardial salvage can also be obtained, which has prognostic value, especially in patients undergoing thrombolytic treatment.³⁴⁵

Delayed enhancement imaging also allows detection of hypoenhanced (dark) areas in the midst of the hyperenhanced area (infarction), which are related to microvascular obstruction (the no-reflow phenomenon), adding prognostic information about this population.³⁴³⁻³⁴⁷

In addition to these applications, CMR is very useful for differentiating ischemic from nonischemic cardiomyopathies;^{327,348} it is used to diagnose myocarditis^{349,350} and Takotsubo syndrome.^{351,352} Furthermore, when there are elevated myocardial necrosis biomarkers and “normal” coronaryography, CMR can confirm the presence of infarction, which could be related to spasm, thrombophilic syndromes, etc. Other differential diagnoses in which CMR can help include LV hypertrophy (primary of hypertrophic cardiomyopathy or secondary) and isolated acute pericarditis without associated myocarditis.

Due to its sensitivity for finding areas of infarction and diagnosing other cardiac abnormalities, CMR has been recommended to assess patients with infarction and those without significant coronary obstructions (MINOCA). The examination allows the correct differentiation between inflammatory processes and actual ischemic necrosis, even without significant atheroma plaque, and can provide fundamental data for managing these cases. Such an approach may be particularly relevant for women, who have a higher incidence of MINOCA.³⁵³

In cases of confirmed CAD, CMR can also help define the infarction-related coronary anatomy when it is not clear in catheterization, such as in patients with severe multivessel disease and non-specific ECG. In these patients, CMR can also differentiate between old and recent infarctions that are related to the current condition. Finally, CMR can provide high-resolution images for assessing post-infarction mechanical complications, such as LV rupture, mitral regurgitation, an extension of the infarction to the right ventricle, and interventricular communication.^{340,354}

Cardiovascular Magnetic Resonance - Summary of recommendations and evidence		
CMR can be used to assess ventricular function, the presence/extent of necrosis, and myocardial viability.	I	A
CMR can be used to search for possible mechanical changes.	I	A
CMR can be used to assess patients with a clinical presentation of ACS but without significant coronary obstructions.	I	A
CMR can be used in the differential diagnosis of patients whose clinical picture is compatible with acute CAD but whose ECG shows nonspecific changes and negative biochemical markers of necrosis.	IIa	B
Use CMR as an adjunct in ACS diagnosis, especially in patients with an intermediate or high probability of ACS.	IIb	B

12. Cardiac Catheterization and Intravascular Coronary Imaging (fractional flow reserve, intravascular ultrasound, optical coherence tomography)

Coronary angiography, which is commonly used to diagnose and determine treatment for patients with NSTEMI, may not show the culprit lesion in UA and NSTEMI. This is due to the fact that the test is not 100% sensitive to plaque ruptures.³⁵⁵ The triggering factors for ACS can range from obstructive atherosclerotic disease (which may be incipient or with or without ruptured plaque) to spasm, embolism, intramural coronary hematoma, spontaneous coronary dissection, and aortic dissection.

In a recent meta-analysis, Barcarawi et al. demonstrated that for patients with NSTEMI-ACS, an early invasive strategy resulted in a lower incidence of major cardiovascular events (defined by each included study) than late invasive strategy (RR 0.65, 95% CI 0.49-0.87; $p = 0.003$), although the benefits persisted only in patients with GRACE scores > 140 .³⁵⁶ However, there were no significant differences in all-cause mortality, cardiovascular mortality, myocardial infarction or hemorrhagic events between the groups. Early invasive treatment was also associated with a lower risk of ischemic outcomes in the SWEDEHEART study.³⁵⁷

The therapeutic strategy, especially with respect to invasive evaluation, depends not only on the anatomical and functional diagnosis but on the comorbidities, clinical presentation, frailty, cognitive status, life expectancy, and, especially, risk stratification, because “very high risk” patients must be evaluated in less than 2 hours and “intermediate risk” patients must be evaluated within 72 hours, as is presented in Table 2.1.³⁵⁸

The invasive strategy allows diagnosis of underlying CAD, identifies the lesion, guides treatment for antithrombotic drugs, and determines the coronary anatomy for PCI or CABG surgery, since up to 40% of NSTEMI-ACS patients have plaques of complex morphology and up to 25% have acute coronary occlusion.

The European Society of Cardiology and the European Association of Cardiothoracic Surgery consider FFR to be the diagnostic standard for functional assessment of injury severity in patients with intermediate-grade stenosis (typically around 40% to 50%) without evidence of ischemia in non-invasive tests or in patients with multivessel disease. This guideline includes the

Table 2.1 – NSTEMI-ACS treatment strategy according to initial risk stratification

Invasive evaluation in NSTEMI-ACS		
Very high risk	High risk	Intermediate risk
Hemodynamic instability or cardiogenic shock	Positive troponin	DM or kidney failure
Recurrent or persistent angina refractory to clinical treatment	Dynamic ST-T change	HF or LVEF <40%
Malignant ventricular arrhythmia or CRA	GRACE > 140	Post-AMI angina
Mechanical complications		Previous PCI or MRS
Acute HF		GRACE 109-140 or recurrent symptoms or positive functional test
Recurrent dynamic ST/T changes		
		
Immediate invasive HF	Early invasive (less than 24 h) AI	Invasive (less than 72 h) AI

Source: adapted from Neumann et al.³⁵⁸

AI: aortic insufficiency; AMI: acute myocardial infarction; CRA: cardiorespiratory arrest; DM: diabetes mellitus; GRACE: Global Registry of Acute Coronary Events; HF: heart failure; LVEF: left ventricular ejection fraction; MRS: myocardial revascularization surgery; PCI: percutaneous coronary intervention

instantaneous wave-free ratio (iFR), a new measure that does not require adenosine-induced hyperemia and has a class IA recommendation like FFR.

For left main coronary disease, functional assessment by FFR or iFR can be technically complex, and evidence supporting their use in this condition is scarce. Consequently, intravascular ultrasound is a class IIaB recommendation, and revascularization should be excluded when the minimum luminal area is > 6 mm². For all lesions outside this area, functional assessment is preferable to intracoronary imaging. Intravascular ultrasound and optical coherence tomography (OCT) are recommended to optimize stenting (class IIaB).

FFR assessment requires the administration of adenosine to obtain maximum and stable hyperemia, unlike iFR, which assesses rest indexes derived only from resting gradients, i.e., the ratio of distal coronary pressure to aortic pressure (Pd/Pa). In the iFR-SWEDEHEART trial, which evaluated iFR-guided revascularization, 17.5% of the patients had ACS at the time of the assessment and, this strategy was not inferior to FFR-guided revascularization regarding the rate of major cardiac events and events up to 12 months after the procedure.³⁵⁹

The DEFINE-FLAIR trial,³⁶⁰ which evaluated 2,492 patients with CAD, found that iFR-guided coronary revascularization was no less efficacious than FFR-guided revascularization regarding the risk of major adverse cardiac events in 1 year, with the added benefit that iFR was more economical than FFR. The cut-off points for defining a lesion as hemodynamically significant were: iFR ≤ 0.89 and FFR ≤ 0.8.

OCT uses infrared light to provide high-resolution in vivo cross-sectional images of the coronary artery. This imaging technique allows a detailed assessment of plaque morphology in patients with ACS and can clarify the underlying mechanisms, including plaque rupture or erosion and calcification. Therefore, OCT is useful for optimizing PCI and evaluating vascular response to coronary intervention and pharmacological therapy.³⁶¹

By identifying the thrombus and plaque rupture or erosion, OCT can help clarify the nature of lesions and determine the underlying mechanisms of ACS, especially when the lesions are ambiguous on angiography.³⁶²

The DOCTORS trial assessed ACS patients referred for angioplasty and stenting in whom a single localized lesion in the culprit artery was considered responsible for ACS.³⁶³ This trial was designed to evaluate the effectiveness of OCT in optimizing percutaneous coronary intervention among patients with NSTEMI-ACS, demonstrating that stent underexpansion was common (approximately 42%) and an independent predictor of adverse outcomes. The authors concluded that an intervention with OCT results in greater functional benefits according to post-intervention FFR assessment than an intervention guided by routine angiography.

Although long-term data demonstrate that physiological assessment has better results in CAD treatment, FFR and iFR are underused in current practice.³⁶⁴ Nevertheless, advances in alternative approaches to FFR, including non-invasive coronary computed tomography, invasive angiography, and OCT, are already being guided by artificial intelligence algorithms and robust tools that allow detailed pre-procedure intervention.

Hemodynamic and coronary angiographic assessment - Summary of recommendations and evidence

Immediate cardiac catheterization should be performed in very high-risk patients	I	A
In high-risk patients, early cardiac catheterization (within 24 h) should be performed.	I	A
In intermediate-risk patients, those with recurrent symptoms, or those with a positive noninvasive test for ischemia, perform cardiac catheterization within 72 h.	I	C

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13. Myocardial Revascularization (Myocardial Revascularization Surgery and Percutaneous Coronary Intervention)

The difference between UA and NSTEMI treatment in chronic CAD is a quick decision to indicate revascularization, thus avoiding cardiovascular complications.³⁶⁵⁻³⁶⁷ Risk stratification is essential for the proper choice of conservative or invasive treatment. The most common risk scores are TIMI and GRACE.^{28,368}

Coronary angiography determines the treatment strategy; revascularization should be immediate in cases of refractory angina and electrical or hemodynamic instability. Earlier approaches also have favorable outcomes and are indicated in high-risk patients.^{28,368-370} In a cohort of 363,500 diabetic patients with NSTEMI, an early invasive assessment strategy was used in 164,740 patients (45.3%). In an analysis adjusted for propensity score, 21,681 diabetics were paired in each arm. Lower in-hospital mortality was associated with the invasive strategy in NSTEMI but not in UA (2.2% vs. 3.8%; RR 0.57, 95% CI; 0.50-0.63, $p < 0.01$).³⁷¹

Invasive strategies include angioplasty or myocardial revascularization surgery.³⁷² The SYNTAX Score is a fundamental tool for making this decision based on coronary anatomy.³⁷³ Patients with SYNTAX scores > 22 (intermediate or high) have the greatest long-term benefits from surgical revascularization.^{374,375}

Approximately 5% to 10% of patients with NSTEMI-ACS require CABG.³⁷⁶ This is a challenging subgroup due to its high-risk characteristics compared to patients undergoing elective myocardial revascularization.³⁷⁷

In patients with ongoing ischemia or hemodynamic instability who are indicated for CABG, surgery should be performed as soon as possible and should not be delayed as a consequence of antiplatelet treatment.

Since data from randomized trials are lacking, the ideal time for myocardial revascularization should be determined individually. The risk of ischemic events related to suboptimal antiplatelet therapy while awaiting surgery is $< 0.1\%$, while that of perioperative bleeding complications associated with platelet inhibitors is $> 10\%$.³⁷⁸

If the patient's clinical condition allows for delayed surgery, antiplatelet therapy should be stopped in a timely manner. Depending on the type and dosage of the agent, the effects should be reduced, e.g., 5, 5, and 7 days before the procedure for clopidogrel, ticagrelor, and prasugrel, respectively. The waiting time for surgery could be shortened by daily platelet aggregation testing to determine whether the patient has recovered from aggregation inhibition. An ongoing Brazilian study (NCT 02516267) is testing this hypothesis.

Current surgical management of NSTEMI-ACS is similar to that of stable disease. Therefore, after discussion with the heart team and appropriate surgical indication, the most important issue is determining the ideal time to perform the procedure. The best results are achieved by considering the systemic repercussions of the acute event while optimizing the patient's clinical condition. This means that patients could undergo surgery in the same hospital immediately, wait for

a reduction of antiplatelet action, or be discharged with an upcoming surgery scheduled.

In an emergency, venous grafts are preferential to arterial grafts. Surgery may be performed with or without cardiopulmonary bypass, according to the technical conditions relevant to each case. In patients with cardiogenic shock, complete revascularization through an angioplasty procedure is an initial option; however, in view of the procedure's limitations, surgery may be indicated according to multi-professional assessment.³⁵⁸

Patients who undergo surgery 1-2 days and 3-7 days after AMI have similar mortality rates, which suggests that, for some patients, it would be possible to reduce the AMI-CABG interval without compromising the results. A higher mortality rate was observed in patients who underwent surgery on the first day after AMI.³⁷⁹

The After Eighty study, conducted in 16 Norwegian centers with NSTEMI and UA patients > 80 years of age, randomized patients to an invasive strategy (ATC or CABG + optimized clinical treatment) vs. conservative strategy with optimized clinical treatment alone. The best outcomes occurred in 93 (40.6%) out of 229 patients in the invasive strategy group and in 140 (61.4%) out of 228 patients in the non-invasive strategy group (RR 0.53 [95% CI 0.41-0.69], $p = 0.0001$). There was no difference in bleeding complications between the two groups.³⁸⁰

A multicenter study of 1810 AMI patients without ST elevation or UA within 48 hours of pain onset also compared invasive and conservative strategies. Although there was no difference in infarction or death rates in the first year of follow up, these rates were significantly lower in the invasive strategy group in 5 years.³⁸¹

A systematic review that included 8915 patients, 4545 of whom were assigned to invasive strategy and 4370 to conservative strategy, also observed lower mortality between 6 and 12 months with the invasive strategy.³⁸² More advanced techniques, such as FFR and intravascular ultrasound, can help determine risk stratification and the therapeutic strategy.³⁸³⁻³⁸⁵

Myocardial revascularization (myocardial revascularization surgery and PCI) - Summary of recommendations and evidence		
According to the clinical picture and SYNTAX score, perform PCI or CABG in multiple vessel lesions.	I	B
Perform routine revascularization (PCI) for injuries unrelated to AMI in cardiogenic shock.	III	B

Part 3 – Discharge Recommendations and Post-discharge Care

1. Lifestyle Change

Secondary prevention is a fundamental part of post-ACS patient care. This stage includes lifestyle changes, cardiovascular rehabilitation, education about risk factors, and promoting better treatment adherence. Despite its proven effectiveness in preventing negative outcomes, secondary prevention is still suboptimal.^{386,387} Patients and family

members must be guided in a clear and understandable way regarding evidence-based benefits.³⁸⁸⁻³⁹⁰ Increasing the scope of secondary prevention is an important goal in this patient population.

Adequate guidance should be given about returning to work, sexual activities, and driving vehicles, working to gradually reintegrate patients into their routine. In addition, special attention should be paid to psychosocial and socioeconomic issues, including attention to the risk of depression and social isolation.³⁹¹⁻³⁹⁸

1.1. Smoking Cessation

Smoking cessation, a particularly important factor in lifestyle change, is a very effective measure for reducing mortality in post-NSTE-ACS patients.³⁹⁹ Cigarettes contain approximately 7,000 chemical components, many of which directly interfere with cardiovascular disease, 69 of which are carcinogenic.⁴⁰⁰ Cigarettes interfere with the cardiovascular system in various ways, increasing the heart rate and myocardial oxygen demand while decreasing supply.⁴⁰¹ Smoking increases the incidence of sudden death,⁴⁰² the risk of thrombosis, inflammation, vasoconstriction, and increased oxidation of LDL cholesterol.⁴⁰³ It is estimated that the risk of atrial fibrillation increases 1.5 to 2 times among smokers.⁴⁰⁴

In patients after NSTEMI-ACS, referral to a smoking cessation program and pharmacological agents, such as nicotine patches or gum, have proven useful.⁴⁰⁵ In an observational study of 12,656 patients, Parasuraman et al. found that, compared to ex-smokers and never smokers, smoking patients underwent coronary intervention at an earlier age, and the intervention was more associated with ACS. Former smokers had similar results to never smokers.⁴⁰⁶

The smoking cessation strategy should play a central role in the patient's overall rehabilitation and begin as soon as possible, even during the hospital phase. Family members who live in the patient's house should also be encouraged to participate in smoking cessation programs, thus reinforcing the patient's commitment, in addition to reducing the risk of secondhand smoke.⁴⁰⁷

Four steps are involved in treating nicotine addiction. The Fagerström test (Table 3.1) is commonly used for the first step, determining the addiction level. The next steps are counseling, medication/behavioral treatment, and clinical follow-up.

To prevent relapse, it is important to identify high-risk situations and act to address them. The strategies basically consist of avoiding, escaping, distracting, and postponing. Parties, alcohol or caffeine intake, and meeting with smokers should be avoided, at least during the first weeks of cessation.

Medications such as bupropion, varenicline, and nicotine replacement therapy may increase the risk of cessation, especially in association with other types of therapy, such as support and counseling groups, psychotherapy, and alcohol withdrawal.

Bupropion is an antidepressant with anxiolytic action that several studies have found to decrease withdrawal symptoms. One study that compared smoking cessation among patients

Table 3.1 – Fagerström tolerance questionnaire

How many cigarettes do you smoke per day?
(0) less than 11
(1) between 11 and 20
(2) between 21 and 30
(3) more than 30
2. How long after waking do you wait before having your first cigarette?
(0) more than 60 min
(1) between 31 and 60 min
(2) between 6 and 30 min
(3) less than 6 min
3. Do you find it difficult to refrain from smoking in places where it is forbidden?
(0) no
(1) yes
4. Does the first cigarette in the morning bring you the most satisfaction?
(0) no
(1) yes
5. Do you smoke more in the morning than during the rest of the day?
(0) no
(1) yes
6. Do you smoke even when you are bedridden due to illness?
(0) no
(1) yes
Interpretation of the results (sum of the points for each question):
0 to 2 points = very low physical dependence
3 to 4 points = low physical dependence
5 points = medium physical dependence
6 to 7 points = high physical dependence
8 to 10 = very high physical dependence

Source: adapted from Ranney et al.⁴⁰⁷

treated with bupropion 300 mg/day vs. placebo found abstinence rates of 44.2% and 9.2% in the bupropion and placebo groups, respectively.⁴⁰⁸ A literature survey revealed that bupropion appears to be more effective in patients who have abandoned and/or failed nicotine replacement therapy.⁴⁰⁹ On the other hand, two studies on smokers hospitalized for acute coronary events found no difference in smoking cessation between bupropion and placebo groups.^{410,411}

Nicotine replacement therapy is effective and increases smoking cessation rates. In one study, any form of nicotine replacement resulted in up to a 60% increase in abstinence (RR: 1.60; 95% CI: 1.53 to 1.68) compared to placebo. The increase in efficacy only occurred when comparing an association of nicotine replacement modes to a single mode (RR: 1.34; 95% CI: 1.18 to 1.51).⁴¹² The most common long-term nicotine replacement mode is transdermal patches, while the most common short-term modes are chewing gum, nasal sprays, and inhalers, some of which are still not available in Brazil.

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Varenicline is a nicotine receptor partial agonist that, by replacing the action of nicotine, reduces the intensity of withdrawal symptoms. Its bond with the receptor also reduces the reward and pleasure effects of smoking, which can reduce some of the effects of deprivation. Its effectiveness has been demonstrated in six clinical trials with a total of 3,659 chronic smokers.⁴¹³⁻⁴¹⁶ Varenicline doubled abstinence rates compared to placebo (RR: 2.24; 95% CI: 2.06 to 2.43).⁴¹⁷ A study involving more than 8,000 smokers compared the use of varenicline, bupropion, nicotine patches, and placebo, randomized in a 1:1:1:1 ratio, and found a higher abstinence rate in the varenicline group at 6 months than the other groups.⁴¹⁸ In a randomized study in patients with chronic coronary disease, the probability of continuous abstinence after 1 year was higher in the varenicline group than the placebo group (OR: 3.14; 95% CI: 1.94 to 5.11).⁴¹⁹ Two randomized studies in smokers with ACS found higher rates of continuous abstinence at 24 weeks and a higher rate of abstinence at 52 weeks in the varenicline group than the placebo group.^{420,421} One of varenicline's main limitations is its high cost and the occurrence of nausea as a limiting side effect in some patients.

An association of methods seems to be more effective than treatment with a single method. In a recent meta-analysis of four studies, an association of varenicline + bupropion resulted in higher abstinence rates at 6 months than varenicline alone. The effects were more pronounced in more nicotine-dependent and heavier smokers. The benefits, however, did not last for 12 months, and the association significantly increased anxiety symptoms.⁴²² Therefore, an association between methods appears to be safer and more effective when varenicline or bupropion is combined with nicotine replacement therapy.

Bupropion and varenicline also appear to be safe for patients with cardiovascular disease. Some studies have found an increased occurrence of neuropsychiatric events with these medications, which led the U.S. Food and Drug Administration to require a label warning. After further study, this risk was reassessed, and the warning was withdrawn in 2016.⁴²³

Replacing traditional cigarettes with low-nicotine cigarettes or vaporizers (electronic cigarettes) is a controversial issue.⁴²⁴ Both strategies are only classified as potential damage control.

Studies on low-nicotine cigarettes indicate that they have little effect, since smokers generally compensate by smoking more cigarettes or adding other forms of nicotine.⁴²⁵ Vaporizers apparently expose the smoker to fewer carcinogens than traditional cigarettes, although there is great variability in the toxic substances they contain. In addition, there has been an explosive increase in their use among young people, especially in the USA.⁴²⁶ Sale of these devices is prohibited in Brazil. They have been associated with several recent deaths in the USA due to acute lung problems from inhaled substances. A total of 2,807 vaping-related hospitalizations and 68 deaths have been confirmed by the U.S. Centers for Disease Control. To date, there is no evidence that these strategies facilitate smoking cessation, and electronic cigarettes, in particular, are potentially dangerous.

Smoking cessation - Summary of recommendations and evidence		
Patients should stop smoking and avoid exposure to environments with smokers, both at work and at home.	I	A
Long-term follow-up and referral to specific programs or pharmacotherapy (including nicotine replacement) are useful when associated with traditional non-pharmacological strategies.	I	A
Low-nicotine cigarettes can be used for damage control.	III	C
Vaporizers can be used as a damage control and smoking cessation strategy in resistant patients	III	B

1.2. Dietary Recommendations

Since patients with NSTEMI-ACS are classified as very high cardiovascular risk, a considerable reduction in cholesterol values is absolutely indispensable. In addition to statin therapy, which is supported by the results of several meta-analyses^{427,428} and randomized trials,⁴²⁹⁻⁴³² dietary therapy is of central importance and is supported by significant evidence.^{433,434}

A standard diet rich in fruits, vegetables, whole grains, healthy protein sources (dairy products, low-fat [skinless] poultry, fish/seafood, and nuts), non-tropical vegetable oils is recommended. Sweets, sugary drinks, and sugar itself should be avoided, as well as excess red meat. The PREDIMED trial tested a Mediterranean-type diet, finding a reduction in cardiovascular events, especially stroke.⁴³⁵

This diet must be adjusted for appropriate caloric requirements, cultural patterns, food preferences, and nutritional therapy for other conditions, including DM. Caloric intake should be adjusted to avoid weight gain and, for overweight/obese patients, it must promote weight loss. Vitamins or antioxidant food supplements should not be routinely prescribed for secondary prevention.⁴³⁶

2. Cardiovascular Rehabilitation

Physical exercise reduces atherogenesis, promotes anti-inflammatory action, improves endothelial function, decreases sympathetic tone, increases HDL, and reduces blood pressure and insulin resistance, among other beneficial effects, and should not be denied to patients after ACS.⁴³⁷ Exercise is included in the therapeutic context of cardiovascular rehabilitation programs. Sedentary lifestyle, a worldwide problem, is the main target of primary prevention and is even more important for secondary prevention of coronary events.

The cardiovascular rehabilitation process of ACS patients should begin during hospitalization with physical therapy, including early walking and passive and active movement of the main muscle groups. Even while hospitalized, the patient should be familiarized with scales of perceived effort (e.g., the BORG scale), which will be useful after discharge.

At discharge, every patient should receive adequate guidance about physical activity, which should initially be mild intensity, a continuation of the exercises performed during the hospital phase (phase 1), including self-monitoring techniques. Early assessment in a formal rehabilitation program should be indicated, or, when unavailable, the patient should be advised about an exercise program that can be administered by a

physical therapist or physical educator according to doctor-imposed limits (phase 2).

Studies have shown that patients referred to exercise programs after an acute coronary event have a better quality of life, less symptom recurrence, and fewer new cardiovascular events.⁴³⁸⁻⁴⁴⁰

Despite the positive effects of rehabilitation programs, systematic referral and compliance are still major challenges.⁴⁴¹ A lack of continuing medical education in cardiac rehabilitation, a lack of knowledge about program safety (event rate of 1 for every 112,000 patients/hour), and difficulty making these programs cost-effective are important parts of the problem.

2.1. Instructions about Physical Activity at Discharge

The first step in assessing patients for a cardiovascular rehabilitation program after clinical evaluation and complementary exams is to determine whether there is any absolute contraindication to physical exertion.^{442,443} Table 3.2 lists contraindications to regular physical activity.

The risk classification for physical activity in cardiac patients is based on clinical data regarding angina, functional classification, ventricular function, residual coronary lesions, and arrhythmias. This classification is useful for determining the level of support required during the program and the need for monitoring during exercise sessions.^{442,443}

Low-risk patients may begin exercising with a physical therapist or physical educator, without necessarily being supervised by a physician. Moderate risk patients, however, should preferably exercise in an environment with medical supervision and advanced life support resources; they can progress to a semi-supervised external program if no complications occur after 12 weeks. When a medically supervised cardiovascular rehabilitation program is not available, these patients can exercise under the supervision of a physical educator or physical therapist, conforming to safety limits predetermined by the cardiologist. The exercise team must have training in at least basic life support and an automatic external defibrillator must be available on site. High-risk patients should exercise under medical supervision, with a physical therapy and/or physical education team trained in basic life support and with local resources for advanced life support.

In all situations, heart rate monitoring should guide exertion intensity. The need for electrocardiographic monitoring during

the rehabilitation program can be defined on a case-by-case basis by the medical team.

Safe exercise zones can be ideally defined through a functional test (cardiopulmonary test or ET) or, in specific cases, they can be guided by perceived effort. When a cardiopulmonary test is available, aerobic exercise should generally involve a heart rate between what is indicated by the anaerobic threshold and the respiratory compensation point, ie, a zone at which, despite the production of lactic acid, there is no decompensated metabolic acidosis, which is associated with a lower risk of arrhythmic events or cardiovascular overload. When a cardiopulmonary test is not available, exercise at between 70% and 85% of the maximum heart rate achieved in an ET or 50% to 80% of the heart rate reserve added to the resting heart rate, where: heart rate reserve = peak heart rate - resting heart rate. In patients with ECG changes or symptoms suggestive of ischemia on exertion, the limit should, in general, be 10 beats less than symptom onset or ST change. In specific cases and under medical supervision, the patient can approach the point of ischemia onset.

The doctor should ideally determine the following exercise parameters:

- Weekly frequency.
- Intensity (using a Borg scale and the heart rate or load determined in a cardiopulmonary or ET).
- Mode (eg, walking, cycling, rowing).
- Session duration.
- Resistance exercises should also be encouraged. The recommended intensity is 40% to 60% of the maximum voluntary contraction (low to moderate intensity), 8 to 15 repetitions, 1 to 3 sets.^{443,444}

Cardiopulmonary rehabilitation - Summary of recommendations and evidence		
Physical activity guidance should be provided at discharge; cardiac rehabilitation programs should be encouraged in all patients after ACS.	I	B
Physical activity guidance should be provided at discharge; cardiac rehabilitation programs should be encouraged in all patients after ACS.	I	B
Physical activity guidance should be provided at discharge; cardiac rehabilitation programs should be encouraged in all patients after ACS.	III	A

Table 3.2 – Risk classification for exercise training in cardiac patients

Low risk	Moderate risk	High risk
• LVEF > 50% • No complex arrhythmias • No symptoms of congestive HF • No angina upon exertion or in the recovery period • No severe or moderate valve injury • Functional capacity ≥ 7 METS	• LVEF: 40% to 49% • Signs/symptoms, including moderate angina during exercise (5 to 6.9 METS) or in the recovery period • Moderate valve injury	• LVEF < 40% • cardiac arrest or sudden death survivors • Complex ventricular arrhythmias at rest or during exercise • Severe valve disease • Uncorrected congenital heart disease • Functional capacity < 5 METS - Ischemic ST-segment depression during exercise > 2 mm

LVEF: left ventricular ejection fraction; METS: metabolic equivalents.

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3. Medications to be Prescribed at Discharge

3.1. Antithrombotic drugs

A. Switching Antiplatelet Treatment

Although a second antiplatelet may have been previously selected for use with ASA, at the time of hospital discharge it may be necessary to switch to a different antiplatelet for some reason, such as:

- Cost.
- Limiting adverse effects (eg, dyspnea with ticagrelor, bleeding while using the most potent drugs, such as ticagrelor and prasugrel).
- Patient preference for a single daily dose (eg, prasugrel, if treated with PCI and without prior stroke/TIA) rather than twice a day (ticagrelor).

The transition from clopidogrel to ticagrelor has been the only such change studied with sufficient power to assess clinical outcomes, despite the fact that the study was not developed for this purpose. In the PLATO trial, 46% of the patients randomized to receive ticagrelor had been pretreated with clopidogrel (300 to 600 mg dose).¹⁵² The safety and efficacy of ticagrelor were not affected by previous use of clopidogrel.²⁴⁸ In the TRITON-TIMI-38 trial, which evaluated the use of prasugrel, previous use of another P2Y₁₂ inhibitor was considered an exclusion criterion.¹⁵⁴ Other changes in P2Y₁₂ inhibitors (e.g., between ticagrelor and prasugrel or from ticagrelor/prasugrel to clopidogrel) have been evaluated by pharmacodynamic and observational studies, which serve more as hypothesis generating, since they were not designed to assess clinical outcomes.⁴⁴⁵⁻⁴⁴⁹ Thus, there is less evidence to support such transitions. Figure 3.1 shows the recommendations for switching P2Y₁₂ agents in patients with ACS for less than 30 days.^{450,451}

Thus, as a general rule, when switching P2Y₁₂ antiplatelet therapy during the acute phase of coronary disease (< 30 days), a loading dose of the new medication should be used, followed by a maintenance dose. One exception to this rule is when prasugrel or ticagrelor is replaced with clopidogrel due to bleeding or increased risk of bleeding. The new drug should be administered 24 hours after the final administration of the first drug, with the exception of when clopidogrel is being replaced.

When the patient has had ACS for more than 30 days, and it becomes necessary to switch agents, see Figure 3.2.

Some differences should be considered:

- In all situations, a 24-hour wait is recommended between the final dose of the previous medication and the first dose of the new medication.
- A loading dose of the new agent is recommended only when ticagrelor is being replaced. Clinical studies have shown greater platelet reactivity in the first 48 hours when changing from ticagrelor to clopidogrel^{448,449} or prasugrel.⁴⁴⁷ This difference is due to the fact that ticagrelor is a reversible P2Y₁₂ inhibitor, while thienopyridines (clopidogrel and prasugrel) are non-reversible.

Switching P2Y₁₂ inhibitors - Summary of recommendations and evidence

In admitted ACS patients who received clopidogrel and wish to change to ticagrelor in the first 30 days, a loading dose of 180 mg should be administered, regardless of the timing and dosage of clopidogrel.	I	B
Other changes in oral P2Y ₁₂ inhibitors should be considered in light of adverse effects or other factors and should follow the regimens recommended in this Guideline.	IIb	C

B. Duration of Dual Antithrombotic Therapy

B.1. More than 12 Months

B.1.1. Antiplatelets

Studies have assessed the use of clopidogrel, prasugrel, and ticagrelor in ACS patients on DAPT for an average of 12 months. This is the recommended time, regardless of therapeutic strategy (clinical treatment, angioplasty, or myocardial revascularization surgery). For patients who receive clinical treatment, the only options for antiplatelet drugs are ticagrelor and clopidogrel, since it has been demonstrated that prasugrel is not superior to clopidogrel in such cases.⁴⁵²

DAPT is a very effective way to prevent stent thrombosis. The risk of late (between 1 month and one year after stent implantation) and very late stent thrombosis (> 1 year after angioplasty) has been decreasing considerably with the use of more modern drug-eluting stents. Thus, continuing DAPT more than one year after an ACS event and angioplasty seems to carry an increased risk of bleeding that is more harmful than the potential benefits of preventing very late stent thrombosis. However, the PEGASUS trial demonstrated that in patients with a history of infarction (> 1 year) and additional high risk criteria (DM, age > 65 years, chronic kidney disease, multivessel coronary disease or two or more previous infarctions), prolonged DAPT with ASA + ticagrelor reduced the incidence of ischemic outcomes, including new cases of infarction unrelated to stent thrombosis or stroke, compared to ASA monotherapy (HR 0.84; 95% CI 0.74 to 0.95; p = 0.004 and HR 0.85; 95% CI 0.75 to 0.96; p = 0.008, for doses of 60 mg and 90 mg, respectively).⁴⁵³ Continuing DAPT beyond 12 months would thus be more associated with systemic protection against thrombotic events than with preventing late stent thrombosis. This finding was reinforced by a subanalysis of the same trial, which found a similar reduction of ischemic cardiovascular events in patients with no history of stent angioplasty and patients with previous angioplasty.⁴⁵⁴ However, the decrease in cardiovascular events was accompanied by an increase in major bleeding episodes (HR 2.32; 95% CI 1.68 to 3.21; p < 0.001 and HR 2.69, 95% CI 1.96 to 3, 70; p < 0.001, for doses of 60 and 90 mg, respectively). There was no increase in fatal bleeding or intracranial hemorrhage with ticagrelor. The highest dose of ticagrelor (90 mg, twice a day) did not reduce ischemic risk and led to higher bleeding rates. Thus, the 60 mg dose is approved

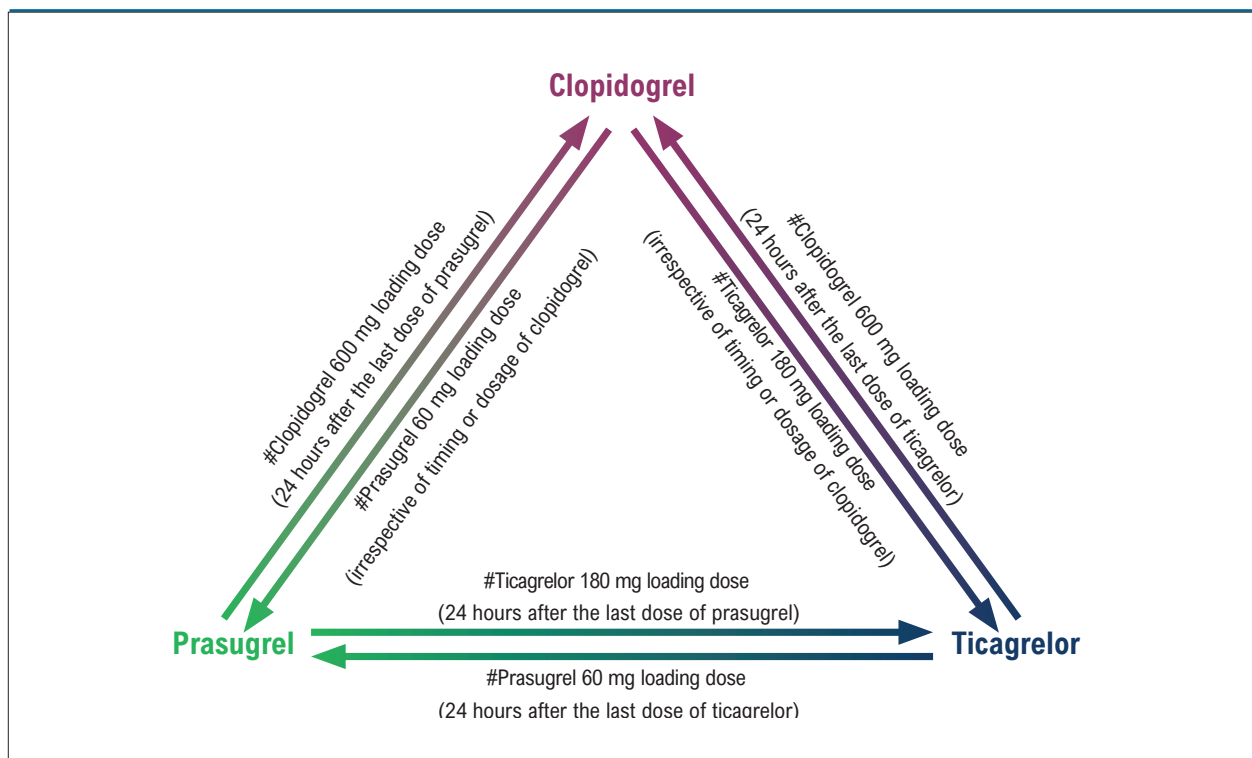


Figure 3.1 – Recommendations for switching P2Y₁₂ inhibitors in the first 30 days after acute coronary syndrome. A loading dose of the new agent is routinely recommended. *If prasugrel or ticagrelor therapy is being de-escalated due to bleeding or an increased risk of bleeding, only a maintenance dose of clopidogrel can be considered. Adapted from Valgimigli et al.⁴⁵¹

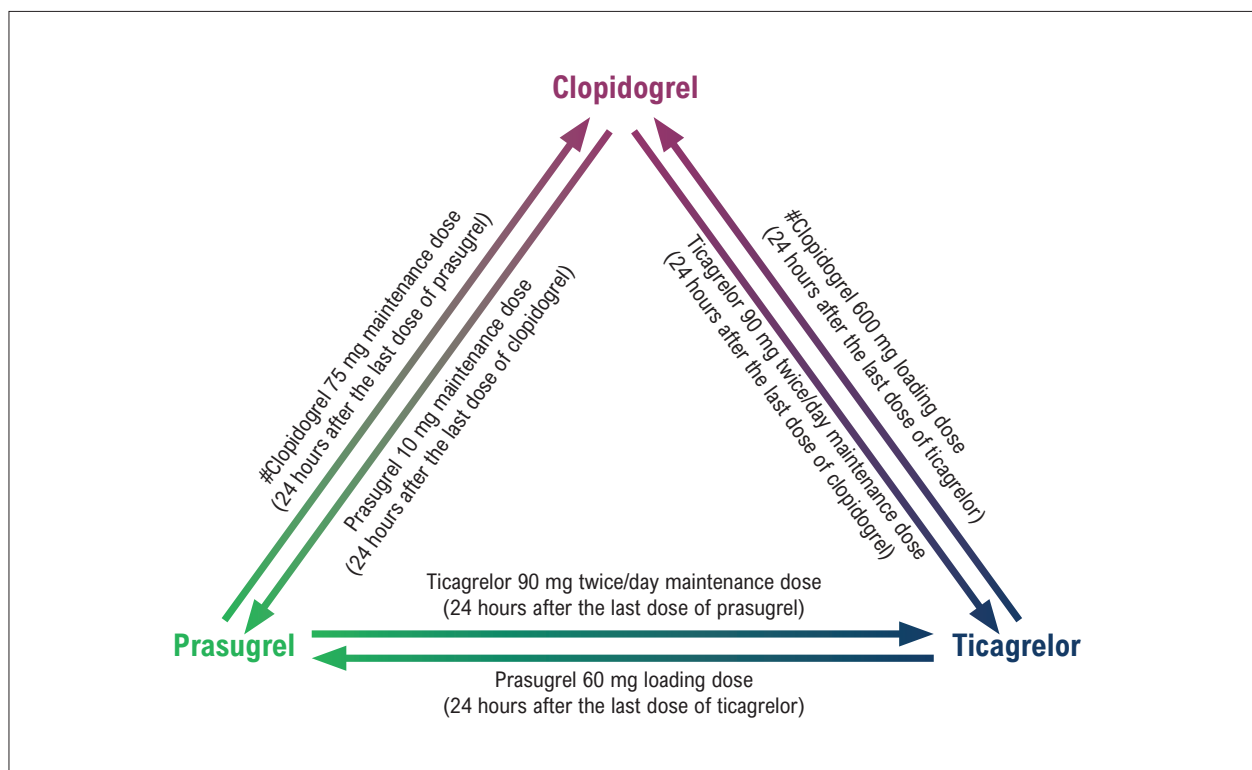


Figure 3.2 – Recommendations for changing P2Y₁₂ inhibitors in patients after 30 days of acute coronary syndrome. * If ticagrelor to clopidogrel therapy is being de-escalated due to bleeding or an increased risk of bleeding, only a maintenance dose of clopidogrel can be considered. Adapted from Valgimigli et al.⁴⁵¹

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for selected patients 1 year after NSTEMI who tolerated DAPT during this period.

The DAPT trial also assessed the use of DAPT for > 12 months with clopidogrel and prasugrel (65.2% and 34.8% of patients, respectively).⁴⁵⁵ All included patients had undergone angioplasty with a drug-eluting stent and angioplasty in the context of NSTEMI-ACS was performed in approximately one third of the patients. In this study, patients received DAPT for a standard 12-month period and, if they adhered to treatment and did not experience relevant bleeding, they were then randomized to continue DAPT or ASA + placebo for another 18 months. Like the PEGASUS trial, a reduction in ischemic events occurred, but this benefit was offset by the increased risk of bleeding. Although stent thrombosis was reduced by one case in every 100 patients treated with prolonged DAPT, major or moderate bleeding occurred in one out of every 111 patients.

A meta-analysis of > 32,000 patients before the publication of the PEGASUS trial found a significant increase in infarction incidence in the group that received DAPT for 12 months (compared with > 12 months; OR = 1.57, 95% CI 1.30 to 1.90), as well as a lower incidence of bleeding (OR = 0.65, 95% CI 0.52 to 0.81).⁴⁵⁶ Subsequent meta-analysis, including the PEGASUS trial, found a significant decrease in all-cause mortality in the DAPT > 12 months group (HR = 0.89, 95% CI 0.79 to 0.99).⁴⁵⁷ It was concluded that any of the three P2Y₁₂ inhibitors available in Brazil (clopidogrel, ticagrelor, and prasugrel) can reduce ischemic events when used in association with ASA for more than 12 months, although at an increased risk of bleeding. Thus, patient risk for ischemic events and bleeding must be individually assessed. Clinical scores allow ischemic and hemorrhagic risk to be estimated with more objective parameters according to the patient's clinical characteristics, assisting with decision making regarding the duration of DAPT.

The PRECISE-DAPT trial assessed 14,963 patients who had undergone angioplasty, using a score that consisted of five variables (age, creatinine clearance, hemoglobin, leukocyte count, and a history of spontaneous bleeding) to predict the risk of bleeding.⁴⁵⁸ The score was also validated in a group of more than 14,000 patients. Patients with low scores (< 25) benefitted from prolonged DAPT, including a reduction in the composite ischemic outcome (AMI, definitive stent thrombosis, stroke, and need for revascularization); the number needed to treat was 65, and there was no significant increasing in risk of bleeding. On the other hand, in patients with high scores ($\geq$ 25), prolonged DAPT was associated with an increased risk of bleeding (number needed to harm = 38) and provided no benefits regarding ischemic outcome prevention. It should be pointed out, however, that this score was derived from randomized studies with PCI (with or without ACS) and not exclusively from a population with ACS, whose risk of ischemic events tends to be higher than that of patients with stable CAD.

The DAPT score (Table 3.3) was derived from a cohort in the DAPT trial.⁴⁵⁹ In this analysis, patients with a high risk score ($\geq$ 2) who received DAPT for 30 months had a significant reduction in ischemic outcomes (number needed to treat = 34) and a small increase in the risk of bleeding (number needed to harm = 272). On the other hand, in patients with a low score (< 2), prolonged DAPT led to no reduction in ischemic risk and a

considerable increase in the risk of bleeding (number needed to harm = 64).

B.1.2. Anticoagulants

The COMPASS study randomized > 27,000 patients with chronic coronary disease to rivaroxaban 2.5 mg twice a day + ASA 100 mg once a day (n = 9152) or rivaroxaban 5 mg twice a day (n = 9117) or ASA 100 mg (n = 9126). In an average follow-up of 23 months, rivaroxaban + ASA was superior to ASA alone (HR = 0.76, 95% CI 0.66 to 0.86 for the primary outcome (cardiovascular death, AMI or stroke), although it increased the incidence of bleeding (HR = 1.70, 95% CI 1.40 to 2.05). Importantly, there was a significant decrease in all-cause mortality (HR = 0.82, 95% CI 0.71 to 0.96) but no significant difference in the incidence of fatal or intracerebral bleeding.⁴⁶⁰ Considering only the rivaroxaban + ASA and ASA groups, 2423 patients had a history of AMI < 2 years, 3279 between 2 and 5 years, and 5673 > 5 years. The comparison between groups showed hazard ratios of 0.70 for patients with AMI < 2 years, 0.81 for those with AMI between 2 and 5 years, and 0.72 for those with AMI > 5 years (P-interaction = 0.93).⁴⁶¹

B.2. Less than 12 Months

Ticagrelor monotherapy was evaluated in the GLOBAL LEADERS trial⁴⁶² in 15,968 patients undergoing PCI (34% with NSTEMI-ACS). The groups received ASA + ticagrelor for 1 month, followed by ticagrelor monotherapy for 23 months or by standard DAPT with ASA + clopidogrel (stable CAD) or ASA + ticagrelor (acute CAD) for 12 months, followed by ASA monotherapy for 12 more months. At the end of 2 years of follow-up, the primary outcome (all-cause mortality or infarction) was similar in both groups (RR 0.87, 95% CI 0.75 to 1.01). The secondary outcome, bleeding (BARC 3 or 5), was also similar in both groups (RR = 0.97, 95% CI 0.78 to 1.20). Secondary analysis in a later publication found a significant decrease in the primary outcome in patients with acute CAD and PCI in more than one coronary artery.⁴⁶³

The TWILIGHT trial evaluated whether early discontinuation of ASA would be safe in patients treated with PCI who had a high risk of thrombosis or bleeding according to clinical and angiographic characteristics.⁴⁶⁴ A total of 7119 patients (4614 with NSTEMI-ACS) were included, all treated for 3 months after PCI with ASA + ticagrelor. After this period, they were randomized to continue with DAPT or ticagrelor monotherapy for another 9 months. The main outcome was bleeding (BARC 2, 3 or 5). At the end of follow-up, the ticagrelor monotherapy group there was a 44% reduction (HR 0.56; 95% CI: 0.45-0.68; $p < 0.001$) in the main outcome, with no increase in ischemic risk (secondary outcome, insufficient sampling power for this conclusion).

In a recently published meta-analysis, O'Donoghue et al. assessed monotherapy with P2Y₁₂ inhibitors vs. DAPT in approximately 17,000 patients with acute coronary disease, finding a hazard ratio of 0.50 (95% CI 0.41 to 0.61) for bleeding, and a hazard ratio of 0.85 (95% CI 0.70 to 1.03) for major adverse cardiac events.⁴⁶⁵

Table 3.3 – Dual Antiplatelet Therapy trial score

Variables	Points
Age $\geq$ 75 years	-2
Age between 65 and 74 years	-1
Age < 65 years	0
Current smoker	1
Diabetes mellitus	1
AMI at initial presentation	1
Previous PCI or AMI	1
Stent diameter < 3 mm	1
Stent eluted with paclitaxel	1
HF or LVEF < 30%	2
PCI in saphenous vein graft	2

AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure; LVEF: left ventricular ejection fraction.

Duration of dual antithrombotic therapy in patients with NSTEMI-ACS in sinus rhythm - Summary of recommendations and evidence			
After NSTEMI-ACS, DAPT should be continued for 12 months, regardless of the clinical strategy (angioplasty, myocardial revascularization surgery, or clinical treatment).	I	A	
In patients with NSTEMI-ACS and increased risk of bleeding, DAPT should be continued for only 6 months, with the P2Y ₁₂ inhibitor suspended after this period, regardless of the clinical strategy (angioplasty, coronary artery bypass surgery, or clinical treatment)	IIa	B	
In NSTEMI-ACS patients undergoing PCI, DAPT may be considered for 3 months, followed by P2Y ₁₂ inhibitor monotherapy (preferably ticagrelor).	IIa	A	
Associate a second antithrombotic medication (see table below) with ASA after 12 months of DAPT in patients with a high ischemic risk and a low risk of bleeding.	IIa	A	
Extended antithrombotic/antiplatelet therapy options			
Medication	Trial	Dose	Indication
Clopidogrel	DAPT	75 mg per day	Post-angioplasty tolerant to DAPT for 1 year
Prasugrel	DAPT	10 mg per day (5 mg if weight < 60 kg or age > 75 years)	Post-angioplasty tolerant to DAPT for 1 year
Ticagrelor	PEGASUS-TIMI-54	60 mg twice/day	Post-infarction with increased ischemic risk
Rivaroxabana	COMPASS	2,5mg 2 vezes/dia	Pacientes coronariopatas ou com doença arterial periférica com alto risco trombótico

Care should be taken when prescribing antiplatelet drugs to patients with ACS who, during hospitalization, undergo CABG. Subanalyses of the CURE,⁴⁶⁶ PLATO,²⁴⁹ and TRITON²³⁷ trials showed that patients undergoing surgical revascularization

seemed to benefit like the other patients included in these trials. Thus, thienopyridine should be reintroduced as soon as it is considered safe after surgical revascularization.

C. Antiplatelet Management in Patients Who Need Chronic Anticoagulation

Evidence about antiplatelet management in patients who need chronic anticoagulation is, for the most part, restricted to atrial fibrillation (AF) patients. The incidence of AF in patients with NSTEMI-ACS ranges from 5% to 23%.⁴⁶⁷ The standard therapy for ACS is DAPT for at least 12 months to prevent ischemic events. In patients with AF and a CHA₂DS₂VAS_c score $\geq$ 2, chronic anticoagulation is recommended to prevent thromboembolic events. When both of these conditions are present, it becomes important to determine the best combination of antithrombotic agents, including the appropriate dose and the ideal duration of each treatment. These questions were evaluated in a series of phase 3 clinical trials.

The first of these studies was the WOEST trial,⁴⁶⁸ which recruited 573 patients with AF who were on anticoagulants and underwent angioplasty. The patients were then randomized into two groups: one that used clopidogrel associated with anticoagulant and another that used triple therapy (anticoagulant + clopidogrel + ASA). Dual therapy was associated with a lower risk of bleeding at 1 year (19.4% vs. 44.4%, HR 0.36, 95% CI 0.26-0.50, $p < 0.0001$) without a greater risk of ischemic events.

The first randomized trial to assess DOAC in the context of double and triple therapy in patients with AF who underwent angioplasty was PIONEER AF-PCI.²⁶⁸ This trial compared three antithrombotic strategies: rivaroxaban 15 mg/day associated with a P2Y₁₂ inhibitor; triple therapy with DAPT and low-dose rivaroxaban (2.5 mg every 12 h); triple therapy with DAPT and a vitamin K antagonist. Strategies involving rivaroxaban were associated with a lower risk of bleeding than triple therapy with vitamin K antagonists. There was no difference in ischemic outcomes, but the sample size (2124 patients) had insufficient power for this outcome. One criticism of this study was the fact

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that the low doses of rivaroxaban had not been approved for antithrombotic treatment in AF.

The following year, the RE-DUAL PCI trial was published, which randomized 2725 patients with AF who underwent angioplasty.²⁶⁹ Dual therapy with dabigatran at different doses (150 mg twice a day and 110 mg twice a day) associated with a P2Y₁₂ inhibitor was compared to triple therapy with warfarin. In the triple therapy group, ASA was continued for 1 month in patients who received a non-drug-eluting stent, and for 3 months in patients who received a drug-eluting stent. The two dabigatran regimens were associated with a lower risk of bleeding than the triple therapy warfarin regimen. No interaction was found between proton pump inhibitors and the effect of the drug, since this class of drugs did not influence the main results of the study.⁴⁶⁹ The design of RE-DUAL PCI and PIONEER AF-PCI did not allow assessment of whether the reduced risk of bleeding in dual therapy was secondary to replacing vitamin K antagonists with DOAC or to excluding ASA from the treatment.

The AUGUSTUS trial, published in 2019,²⁷⁰ set out to answer this question by randomizing 4,614 patients with AF who had undergone PCI or had ACS in the last 14 days. The study used a 2x2 factorial design; patients were randomized into groups that compared apixaban 5 mg twice a day to warfarin, and groups that compared ASA to placebo. All patients received a P2Y₁₂ inhibitor, which was clopidogrel in more than 90% of cases. Thus, four groups were studied: (1) P2Y₁₂ inhibitor + warfarin + ASA; (2) P2Y₁₂ inhibitor + warfarin + placebo; (3) P2Y₁₂ inhibitor + apixaban + ASA; (4) P2Y₁₂ inhibitor + apixaban + placebo. In the comparison between apixaban and warfarin, there was a lower risk of bleeding with apixaban. One major or clinically relevant bleeding episode was avoided during the study period for every 24 patients treated with apixaban when compared with warfarin. In the comparison of ASA vs. placebo, it was demonstrated that ASA increased the risk of bleeding. There was one additional significant bleeding episode in 6 months for every 14 patients treated with ASA when compared with placebo. Compared to triple therapy, there was no increase in ischemic outcomes with double therapy; however, the study was not powered to assess efficacy outcomes. It is important to point out that in the AUGUSTUS trial, patients were randomized an average of 6 days after PCI or ACS. Thus, patients received at least a short course of ASA and triple therapy prior to randomization. Another relevant fact about this study is that it also included patients with AF and medically managed ACS (approximately 25% of the sample).

The ENTRUST trial randomized 1506 patients with AF who underwent coronary angioplasty, following them for 12 months.²⁷¹ The study design compared double therapy with edoxaban 60 mg/day associated with clopidogrel 75 mg/day to traditional triple therapy (warfarin + double antiplatelet therapy with ASA + clopidogrel). Dual therapy with edoxaban was non-inferior to triple therapy with warfarin regarding the primary outcome of bleeding. However, this was the only randomized clinical trial that did not demonstrate a superiority for bleeding outcomes of a dual therapy with a DOAC compared to a triple therapy with warfarin.

One possible concern with dual therapy in AF patients who undergo angioplasty would be an increased ischemic risk, especially for stent thrombosis. The five previously mentioned trials (WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST) were designed to determine whether less aggressive

antithrombotic therapy resulted in reduced bleeding. None of them, however, had sufficient power to adequately assess increased ischemic risk. To assess this issue, two meta-analyses were developed, both of which demonstrated that, compared to warfarin + DAPT, dual antithrombotic therapy decreases hemorrhagic events.^{272,470,471} However, when comparing double and triple antithrombotic therapy, Gargiulo et al.⁴⁷² found that dual antithrombotic therapy led to a significant decrease in bleeding at the expense of a significantly higher incidence of stent thrombosis (RR = 1.59, 95% CI 1.01 to 2.50) and a trend toward increased AMI, suggesting that some patients with a very high risk of ischemic events and (especially) a low risk of bleeding events may benefit from triple antithrombotic therapy for up to 30 days after the index event (Figure 3.3).

Antithrombotic therapy in patients after ACS who have AF and are indicated for anticoagulation - Summary of recommendations and evidence		
DOAC is preferable to warfarin	I	A
Clopidogrel is the preferred P2Y ₁₂ inhibitor, since it has been the most studied drug in this context	I	A
Triple therapy should be continued for the shortest possible time due to the high risk of associated bleeding.	IIa	A
When using warfarin, an INR between 2 and 2.5 is desirable.	IIa	C
ASA should be used in low doses, preferably ≤ 100 mg/day.	IIa	C
During hospitalization, triple therapy with ASA + P2Y ₁₂ inhibitor + anticoagulant should be used.	IIa	C
After hospital discharge, P2Y ₁₂ inhibitor and anticoagulant should be routinely continued for up to 12 months after the event. The P2Y ₁₂ inhibitor should be discontinued after 12 months, continuing only with the anticoagulant.	IIa	A
In patients with increased ischemic risk, triple therapy can be maintained for a longer period.	IIa	B
PPI should be considered the first choice as prophylaxis for stress ulcers due to the high risk of gastrointestinal bleeding.	IIa	C

INR: *in*Internationalized ratio

3.2. Renin-Angiotensin-Aldosterone System Inhibitors

ACE inhibitors are recommended for post-ACS patients with systolic LV dysfunction/HF, systemic arterial hypertension or DM. Angiotensin receptor blockers can be used in patients intolerant to ACE inhibitors.

Mineralocorticoid antagonists are indicated in post-ACS patients with LVEF ≤ 40% associated with evidence of HF or DM.²⁸³

When managing arterial hypertension after hospitalization for ACS and in the long term, special care must be taken to maintain adequate blood pressure control, as recommended by the Brazilian Hypertension Guidelines.⁴⁷³ However, the J-curve should also be considered, despite the controversy about its existence and role. The ONTARGET study^{474,4475} demonstrated that excessive reductions in SBP were associated with an increase in ischemic events and that a SBP of 126 mmHg was associated with the lowest occurrence of AMI. The TNT study⁴⁷⁶ assessed the impact of blood pressure levels on more than 10,000 coronary

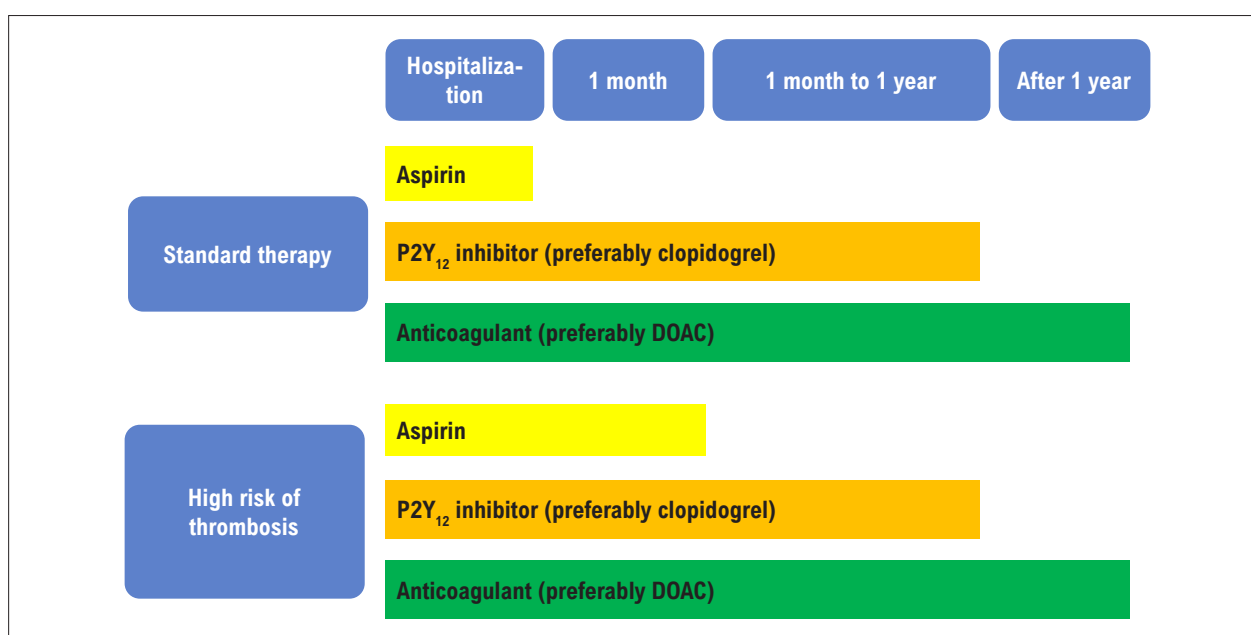


Figure 3.3 – Antithrombotic regimen proposed for patients with non-ST-elevation acute coronary syndrome who have AF and are indicated for anticoagulation.

disease patients. More ischemic events occurred when SBP was below 110-120 mmHg, and diastolic blood pressure was below 60-70 mmHg. However, the SPRINT study, which randomized 9,361 patients without DM and high cardiovascular risk to an intensive control goal (SBP < 120 mmHg) or a conventional goal (SBP < 140 mmHg), found that intensive treatment reduced the occurrence of the composite outcome (cardiovascular death, infarction, stroke, ACS, or HF) (HR 0.75; 95% CI 0.64 to 0.89; $p < 0.001$), as well as all-cause mortality (HR 0.73; 95% CI 0.60 to 0.90; $p = 0.003$). There was an increased incidence of adverse events from falls, syncope, hypotension, and acute renal failure in the intensive group. No increase in infarction or ACS was found in the intensive treatment group. However, the study included less than 20% of patients with overt cardiovascular disease.⁴⁷⁷ No other studies have been conducted specifically on patients with a history of ACS. Thus, due to the potential for worsening ischemia, lowering the patient's blood pressure should be viewed with caution. To avoid reducing coronary perfusion pressure, diastolic blood pressure should not fall below 60 mmHg.

Renin-angiotensin-aldosterone system inhibitors in patients after NSTEMI-ACS - Summary of recommendations and evidence		
Renin-angiotensin-aldosterone system inhibitors in patients after NSTEMI-ACS - Summary of recommendations and evidence	I	A
Spironolactone is recommended in patients with LVEF ≤ 40% associated with HF or DM.	I	A

3.3. Beta-blockers

Long-term use of beta-blockers is recommended in patients with HF and an EF ≤ 40%. In patients with preserved LV systolic function, the data are less robust. Evidence favorable to beta-blockers emerged in the early 1980s, when ACS treatment

differed substantially from current protocols.^{478,479} Their use in NSTEMI-ACS patients without HF has not been evaluated in randomized clinical trials. The data available for this population are derived from observational studies suggesting that long-term beta-blocker use after AMI is useful.^{480,481} A specifically designed Brazilian study that followed NSTEMI-ACS patients for approximately 17 years suggested that the long-term use of beta-blockers benefits populations with LV dysfunction, but not those with normal EF.¹³⁷ The ongoing DANBLOCK study (NCT 03778554) is randomizing patients with recent myocardial infarction and EF > 40% to assess whether beta-blockers reduce ischemic outcomes in the context of current ACS therapy. The results are expected in 2023.

Use of beta-blockers in patients after non-ST-segment elevation acute coronary syndrome - Summary of recommendations and evidence

The indefinite use of beta-blockers is recommended in patients with LV dysfunction. Agents with proven effectiveness in this context should be used.

I B

3.4. Antidiabetic drugs

Over 30% of NSTEMI-ACS patients have DM.⁴⁸² The treatment of this comorbidity has undergone major changes in recent years with the arrival of drugs that not only lower blood glucose levels, but also reduce the incidence of cardiovascular events. There is evidence that more intensive control of glycated hemoglobin (HbA1c) in diabetic patients reduces the risk of microvascular complications.^{483,484} Their impact on macrovascular events has been more heterogeneous, although there seem to be benefits in long-term follow-up (> 10 years), as long as treatment begins soon after diagnosis.⁴⁸⁵ Based on microvascular event findings, an HbA1c target of less than 7% is recommended in most diabetic patients. It is important to point out, however, that this number

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is more of a general principle and it should be individualized for each patient. In the ACCORD trial, for example, more aggressive glycemic control, in addition to not reducing major cardiovascular outcomes, was associated with higher overall mortality, which led to early interruption of the study.⁴⁸⁶ The included patients had long-standing DM (10 years on average), in addition to a high prevalence of cardiovascular disease (approximately 35%). Therefore, in patients with low life expectancy, long-standing DM, a history of severe hypoglycemia, advanced microvascular or macrovascular disease, less stringent HbA1c targets (eg, < 8%) can be considered. Conversely, in patients with recent-onset DM, no relevant comorbidities, and a good understanding of the disease, more intensive targets (eg, HbA1c < 7%) can be targeted.

Once the glycemic targets have been determined, the drugs must be chosen. Every patient diagnosed with DM should receive metformin unless it is formally contraindicated.⁴⁸⁷ This low-cost medication is widely available in the public health system and has favorable effects on weight reduction and glycemic control, in addition to potentially reducing the incidence of cardiovascular events.⁴⁸⁴ Recent randomized trials have shown that treatment with new antidiabetics in association with metformin has reduced cardiovascular outcomes in more than 70% to 80% of patients.

The main side effects of metformin are gastrointestinal (feeling of bloating, abdominal pain, diarrhea) and can be avoided with a slower dose progression. Patients with creatinine clearance below 30 mL/min are formally contraindicated to the drug.⁴⁸⁸ Chronic metformin treatment is associated with a higher incidence of low vitamin B12 levels, and monitoring should be considered in this population, especially if there is associated anemia or neuropathy.⁴⁸⁹

In patients with a history of coronary disease, therapy with SGLT2 inhibitors or GLP1 receptor agonists should be considered, regardless of the HbA1c level. Medications that have already shown benefits in reducing cardiovascular events in phase 3 studies should be selected.

Choosing between SGLT2 inhibitors and GLP1 receptor agonists depends on several factors, some of which are shown in Table 3.4. Both drug classes have similar reductions in major cardiovascular outcomes in secondary prevention patients.⁴⁹⁰ Ideally, the decision should be shared with the patient, weighing practical aspects such as route of administration (oral vs. subcutaneous) and price, as well as the clinical benefits found in randomized studies. Due to their benefits beyond glycemic control, these drugs should be prescribed as soon as possible after ACS, since diabetic patients with ACS are a very high risk group and therapeutic inertia should be avoided. In a subanalysis of patients with previous AMI from the DECLARE trial, dapagliflozin reduced the composite outcome of cardiovascular death, infarction and ischemic stroke (mainly driven by a reduction in reinfarction) compared to placebo, and this benefit appeared to be greater closer to the acute phase of a coronary event.⁴⁹¹

Importantly, in the DAPA-HF study, dapagliflozin showed cardiovascular benefits in patients with HF and a LVEF <40%, regardless of DM.⁴⁹² In this trial, coronary disease was the cause of HF in 55% of the patients and there was a 23% reduction in the composite outcome (worsening HF and cardiovascular death), regardless of the patient's HbA1c levels. Thus, in patients with LV dysfunction due to coronary disease and associated DM, there

is more evidence for the benefit of SGLT2 inhibitors than GLP1 receptor agonists.

Another situation in which SGLT2 inhibitors showed benefits was in diabetic patients with chronic kidney disease. In the CREDENCE trial, canagliflozin at a dose of 100 mg per day reduced the progression of nephropathy in diabetic patients with creatinine clearance between 30 and 90 mL/min associated with proteinuria (albumin to urinary creatine ratio ≥ 300 mg/g).⁴⁹³ In end-stage renal disease, the primary endpoint (a 2-fold increase in creatinine levels or death from renal or cardiovascular causes) was reduced by 30% with the use of SGLT2 inhibitors (HR 0.70; 95% CI 0.59 to 0.82 ; $p = 0.00001$).

Most of the other antidiabetics had no effect on cardiovascular events. However, in some cases, the outcomes worsened. In the SAVOR-TIMI 53 trial, the DPP-4 inhibitor saxagliptin was tested against placebo in a population of 16,492 diabetic patients.⁴⁹⁴ In addition to not reducing cardiovascular outcomes, saxagliptin increased the hospitalization rate for HF (from 2.8% to 3.5%, HR 1.27; 95%CI 1.07 to 1, 51; $p = 0.007$). Thus, this medication should be avoided in patients with HF.

Outpatient management of diabetic patients with a history of the acute coronary syndrome - Summary of recommendations and evidence

An HbA1c target < 7% should be used in most diabetic patients to reduce microvascular events.	I	A
The HbA1c target must be individualized, considering characteristics such as comorbidities, life expectancy and the duration of DM	I	C
Unless contraindicated, metformin is the drug of choice for initial DM treatment.	I	A
After ACS, consider combined treatment including an SGLT2 inhibitor or a GLP1-RA with proven cardiovascular benefits regardless of HbA1c level.	I	A
In patients with HF or nephropathy (creatinine clearance between 30 and 90 mL/min and/or with proteinuria), SGLT2 inhibitors are the drug of choice.	I	A
Use saxagliptin and pioglitazone in diabetic patients with HF.	III	A

3.5. Lipid lowering drugs

Treatment with statins should begin early, preferably with high-intensity therapy (ie, rosuvastatin 20-40 mg or atorvastatin 40-80 mg). In patients who are already using this medication, treatment should not be interrupted. If the previously used statin is of low or moderate intensity, changing to a high potency statin should be considered.

In outpatient follow-up, consider therapeutic LDL-c and HDL-c goals of < 50 mg/dL and < 80 mg/dL, respectively. If the goals are not achieved, and the patient is not yet using high-potency statins, prescribing a medication from this group is recommended. However, if LDL targets are still not achieved, an association with ezetimibe 10 mg/day is recommended. After these measures, if the LDL remains above the target, PCSK9 inhibitors should be considered.

The FOURIER trial (2017) was the first study to evaluate clinical outcomes associated with PCSK9 inhibitors⁴⁹⁵. It included 27,564 patients with a history of cardiovascular disease

Table 3.4 – Factors to be considered when deciding on the best new antidiabetic treatment in coronary patients

	SGLT2 inhibitors	GLP1-RA
Method of administration	Daily oral administration	Subcutaneous (oral semaglutide already exists, but is not yet available in Brazil) Daily or weekly administration
Benefits	Reduces MACE Reduces cardiovascular death (empagliflozin) Reduces HF Reduces (slightly) AP Prevents progression of nephropathy	Reduces MACE Reduces cardiovascular death (liraglutide) Weight loss Prevents progression of nephropathy (liraglutide)
Caution	Creatinine clearance < 30 mL/min/1.73 m ² History of genital infections History of ketoacidosis Osteoporosis/fractures (canagliflozin) Peripheral arterial disease (canagliflozin)	Creatinine clearance < 30 mL/min/1.73 m ² Nausea History of pancreatitis Retinopathy (semaglutide)

MACE: major adverse cardiac events.

with LDL ≥ 70 mg/dL despite statin use. The patients were randomized to evolocumab (140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once a month, according to the patient's preference) or placebo. A significant reduction in the composite outcome (cardiovascular death, AMI, stroke, coronary revascularization, or hospitalization due to UA) occurred in the evolocumab group. This outcome occurred in 11.3% of the control group and in 9.8% of the evolocumab group over a mean follow-up of 26 months. There was no difference in mortality.

The ODYSSEY-OUTCOMES trial (2018) evaluated alirocumab in patients with ACS in the year prior to inclusion.⁴⁹⁶ The patients, who had LDL ≥ 70 mg/dL despite using high-potency statins, were randomized to receive alirocumab 75 mg subcutaneously every 2 weeks or placebo. In an average follow-up of 2.8 years, there was a 14.4% reduction in the composite outcome (death from coronary heart disease, AMI, stroke, or hospitalization for UA). In this trial there was an apparent reduction in overall mortality (from 4.1% to 3.5%), although there was no reduction in cardiovascular death. The benefits of the new medication were more prominent in patients with baseline LDL above 100 mg/dL. Although the absolute risk of mortality was reduced by 0.6% in the general group, the reduction was 1.7% in the group with LDL > 100 mg/dL.

One relevant fact about the ODYSSEY-OUTCOMES trial is that the PCSK9 inhibitor was initiated an average of 2.6 months after the ACS episode. In the FOURIER study, however, in patients with a history of AMI (about 80% of the total population), evolocumab was initiated an average 3.4 years after the last AMI. In other words, based on the evidence from these studies, PCSK9 inhibitors, as a rule, should be considered in outpatient follow-up for infarcted patients and in the acute in-hospital phase.

Another lipid lowering drug that reduced cardiovascular events in secondary prevention was omega-3 supplementation (eicosapentaenoic acid: icosapent-ethyl 4 g/day). This strategy was evaluated in the REDUCE-IT study, which randomized high-risk patients (secondary prevention or DM with another associated risk factor) who had hypertriglyceridemia despite statin use.⁴⁹⁷ Most patients (70.7%) were on secondary prevention. There was a reduction in the primary endpoint (cardiovascular death, AMI, stroke, need for revascularization, or UA) from 22% to 17.2%.

There was also a reduction in cardiovascular death from 5.2% to 4.3% (CI 0.66 to 0.98; $p = 0.03$). For every 21 patients treated during the mean 4.9 years of follow-up, one cardiovascular event was prevented. One criticism about the REDUCE-IT trial was that the placebo, mineral oil, led to an LDL increase of 5 mg/dL in the control group compared to the EPA group, which could have increased the risk of events in the placebo group.

It should be pointed out that in the REDUCE-IT trial, a specific formulation of omega 3 based on eicosapentaenoic acid (icosapent-ethyl) was used, which had no relevant impact on LDL during the trial (an increase of 2 mg/dL). There is evidence that omega 3 formulations containing docosahexaenoic acid raise LDL levels.⁴⁹⁸ Thus, it is recommended that, for omega-3 supplementation in post-ACS patients, the REDUCE-IT formulation should be used. It will not be available in Brazil until after this Guideline has been published.

Use of lipid-lowering drugs in NSTEMI-ACS patients after discharge - Summary of recommendations and evidence

In patients with a previous ACS diagnosis, LDL-c should be reduced to < 50 mg/dL, and HDL-c should be reduced to < 80 mg/dL.	I	B
When tolerated, preference should be given to high-intensity statins.	I	A
When the LDL-c target is not achieved with statins at the maximum tolerated dose, ezetimibe should be added.	I	A
PCSK9 inhibitors can be considered in patients who are receiving statin treatment at the highest tolerated dose, associated or not with ezetimibe, and who have not reached recommended LDL-c or HDL-c target levels.	IIa	A

3.6. Other Medications

Post-ACS patients are at increased risk of bleeding due to antithrombotic therapy. The gastrointestinal tract is the most frequent site of clinically relevant bleeding in patients on chronic antiplatelet therapy.⁴⁹⁹ Gastric protection is one way to reduce the risk of these events. PPIs have been shown to be more effective than H2 receptor antagonists in observational studies.⁵⁰⁰ However, some in vitro studies have suggested that associating PPIs with clopidogrel could reduce its antiplatelet activity.^{225,226} The

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COGENT trial (see Part 2) showed that combining omeprazole with clopidogrel reduced the risk of gastrointestinal complications without an apparent increase in ischemic events. However, given that the study was discontinued early, it cannot be ruled out that omeprazole would have led to an increase in ischemic events.²³¹

Therefore, PPIs are recommended for patients receiving DAPT who are at increased risk of bleeding, i.e., those with a history of gastrointestinal bleeding, a history of peptic ulcer disease, anticoagulant use, chronic NSAID use, chronic corticosteroid use, or those with two or more of the following factors: age ≥ 65 years, dyspepsia, gastroesophageal reflux disease, *H. pylori* infection, or chronic alcohol use.

After discharge, patients must be instructed that if they have angina at rest, they should use sublingual nitrate (dinitrate, mononitrate, or nitroglycerin), as long as there are no contraindications. If the pain does not improve in 3 to 5 minutes, the emergency department should be called.

Viral and bacterial infections can trigger an acute cardiovascular event in patients with heart disease. There is evidence that vaccinating for influenza and pneumococcus can reduce hospitalizations and even mortality in these patients.⁵⁰¹ Thus, annual vaccination for influenza is recommended for patients with coronary disease. Ideally, the vaccine should be administered during the normal vaccination campaign (April and May in Brazil). Regarding the pneumococcal vaccine, a dose of the 23-valent polysaccharide (Pneumo 23) vaccine with a booster after 5 years is recommended.⁵⁰² An ongoing Brazilian randomized trial is testing whether a double-dose of anti-influenza vaccine during hospitalization for ACS is superior to conventional vaccination 30 days after the event for reducing cardiovascular outcomes (NCT 04001504).

Therapy aimed at reducing plaque inflammation has begun to yield promising results. In the CANTOS trial, canakinumab, an anti-interleukin 1- β monoclonal antibody, reduced major cardiovascular events (cardiovascular death, reinfarction or stroke) in patients with previous infarction (at least 30 days after the index event) and elevated C-reactive protein (HR 0.88; 95% CI 0.79 to 0.97; $p = 0.02$).⁵⁰³ However, there was an increase in death from infection. Moreover, due to its prohibitive cost, this medication has not been incorporated into normal clinical practice. Colchicine, a widely available and low-cost drug, significantly reduced the composite outcome (cardiovascular death, reinfarction, hospitalization for UA with a need for revascularization, stroke, or resuscitated cardiac arrest (HR 0.77; 95% CI 0.61 to 0.96; $p = 0.02$) in patients with recent AMI (within 30 days of the index event). However, there was an increase in the incidence of pneumonia.⁵⁰⁴ Figure 3.4 summarizes the recommended drugs for NSTE-ACS patients after discharge.

Other pharmacological interventions in ACS patients after discharge - Summary of recommendations and evidence		
If there are no contraindications, patients should use sublingual nitrate if they have angina at rest.	I	C
Patients should be vaccinated against influenza and pneumococcus to reduce morbidity and mortality.	I	B
PPI should be used in patients receiving DAPT who have an increased risk of bleeding (history of gastrointestinal bleeding or peptic ulcer disease, anticoagulant use, chronic NSAID use, chronic corticosteroid use) or have two or more of the following characteristics: age ≥ 65 years, dyspepsia, gastroesophageal reflux disease, <i>H. pylori</i> infection, or chronic alcohol use.	IIa	B

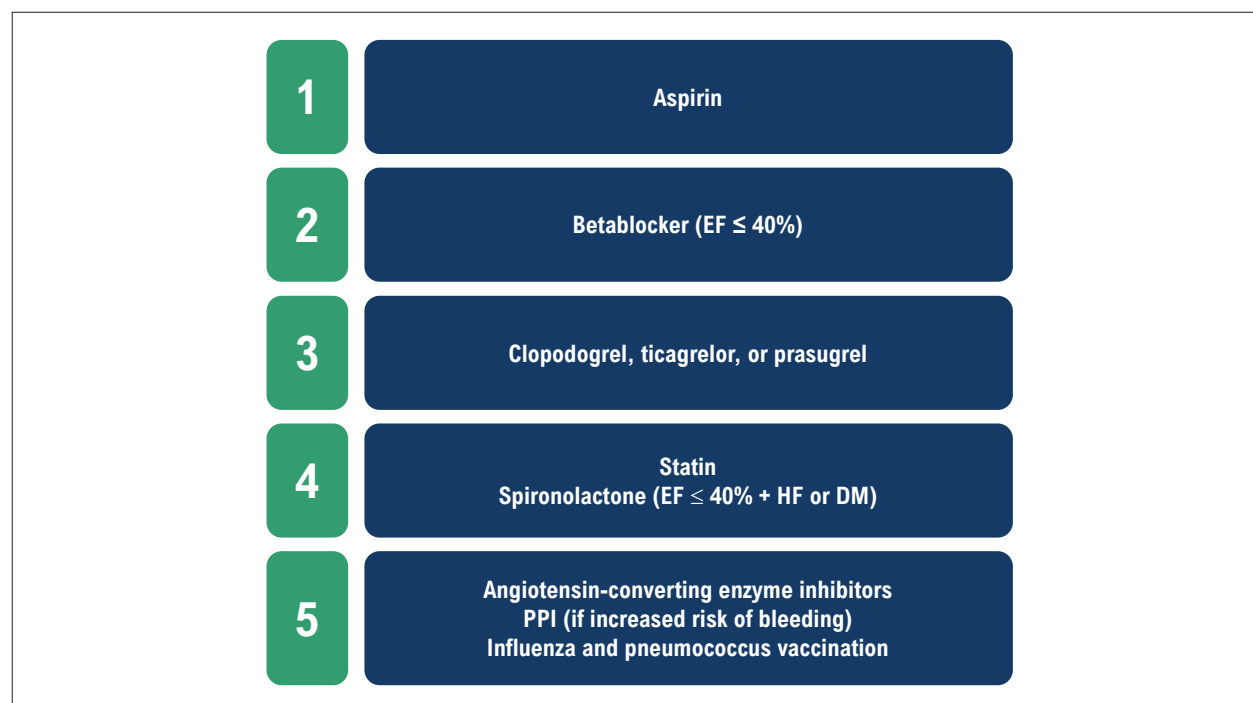


Figure 3.4 – Summary of discharge prescriptions after non-ST-elevation acute coronary syndrome.

4. Post-discharge Clinical Screening

When early reassessment is recommended for low-risk patients and those revascularized after NSTEMI-ACS, it should be performed between 2 and 6 weeks after discharge. In patients with greater severity, reassessment is recommended within 14 days.⁵⁰⁵ Obviously, these deadlines must consider the particularities of each situation since the procedural complications, health care access, and individual characteristics of each patient can vary considerably.

Since there is a risk of complications even in asymptomatic patients, risk assessment should be applied to both symptomatic and asymptomatic patients. Patients should be closely monitored in the first 12 months after revascularization and/or stabilized ACS because they are at higher risk for complications and are subject to changes in pharmacological treatment.⁵⁰⁶ Therefore, at least two visits are recommended in the first year of follow-up, the first occurring ideally within 3 months.

In patients with LV systolic dysfunction prior to the revascularization procedure or after ACS, LV function should be reassessed 8 to 12 weeks after the intervention.^{507,508}

Cardiac function may improve due to mechanisms such as recovery from myocardial hibernation or hibernating myocardium, which can be reversed through revascularization or worsened due to other comorbidities, such as heart valve disease, arrhythmia, inflammation, etc. These conditions should be identified and treated.⁵⁰⁹

Similarly, non-invasive ischemia testing can be performed after revascularization to identify residual ischemia and serve as a reference for subsequent comparisons.⁵⁰⁹ This approach must be individualized since each revascularization involves anatomical peculiarities and varies greatly from patient to patient. These recommendations are mostly based on expert opinion.

In patients who have been asymptomatic for more than 1 year, at least one annual reassessment is recommended.⁵⁰⁹ The assessment should include the patient's general clinical status, treatment adherence, and risk profile based on risk scores. Laboratory tests, including a lipid profile, kidney function, a complete blood count, and biomarkers, should be performed at least every 2 years.^{507,508}

The lipid profile and glycemic status should be evaluated periodically and, although there is no evidence to support a specific periodicity, an annual evaluation is generally recommended.⁵⁰⁹

Certain inflammatory biomarkers appear to be event markers. The high-sensitive C-reactive protein has been tested in multiple studies, even in primary prevention. NT-proBNP, von Willebrand factor, and interleukin-6 also seem to predict events.⁵¹⁰ Scores based on an association of biomarkers (LDL, NT-proBNP, troponin T, fibrin degradation products) have been found to have better reclassification power and higher C-statistics than scores based on clinical models, and they are promising tools for predicting events in patients with coronary disease.^{511,512} However, the lack of more robust evidence limits the routine application of these biomarkers, which should be reserved for selected cases.

An ECG should be requested at each visit to determine heart rate and rhythm. Echocardiograms can help assess LV function (diastolic and systolic), valve status, and cardiac dimensions in apparently asymptomatic patients every 3 to 5 years. Likewise, it may be beneficial to non-invasively assess the presence of silent ischemia in apparently asymptomatic patients every 3 to 5 years, preferably with stress imaging tests.⁵¹³

Due to the lack of functional information, coronary CCTA should not be used for evaluation. In specific cases, it can help assess the patency of coronaries and grafts.⁵¹²

For patients with a history of NSTEMI-ACS and/or revascularization and unequivocal symptoms of angina, the vast majority of evidence indicates that invasive stratification is the best option. For patients with unclear symptoms, stress imaging is recommended.⁵¹³

Post-discharge clinical screening - Summary of recommendations and evidence		
Asymptomatic patients		
Patients should visit a cardiologist (preferably within 3 months) to reassess any potential changes in their risk situation, including clinical assessment of lifestyle modification measures, adherence to the target risk factors, and new comorbidities that could affect treatment and results.	I	C
In patients with mild or no symptoms in whom non-invasive risk stratification indicates high risk and for whom revascularization could improve prognosis, invasive coronary angiography is recommended (FFR, when necessary and available).	I	C
Risk stratification by stress imaging can be performed in high-risk patients approximately 6 months after revascularization.	IIb	C
A new angiography may be considered in high-risk revascularization patients (e.g., unprotected left main coronary artery disease), regardless of the symptoms.	IIb	C
Routine stress imaging should be performed in patients who were revascularized percutaneously > 1 year or surgically > 5 years.	IIb	C
CCTA alone can be used for routine stratification.	III	C
Coronary angiography alone can be used for risk stratification in an asymptomatic patient.	III	C
Asymptomatic patients		
Evaluate coronary disease status in patients who have impaired LV systolic function with no identifiable cause.	I	C
Perform stress imaging (preferably) in patients with new symptoms and/or worsening symptoms.	I	C
Perform angiography (with FFR or iFR, if necessary) in patients with unmistakable symptoms of coronary disease, especially if it is refractory to drug treatment or if they fit the high-risk profile.	I	C
Perform angiography in patients with high-risk stress imaging findings.	I	C
In a previously revascularized patient, stress imaging should be performed rather than ET.	IIa	C

References

- Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart*. 2005;91(2):229-30.
- Barstow C, Rice M, McDivitt JD. Acute Coronary Syndrome: Diagnostic Evaluation. *Am Fam Physician*. 2017;95(3):170-7.
- Gibler WB, Racadio JM, Hirsch AL, Roat TW. Continuum of Care for Acute Coronary Syndrome: Optimizing Treatment for ST-Elevation Myocardial Infarction and Non-ST-Elevation Acute Coronary Syndrome. *Crit Pathw Cardiol*. 2018;17(3):114-38.
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237-69.
- Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131(10):861-70. Erratum in: *Circulation*. 2015;131(19):e475.
- Scalone G, Niccoli G, Crea F. Editor's Choice- Pathophysiology, diagnosis and management of MINOCA: an update. *Eur Heart J. Acute Cardiovasc Care*. 2019;8(1):54-62.
- Niccoli G, Camici PG. Myocardial infarction with non-obstructive coronary arteries: what is the prognosis?. *Eur Heart J Suppl*. 2020;22(Suppl E):E40-5.
- Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(18):e891-e908.
- Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv*. 2014;7(3):285-93.
- Pasupathy S, Tavella R, Beltrame JF. Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): The Past, Present, and Future Management. *Circulation*. 2017 Apr 18;135(16):1490-3.
- Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation*. 1994 Apr;89(4):1545-56.
- Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation*. 1998 Mar 31;97(12):1195-206.
- Zacks SM, Liebson PR, Calvin JE, Parrillo JE, Klein LW. Unstable angina and non-Q wave myocardial infarction: does the clinical diagnosis have therapeutic implications? *J Am Coll Cardiol*. 1999 Jan;33(1):107-18.
- Calvin JE, Klein LW, VandenBerg BJ, Meyer P, Ramirez-Morgen LM, Parrillo JE. Clinical predictors easily obtained at presentation predict resource utilization in unstable angina. *Am Heart J*. 1998 Sep;136(3):373-81.
- Kong DF, Blazing MA, O'Connor CM. The health care burden of unstable angina. *Cardiol Clin*. 1999 May;17(2):247-61.
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
- Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al; GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385(9963):117-71.
- Brasil.Ministério da Saúde. Informação em saúde: Estatísticas vitais. [Citado em 2020 fev 26]. Disponível em: <http://datasus.saude.gov.br/>.
- Franken M, Giugliano RP, Goodman SG, Baracioloi L, Godoy LC, Furtado RHM, et al. Performance of acute coronary syndrome approaches in Brazil. A report from the BRACE (Brazilian Registry in Acute Coronary syndromEs) [published online ahead of print, 2019 Aug 10]. *Eur Heart J Qual Care Clin Outcomes*. 2019;qc045.
- Libby P. Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy. *N Engl J Med*. 2013;368(21):2004-13.
- Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol*. 2015;65(14):1454-71.
- The Principal Investigators of CASS and Their Associates. The National Heart, Lung and Blood Institute Coronary Artery Surgery Study: historical background, design, methods, the registry, the randomized trial, clinical database. *Circulation*. 1981;63(suppl I):I-1-I-81.
- Stone PH, Thompson B, Anderson HV, Kronenberg MW, Gibson RS, Rogers WJ, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: The TIMI III registry. *JAMA*. 1996 Apr 10;275(14):1104-12.
- Nicolau JC, Franci A, Barbosa CJ, Baracioloi LM, Franken M, Furtado RH, et al. Influence of proven oral therapies in the very old with acute coronary syndromes: A 15 year experience. *Int J Cardiol*. 2015 Nov 1;198:213-5.
- Kleiman NS, Anderson HV, Rogers WJ, Theroux P, Thompson B, Stone PH. Comparison of outcome of patients with unstable angina and non-Q-wave acute myocardial infarction with and without prior coronary artery bypass grafting (Thrombolysis in Myocardial Ischemia III Registry). *Am J Cardiol*. 1996 Feb 1;77(4):227-31.
- Barbash GI, Reiner J, White HD, Wilcox RG, Armstrong PW, Sadowski Z, et al. Evaluation of paradoxical beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1995 Nov 1;26(5):1222-9.
- Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkilä J, et al. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. *Circulation*. 1993 Jan;87(1):53-8.
- Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000 Aug 16;284(7):835-42.
- Braunwald E, Jones RH, Mark DB, Brown J, Brown L, Cheitlin MD, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation*. 1994 Jul;90(1):613-22.
- Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. *N Engl J Med*. 2000 Jan 13;342(2):101-14.
- Braunwald E, Califf RM, Cannon CP, Fox KA, Fuster V, Gibler WB, et al. Redefining medical treatment in the management of unstable angina. *Am J Med*. 2000 Jan;108(1):41-53.
- Bosch X, Theroux P, Pelletier GB, Sanz G, Roy D, Waters D. Clinical and angiographic features and prognostic significance of early postinfarction angina with and without electrocardiographic signs of transient ischemia. *Am J Med*. 1991 Nov;91(5):493-501.
- Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol*. 1987 Oct;10(4):756-60.

34. Armstrong PW, Fu Y, Chang WC, Topol EJ, Granger CB, Betriu A, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. The GUSTO-IIb Investigators. *Circulation*. 1998 Nov 3;98(18):1860-8.
35. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schachtman M, Thompson BW, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *Thrombolysis in Myocardial Ischemia*. *J Am Coll Cardiol*. 1997 Jul;30(1):133-40.
36. Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. *Ann Intern Med*. 1986 Aug;105(2):221-33.
37. Newby LK, Christenson RH, Ohman EM, Armstrong PW, Thompson TD, Lee KL, et al. Value of serial troponin T measures for early and late risk stratification in patients with acute coronary syndromes. The GUSTO-IIa Investigators. *Circulation*. 1998 Nov 3;98(18):1853-9.
38. Amsterdam EA, Kirk JD, Bluemke DA, Diercks DE, Farkouh ME, Garvey JE, et al. Testing of low-risk patients presenting to the emergency department with chest pain. A Scientific Statement From the American Heart Association. *Circulation*. 2010;122(17):1756-776.
39. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med*. 1996 Oct 31;335(18):1333-41.
40. Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, et al. It's time for a change to a troponin standard. *Circulation*. 2000 Sep 12;102(11):1216-20.
41. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361(9):858-67.
42. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem*. 2010;56(2):254-61.
43. Mueller C. Biomarkers and acute coronary syndromes: an update. *Eur Heart J*. 2014;35(9):552-6.
44. Westermann D, Neumann J, Sørensen N, Blankenberg S. High-sensitivity assays for troponin in patients with cardiac disease. *Nat Rev Cardiol*. 2017;14(8):472-83.
45. Stoyanov KM, Hund H, Biener M, Gandowitz J, Riedle C, Lohr J, et al. RAPID-CPU: a prospective study on implementation of the ESC 0/1-hour algorithm and safety of discharge after rule-out of myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2020;9(1):39-51.
46. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, et al. Direct Comparison of 4 Very Early Rule-Out Strategies for Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin I. *Circulation*. 2017 Apr 25;135(17):1597-11.
47. Mair J, Morandell D, Genser N, Lechleitner P, Dienstl F, Puschendorf B. Equivalent early sensitivities of myoglobin, creatine kinase MB mass, creatine kinase isoform ratios, and cardiac troponins I and T for acute myocardial infarction. *Clin Chem*. 1995 Sep;41(9):1266-72.
48. Costa TN, Strunz CM, Nicolau JC, Gutierrez PS. Comparison of MB fraction of creatine kinase mass and troponin I serum levels with necropsy findings in acute myocardial infarction. *Am J Cardiol*. 2008 Feb 1;101(3):311-4.
49. Lin JC, Apple FS, Murakami M, Luepker RV. Rates of positive cardiac troponin I and creatine kinase MB mass among Patients Hospitalized for Suspected Acute Coronary Syndromes. *Clin Chem*. 2004;50(2):333-8.
50. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol*. 2002;40(2):251-6. 165.
51. Meneghelo RS, Araújo CG, Stein R, Mastrocola LE, Albuquerque PF, Serra SM, et al. Sociedade Brasileira de Cardiologia. III Diretrizes da Sociedade Brasileira de Cardiologia sobre teste ergométrico. *Arq Bras Cardiol*. 2010;95(5 Suppl 1):1-26.
52. Peels CH, Visser CA, Kupper AJ, Visser FC, Roos JP. Usefulness of two-dimensional echocardiography for immediate detection of myocardial ischemia in the emergency room. *Am J Cardiol*. 1990 Mar 15;65(11):687-91.
53. Sabia P, Abbott RD, Afrookteh A, Keller MW, Touchstone DA, Kaul S. Importance of two-dimensional echocardiographic assessment of left ventricular systolic function in patients presenting to the emergency room with cardiac-related symptoms. *Circulation*. 1991 Oct;84(4):1615-24.
54. Feigenbaum H. Role of echocardiography in acute myocardial infarction. *Am J Cardiol*. 1990 Nov 20;66(18):17H-22H.
55. Parisi AF. The case for echocardiography in acute myocardial infarction. *J Am Soc Echocardiogr*. 1988 May;1(3):173-8.
56. Reeder GS, Seward JB, Tajik AJ. The role of two-dimensional echocardiography in coronary artery disease: a critical appraisal. *Mayo Clin Proc*. 1982 Apr;57(4):247-58.
57. Gibson RS, Bishop HL, Stamm RB, Crampton RS, Beller GA, Martin RP. Value of early two dimensional echocardiography in patients with acute myocardial infarction. *Am J Cardiol*. 1982 Apr 1;49(5):1110-9.
58. Visser CA, Lie KI, Kan G, Meltzer R, Durrer D. Detection and quantification of acute, isolated myocardial infarction by two dimensional echocardiography. *Am J Cardiol*. 1981 May;47(5):1020-5.
59. Heger JJ, Weyman AE, Wann LS, Rogers EW, Dillon JC, Feigenbaum H. Cross-sectional echocardiographic analysis of the extent of left ventricular asynergy in acute myocardial infarction. *Circulation*. 1980 Jun;61(6):1113-8.
60. Ryan T, Vasey CG, Presti CF, O'Donnell JA, Feigenbaum H, Armstrong WF. Exercise echocardiography: detection of coronary artery disease in patients with normal left ventricular wall motion at rest. *J Am Coll Cardiol*. 1988 May;11(5):993-9.
61. Sawada SG, Ryan T, Conley MJ, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. *Am Heart J*. 1990 Jul;120(1):49-55.
62. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation*. 1997 Mar 18;95(6):1686-744.
63. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, Hassager C, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2013 Jun 11;61(23):2365-73.
64. Lin SS, Lauer MS, Marwick TH. Risk stratification of patients with medically treated unstable angina using exercise echocardiography. *Am J Cardiol*. 1998 Sep 15;82(6):720-4.
65. Colon PJ, III, Guarisco JS, Murgo J, Cheirif J. Utility of stress echocardiography in the triage of patients with atypical chest pain from the emergency department. *Am J Cardiol*. 1998 Nov 15;82(10):1282-4, A10.
66. Markman Filho B, Almeida MC, Markman M, Chaves A, Moretti M, Ramires JA, Cesar LA. Stratifying the risk in unstable angina with dobutamine stress echocardiography. *Arq Bras Cardiol*. 2006; 87(3):294-9.
67. Jain D, Thompson B, Wackers FJ, Zaret BL. Relevance of increased lung thallium uptake on stress imaging in patients with unstable angina and non-Q wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI)-IIIB Study. *J Am Coll Cardiol*. 1997 Aug;30(2):421-9.

Guidelines

68. Geleijnse ML, Elhendy A, van Domburg RT, Cornel JH, Rambaldi R, Salustri A, et al. Cardiac imaging for risk stratification with dobutamine-atropine stress testing in patients with chest pain. Echocardiography, perfusion scintigraphy, or both? *Circulation*. 1997 Jul 1;96(1):137-47.
69. Kontos MC, Jesse RL, Schmidt KL, Ornato JP, Tatum JL. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol*. 1997 Oct;30(4):976-82.
70. Kapetanopoulos A, Heller GV, Selker HP, Ruthazer R, Beshansky JR, Feldman JA, et al. Acute resting myocardial perfusion imaging in patients with diabetes mellitus: results from the Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE Chest Pain) trial. *J Nucl Cardiol*. 2004 Sep;11(5):570-7.
71. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, Pohost GM, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging. *Circulation*. 2009 Jun 9;119(22):e561-87.
72. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al.; American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology. American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American Society for Nuclear Cardiology. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the clinical use of cardiac radionuclide imaging). *J Am Coll Cardiol*. 2003;42(7):1318-33.
73. Notghi A, Low CS. Myocardial perfusion scintigraphy: past, present and future. *Br J Radiol*. 2011;84(Spec 3):S229-36.
74. Wackers FJ, Brown KA, Heller GV, Kontos MC, Tatum JL, Udelson JE, et al. American Society of Nuclear Cardiology position statement on radionuclide imaging in patients with suspected acute ischemic syndromes in the emergency department or chest pain center. *J Nucl Cardiol*. 2002;9(2):246-50.
75. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52(21):1724-32.
76. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Gottlieb NH, Clouse ME, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359(22):2324-36.
77. Meijboom WB, Meijs MF, Schuijff JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52(25):2135-44.
78. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, et al.; PROMISE Investigators. Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135(24):2320-32.
79. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018 Nov 1;39(41):3689-98.
80. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58(14):1414-22.
81. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med*. 2012;366(15):1393-403.
82. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367(4):299-308.
83. Hulten E, Pickett C, Bittencourt MS, Villines TC, Petrillo S, Di Carlo MF, et al. Outcomes After Coronary Computed Tomography Angiography in the Emergency Department: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. *J Am Coll Cardiol*. 2013;61(8):880-92.
84. Schertler T, Frauenfelder T, Stolzmann P, Scheffel H, Desbiolles L, Marincek B, Kaplan V, Kucher N, Alkadhi H. Triple rule-out CT in patients with suspicion of acute pulmonary embolism: findings and accuracy. *Acad Radiol*. 2009 Jun;16(6):708-17.
85. Takakuwa KM, Halpern EJ, Shofer FS. A time and imaging cost analysis of low-risk ED observation patients: a conservative 64-section computed tomography coronary angiography "triple rule-out" compared to nuclear stress test strategy. *Am J Emerg Med*. 2011 Feb;29(2):187-95.
86. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, de Oliveira AC, de Albuquerque AS, et al. II Guidelines on Cardiovascular Magnetic Resonance and Computed Tomography of the Brazilian Society of Cardiology and the Brazilian College of Radiology. *Arq Bras Cardiol*. 2014 Dec;103(6 Suppl 3):1-86.
87. Goehler A, Mayrhofer T, Pursnani A, Ferencik M, Lumish HS, Barth C, et al. Long-term health outcomes and cost-effectiveness of coronary CT angiography in patients with suspicion for acute coronary syndrome. *J Cardiovasc Comput Tomogr*. 2020 Jan-Feb;14(1):44-54.
88. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van der Wee F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091.
89. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med*. 2003;163(19):2345-53.
90. Fox KAA, FitzGerald G, Puymirat E, Huang W, Carruthers K, Simon T, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open*. 2014;4(2):e004425.
91. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2000 Sep;36(3):970-1062.
92. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119(14):1873-82.
93. Nicolau JC, Moreira HG, Baracioli LM, Serrano CV Jr, Lima FG, Franken M, et al. The bleeding risk score as a mortality predictor in patients with acute coronary syndrome. *Arq Bras Cardiol*. 2013 Dec;101(6):511-8.
94. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55(23):2556-66.
95. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020 Aug 29;ehaa575.
96. Six AJ, Backhaus BE, Kelder SC. Chest pain in the emergency room: value of the Heart score. *Neth Heart J*. 2008;16(6):191-6.

97. Than M, Cullen L, Aldous S, Goodacre S, Frampton CM, Troughton R, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol*. 2012;59(23):2091-8.
98. Than M, Flaws D, Sanders S, Doust J, Glasziou P, Kline J, et al. Development and validation of the Emergency Department Assessment of Chest pain Score and 2 h accelerated diagnostic protocol. *Emerg Med Australas*. 2014;26(1):34-44.
99. Greenslade JH et al. Diagnostic Accuracy of a New High-Sensitivity Troponin I Assay and Five Accelerated Diagnostic Pathways for Ruling Out Acute Myocardial Infarction and Acute Coronary Syndrome. *Ann Emerg Med*. 2018;71(4):439-51.e3.
100. Santi L, Farina G, Gramenzi A, Trevisani F, Baccini M, Bernardi M, et al. The HEART score with high-sensitive troponin T at presentation: ruling out patients with chest pain in the emergency room. *Intern Emerg Med*. 2017;12(3):357-64.
101. Carlton EW, Cullen L, Than M, Gamble J, Khattab A, Greaves K. A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. *Heart*. 2015;101(13):1041-6.
102. Aarts GWA, Camaro C, van Geuns RJ, et al. Acute rule-out of non-ST-segment elevation acute coronary syndrome in the (pre) hospital setting by HEART score assessment and a single point-of-care troponin: rationale and design of the ARTICA randomised trial. *BMJ Open*. 2020;10(2):e034403.
103. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, Monnick SH, van Tooren RM, Doevendans PA. Chest pain in the emergency room: a multicenter validation of the HEART Score. *Crit Pathw Cardiol*. 2010 Sep;9(3):164-9.
104. Backus BE, Six AL, Kelder SC, Bosschaert EG, Mast A, Mosterd RF, et al. A prospective validation of the Heart score for chest pain patients at the emergency department. *Int J Cardiol*. 2013; 168:2153-8.
105. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol*. 2013;12(3):121-6.
106. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care*. 2018; 7(2): 111-9.
107. Polderwaard JM, Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, Hoes AW, Reitsma JB. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol*. 2017 Jan 15;227:656-61.
108. Sakamoto JT, Liu N, Koh ZX, Fung NX, Heldeweg ML, Ng JC. Comparing HEART, TIMI, and GRACE scores for prediction of 30-day major adverse cardiac events in high acuity chest pain patients in the emergency department. *Int J Cardiol*. 2016 Oct 15;221:759-64.
109. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):195-203.
110. Stopyra JP, Riley RF, Hiestand BC, Russell G, Holkstra JW, Lefebvre CW, et al. The HEART Pathway Randomized Controlled Trial One-year Outcomes. *Acad Emerg Med*. 2019;26(1):41-50.
111. Reinhardt SW, Lin CJ, Novak E, Brown DL. Noninvasive Cardiac Testing vs Clinical Evaluation Alone in Acute Chest Pain: A Secondary Analysis of the ROMICAT-II Randomized Clinical Trial. *JAMA Intern Med*. 2018;178(2):212-9.
112. O'Neill L, Smith K, Currie P, Elder Dhj, Wei J, Lang CC, et al. Nurse-led Early Triage (NET) study of chest pain patients: a long term evaluation study of a service development aimed at improving the management of patients with non-ST-elevation acute coronary syndromes. *Eur J Cardiovasc Nurs*. 2014; 13(3):253-60.
113. Roche TE, Gardner G, Jack L. The effectiveness of emergency nurse practitioner service in the management of patients presenting to rural hospitals with chest pain: a multisite prospective longitudinal nested cohort study. *BMC Health Serv Res*. 2017; 17(1): 445.
114. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015;131(24):2143-50.
115. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med*. 2017 Sep 28;377(13):1240-9.
116. Hobl EL, Stimpfl T, Ebner J, Schoergenjofer C, Derhaschnig U, Plassman RS, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2014;63(7):630-5.
117. Thomas MR, Morton AC, Hossain R, Chen b, Luo L, Shahari NN, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb Haemost*. 2016; 116(7):96-102.
118. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Srooka WD, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J*. 2016;37(3):245-52.
119. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, et al; CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149(6):1043-9.
120. Duarte GS, Nunes-Ferreira A, Rodrigues FB, Pinto FJ, Ferreira JJ, Costa J, et al. Morphine in acute coronary syndrome: systematic review and meta-analysis. *BMJ Open*. 2019;9(3):e025232.
121. Furtado RHM, Nicolau JC, Guo J, Im K, White JA, Sabatine MS, et al. Morphine and Cardiovascular Outcomes Among Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Undergoing Coronary Angiography. *J Am Coll Cardiol*. 2020 Jan 28;75(3):289-300.
122. Dixon RA, Edwards IR, Pilcher J. Diazepam in immediate post-myocardial infarct period. A double blind trial. *Br Heart J*. 1980 May;43(5):535-40.
123. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006;113(25):2906-13.
124. Conaway DG, O'Keefe JH, Reid KJ, Spertus J. Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. *Am J Cardiol*. 2005;96(3):363-5.
125. Goyal A, Mahaffey KW, Garg J, Nicolau JC, Hochman JS, Weaver WD, Theroux P, Oliveira GB, Todaro TG, Mojca CF, Armstrong PW, Granger CB. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J*. 2006 Jun;27(11):1289-97.
126. Nicolau JC, Serrano CV Jr, Giraldez RR, Baracioli LM, Moreira HG, Lima F, et al. In patients with acute myocardial infarction, the impact of hyperglycemia as a risk factor for mortality is not homogeneous across age-groups. *Diabetes Care*. 2012 Jan;35(1):150-2.
127. Finfer S, Chittock DR, Su SY, Bleir D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-97.
128. DePace NL, Herling IM, Kotler MN, Hakki AH, Spielman SR, Segal BL. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. *Arch Intern Med*. 1982 Oct;142(10):1806-9.

Guidelines

129. Kaplan K, Davison R, Parker M, Przybylek J, Teagarden JR, Lesch M. Intravenous nitroglycerin for the treatment of angina at rest unresponsive to standard nitrate therapy. *Am J Cardiol.* 1983 Mar 1;51(5):694-8.
130. Roubin GS, Harris PJ, Eckhardt I, Hensley W, Kelly DT. Intravenous nitroglycerine in refractory unstable angina pectoris. *Aust N Z J Med.* 1982 Dec;12(6):598-602.
131. Curfman GD, Heinsimer JA, Lozner EC, Fung HL. Intravenous nitroglycerin in the treatment of spontaneous angina pectoris: a prospective, randomized trial. *Circulation.* 1983 Feb;67(2):276-82.
132. Dellborg M, Gustafsson G, Swedberg K. Buccal versus intravenous nitroglycerin in unstable angina pectoris. *Eur J Clin Pharmacol.* 1991;41(1):5-9.
133. Gottlieb SO, Weisfeldt ML, Ouyang P, Achuff SC, Baughman KL, Traill TA, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation.* 1986 Feb;73(2):331-7.
134. Telford AM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet.* 1981 Jun 6;1(8232):1225-8.
135. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol.* 1987 Jul 15;60(2):18A-25A.
136. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA.* 1988 Oct 21;260(15):2259-63.
137. Nicolau JC, Furtado RHM, Baracioli LM, Lara LM, Dalçóquio TF, Scanavini Junior MA, et al. The Use of Oral Beta-Blockers and Clinical Outcomes in Patients with Non-ST-Segment Elevation Acute Coronary Syndromes: a Long-Term Follow-Up Study. *Cardiovasc Drugs Ther.* 2018 Oct;32(5):435-42.
138. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005 Nov 5;366(9497):1622-32.
139. Kontos MC, Diercks DB, Ho PM, Wang TY, Chen AY, Roe MT. Treatment and outcomes in patients with myocardial infarction treated with acute β -blocker therapy: results from the American College of Cardiology's NCDR®. *Am Heart J.* 2011 May;161(5):864-70.
140. Crea F, Libby P. Acute Coronary Syndromes: The Way Forward From Mechanisms to Precision Treatment. *Circulation.* 2017 Sep 19;136(12):11556.
141. Bhatt DL, Hulot JS, Moliterno DJ, Harrington RA. Antiplatelet and anticoagulation therapy for acute coronary syndromes. *Circ Res.* 2014;114(12):1929-43.
142. Lüscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation.* 2007 Feb 27;115(8):1051-8.
143. Bellemain-Appaix A, Kerneis M, O'Connor SA, Silvain J, Cucherat M, Beygui F, et al. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis. *BMJ.* 2014;349:g6269.
144. Golwala H, Bhatt DL. The Timing of P2Y12 Inhibitor Initiation in the Treatment of ACS? Does the Evidence Exist in This Era? *Prog Cardiovasc Dis.* 2018 Jan-Feb;60(4-5):471-7.
145. Dworeck C, Redfors B, Angerås O, Haraldsson I, Odenstedt J, Ioanes D, et al. Association of Pretreatment With P2Y12 Receptor Antagonists Preceding Percutaneous Coronary Intervention in Non-ST-Segment Elevation Acute Coronary Syndromes With Outcomes. *JAMA Netw Open.* 2020;3(10):e2018735.
146. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. PRINCIPLE-TIMI 44 Investigators. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation.* 2007 Dec 18;116(25):2923-32.
147. Gurbel PA1, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation.* 2009 Dec 22;120(25):2577-85.
148. Bonello L, Laine M, Camoin-Jau L, Noirot F, Guieu R, Dignat-George F, et al. Onset of optimal P2Y12-ADP receptor blockade after ticagrelor and prasugrel intake in Non-ST elevation acute coronary syndrome. *Thromb Haemost.* 2015;114(4):702-7.
149. Singh S, Singh M, Grewal N, Khosla S. Comparative Efficacy and Safety of Prasugrel, Ticagrelor, and Standard-Dose and High-Dose Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention: A Network Meta-analysis. *Am J Ther.* 2016;23(1):e52-e62.
150. Yusuf S, Björkstén N, Moons A. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation: the clopidogrel in unstable angina to prevent recurrent events trial investigators. *New Engl J Med.* 2001; 345(7):494-502.
151. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358(9281):527-33.
152. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361(1):1045-57.
153. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H et al. PLATElet inhibition and patient Outcomes (PLATO) investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet.* 2010; 375(9791): 283-93.
154. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007; 357(20): 2001-15.
155. Di Sciascio MG, Patti G, Pasceri V, Gatto L. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* 2010;56(7):550-7.
156. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, Delago A, Wilmer CH, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288(19):2411-20.
157. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay J-F, ten Berg JM, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med.* 369(11):999-1010.
158. Tarantini G, Mojoli M, Varbella F, Caporale R, Riggatieri S, Condo G, et al. Timing of Oral P2Y12 Inhibitor Administration in Non-ST Elevation Acute Coronary Syndrome. *J Am Coll Cardiol.* 2020;S0735-1097(20)36444-5.
159. Nairooz R, Valgimigli M, Rochlani Y, Pothineni NV, Raina S, Sardar P, et al. Meta-analysis of clopidogrel pretreatment in acute coronary syndrome patients undergoing invasive strategy. *Int J Cardiol.* 2017 Feb 15;229:82-9.
160. Komosa A, Lesiak M, Krasinski Z, Grygier M, Siniawski A, Skorupski W, et al. Optimal Timing of P2Y12 Inhibitor Loading in Patients Undergoing PCI: A Meta-Analysis. *Thromb Haemost.* 2019 Jun;119(6):1000-20.
161. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, et al. the TARGET Investigators. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med.* 2001;344(25):1888-94.

162. Valgimigli M, Biondi-Zoccai G, Tebaldi M, van't Hof AWJ, Campo G, Hamm C, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J*. 2010;31(1):35-49.
163. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001 Jun 21;344(25):1879-87.
164. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 2000 Dec 16;356(9247):2037-44.
165. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med*. 1998 May 21;338(21):1498-505.
166. International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation*. 1998 Jun 23;97(24):2386-95.
167. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med*. 1998 Aug 13;339(7):436-43.
168. Mukherjee D, Mahaffey KW, Moliterno DJ, Harrington RA, Yadav JS, Pieper KS, et al. Promise of combined low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibition: results from Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B). *Am Heart J*. 2002 Dec;144(6):995-1002.
169. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet*. 2001 Jun 16;357(9272):1915-24.
170. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de WF, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet*. 2002 Jan 19;359(9302):189-98.
171. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994 Apr 7;330(14):956-61.
172. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet*. 1997 May 17;349(9063):1429-35. Erratum in: *Lancet* 1997 Sep 6;350(9079):744.
173. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med*. 1997 Jun 12;336(24):1689-96.
174. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet*. 1998 Jul 11;352(9122):87-92.
175. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet*. 1997 May 17;349(9063):1422-8.
176. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation*. 1997 Sep 2;96(5):1445-53.
177. O'Shea JC, Hafley GE, Greenberg S, Hasselblad V, Lorenz TJ, Kitt MM, et al. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. *JAMA*. 2001 May 16;285(19):2468-73.
178. Karvouni E, Katritsis DG, Ioannidis JP. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. *J Am Coll Cardiol*. 2003 Jan 1;41(1):26-32.
179. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, Ten BJ, Bollwein H, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA*. 2006 Apr 5;295(13):1531-8.
180. Stone GW, Bertrand ME, Moses JW, Ohman EM, Lincoff AM, Ware JH, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. *JAMA*. 2007 Feb 14;297(6):591-602.
181. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009;360(21):2176-90.
182. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000 Jun 3;355(9219):1936-42.
183. Spinler SA, Mahaffey KW, Gallup D, Levine GM, Ferguson JJ, Rao SV, et al. Relationship between renal function and outcomes in high-risk patients with non-ST-segment elevation acute coronary syndromes: results from SYNERGY. *Int J Cardiol*. 2010;144(1):36-41.
184. Bazinet A, Almanic K, Brunet C, Martineau J, Turcotte I, Caron S, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res*. 2005;116(1):41-50.
185. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 May;141(2 Suppl):e24S-e43S.
186. Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. *J Thromb Thrombolysis*. 2015;39(4):516-21.
187. Lee YR, Palmere PJ, Burton CE, Benavides TM. Stratifying Therapeutic Enoxaparin Dose in Morbidly Obese Patients by BMI Class: A Retrospective Cohort Study. *Clin Drug Investig*. 2020;40(1):33-40.
188. Spinler SA, Ou FS, Roe MT, Gibler WB, Ohman EM, Pollack CV, et al. Weight-based dosing of enoxaparin in obese patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE initiative. *Pharmacotherapy*. 2009 Jun;29(6):631-8.
189. Chua D, Tataru A. Enoxaparin Dosing for Acute Coronary Syndromes in Obese Patients-Should There be a Maximum Dose. *J Cardio Cardiovasc Med*. 2016;1:002.
190. White HD, Kleiman NS, Mahaffey KW, Lokhnygina Y, Pieper K, Cheswell K, et al. Efficacy and safety of enoxaparin compared with unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial [published correction appears in *Am Heart J*. 2007 Feb;153(2):327]. *Am Heart J*. 2006;152(6):1042-50.
191. Silvain J, Beygui F, Barthelemy O, Pollack C, Jr., Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ*. 2012;344:e553.
192. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004; 292(1): 89-96.
193. Califf RM, Petersen JL, Hasselblad V, Mahaffey KW, Ferguson JJ. A perspective on trials comparing enoxaparin and unfractionated heparin in the treatment of non-ST-elevation acute coronary syndromes. *Am Heart J*. 2005 Apr;149(4 Suppl):S91-9.

Guidelines

194. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006 Apr 6;354(14):1464-76.
195. Karthikeyan G, Mehta SR, Eikelboom JW. Fondaparinux in the treatment of acute coronary syndromes: evidence from OASIS 5 and 6. *Expert Rev Cardiovasc Ther*. 2009 Mar;7(3):241-9.
196. Serrano Jr. CV, Soeiro AM, Leal TCAT, Godoy LC, Biselli B, Hata LA et al. Posicionamento sobre Antiagregantes Plaquetários e Anticoagulantes em Cardiologia – 2019. *Arq Bras Cardiol*. 2019; 113(1):111-34.
197. Mason PJ, Shah B, Tamis-Holland JE, Bitt JA, Cohen MG, Safirstein J, et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circ Cardiovasc Interv*. 2018;11(9):e000035. doi:10.1161/HCV.0000000000000035
198. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganisats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *Circulation*. 2014;130(25):e344-e426.
199. Borzak S, Cannon C P, Kraft PL, Douthat L, Becker R C, Palmeri S T et al. Effects of Prior Aspirin and Anti-Ischemic Therapy on Outcome of Patients With Unstable Angina. *Am J Cardiol*. 1998;81(6):678-81.
200. Theroux P, Teymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol*. 1985;5(3):717-22.
201. Parodi O, Simonetti I, Michelassi C, Carpeggiani C, Biagini A, L'Abbate A, et al. Comparison of verapamil and propranolol therapy for angina pectoris at rest: a randomized, multiple-cross-over, controlled trial in the coronary care unit. *Am J Cardiol*. 1986;57(11):899-906.
202. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ*. 1989;299(6709):1187-92.
203. Smith NL, Reiber GE, Psaty BM, Heckbert SR, Siscovick DS, Ritchie JL, et al. Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. *J Am Coll Cardiol*. 1998;32(5):1305-11.
204. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol*. 1991;67(15):1295-7.
205. Boden WE, van Gilst WH, Scheldewaert RG, Starkey IR, Carlier MF, Julian DG, et al. Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT). *Lancet*. 2000;355(9217):1751-6.
206. De Luca G, Verdoia M, Binda G, Schaffer A, Suryapranata H, Marino P. Aspirin desensitization in patients under-going planned or urgent coronary stent implantation: a single-center experience. *Int J Cardiol*. 2013;167(2):561-3.
207. Rossini R, Angiolillo DJ, Musumeci G, Scuri P, Invernizzi P, Bass TA, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol*. 2008;101(6):786-9.
208. Page NA, Schroeder WS. Rapid desensitization protocols for patients with cardiovascular disease and aspirin hypersensitivity in an era of dual antiplatelet therapy. *Ann Pharmacother*. 2007;41(1):61-7.
209. McMullan KL, Wedner HJ. Safety of aspirin desensitization in patients with reported aspirin allergy and cardiovascular disease. *Clin Cardiol*. 2013;36(1):25-30.
210. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. *Lancet*. 1990;336(8719):827-30.
211. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med*. 1988;319(17):1105-11.
212. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al; CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet*. 2010;376(9748):1233-43.
213. Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, et al; Clopidogrel in Unstable angina to prevent Recurrent Events Trial Investigators. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation*. 2003;107(7):966-72.
214. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation*. 2003;108(14):1682-7.
215. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339(23):1665-71.
216. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, et al; CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med*. 2010;363(10):930-42. Erratum in: *N Engl J Med*. 2010;363(16):1585.
217. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2010;303(8):754-62. Erratum in: *JAMA*. 2010;303(13):1257. *JAMA*. 2011;305(21):2174. *JAMA*. 2011;305(21):2172-3.
218. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Panizza R, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol*. 2007; 49(24): 2312-7.
219. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, et al. Prognostic significance of postclopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J*. 2008;29(8):992-1000.
220. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a metaanalysis. *JAMA*. 2010;304(16):1821-30.
221. Taubert D, von Beckerath N, Grimberg G, Lazar A, Jung N, Goesser T, et al. Impact of P-glycoprotein on clopidogrel absorption. *Clin Pharmacol Ther*. 2006;80(5):486-501.
222. Angiolillo DJ, Gibson CM, Cheng S, Ollier C, Nicolas O, Bergougnan L, et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther*. 2011;89(1): 65-74.
223. Cuisset T, Frere C, Quilici J, Poyet R, Gaborit B, Bali L, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol*. 2009;54(13):1149-53.
224. Frelinger AL 3rd, Lee RD, Mulford DJ, Wu J, Nudurupati S, Nigam A, et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *J Am Coll Cardiol*. 2012;59(14):1304-11. Erratum in *J Am Coll Cardiol*. 2012;60(6):566-7.
225. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. *J Am Coll Cardiol*. 2008;51(3):256-60.

226. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301(9):937-44.
227. Juurlink DN, Gomes T, Ko DT, Szmítok PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. 2009;180(7):713-8.
228. Nicolau JC, Bhatt DL, Roe MT, Lokhnygina Y, Neely B, Corbalán R, et al. TRILOGY ACS investigators. Concomitant proton-pump inhibitor use, platelet activity, and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel and managed without revascularization: insights from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes trial. *Am Heart J*. 2015;170(4):683-694.
229. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet*. 2009;374(9694):989-97.
230. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation*. 2012;125(8):978-86.
231. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanasa A, Schnitzer TJ, et al; COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363(20):1909-17.
232. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, et al; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305(11):1097-105. Erratum in *JAMA*. 2011 Jun 1;305(21):2174.
233. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, et al; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med*. 2012;367(22):2100-9.
234. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L. Prasugrel: a novel thienopyridine antiplatelet agent: a review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. *Cardiovasc Drug Rev*. 2007;25(4):357-74.
235. Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedure myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation*. 2009;119(21):2758-64.
236. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, et al; TRITON-TIMI 38 Investigators. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation*. 2008;118(16):1626-36.
237. Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. *J Am Coll Cardiol*. 2012;31(605):388-96.
238. Gurbel PA, Erlinge D, Ohman EM, Neely B, Neely M, Goodman SG, et al. Platelet function during extended prasugrel and clopidogrel therapy for patients with ACS treated without revascularization: the TRILOGY ACS platelet function substudy. *JAMA*. 2012;308(17):1785-94.
239. Ohman J, Kudira R, Albinsson S, Olde B, Erlinge D. Ticagrelor induces adenosine triphosphate release from human red blood cells. *Biochem Biophys Res Commun*. 2012;418(4):754-8.
240. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromont J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. *J Am Coll Cardiol*. 2014;63(9):872-7.
241. Orme RC, Parker WAE, Thomas MR, Judge HM, Baster K, Sumaya W, et al. Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI). *Circulation*. 2018;138(13):1290-300.
242. Ortega-Paz L, Brugaletta S, Ariotti S, Akkerhuis KM, Karagiannis A, Windecker S, et al. HI-TECH investigators. Adenosine and Ticagrelor Plasma Levels in Patients With and Without Ticagrelor-Related Dyspnea. *Circulation*. 2018;138(6):646-48.
243. Scirica BM, Cannon CP, Emanuelsson H, Michelson EL, Harrington RA, Husted S, et al; PLATO Investigators. The incidence of bradyarrhythmias in a clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial: results of the continuous electrocardiographic assessment substudy. *J Am Coll Cardiol*. 2011;57(19):1908-16.
244. Nilsen DW. Potential benefits of ticagrelor beyond platelet inhibition. *Cardiology*. 2013;125(1):31-3.
245. Ames S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, et al; PLATO Study Group. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATElet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J*. 2010;31(24):3006-16.
246. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2010;122(11):1056-67.
247. James SK, Storey RF, Khurmi NS, Husted S, Keltai M, Mahaffey KW, et al; PLATO Study Group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation*. 2012;125(23):2914-21.
248. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al; PLATElet inhibition and patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010;375(9711):283-93.
249. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol*. 2011;57(6):672-84.
250. Kohli P, Wallentin L, Reyes E, Horrow J, Husted S, Angiolillo DJ, et al. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO Study. *Circulation*. 2013;127(6):673-80.
251. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M; PLATO Health Economic Substudy Group. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. *Eur Heart J*. 2013;34(3):220-8.
252. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2019;381(16):1524-34.
253. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, et al. ANTARCTIC investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet*. 2016;388(10055):2015-22.
254. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y₁₂ Inhibitors in Primary PCI. *N Engl J Med*. 2019;381(17):1621-31.
255. Pereira NL, Farkouh ME, So D. Effect of Genotype-Guided Oral P2Y₁₂ Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA*. 2020;324(8):761-77.

Guidelines

256. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS. Heparin and Low-Molecular-Weight Heparin, Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety. *Chest*. 2001; 119(1 Suppl):64S-94S.
257. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of Action and Pharmacology of Unfractionated Heparin. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1094-96.
258. Lee MS, Wali AU, Menon V, Berkowitz SD, Thompson TD, Califf RM, et al. The determinants of activated partial thromboplastin time, relation of activated partial thromboplastin time to clinical outcomes, and optimal dosing regimens for heparin treated patients with acute coronary syndromes: are view of GUSTO-IIb. *J Thromb Thrombolysis* 2002;14(2):91-101.
259. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, et al. Enoxaparin prevents death and cardiac Ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation*. 1999;100(15):1593-601.
260. Cohen M, Demers C, Gurfinkel EP, Turpie AGG, Fromell GJ, Goodman S, et al. A Comparison of Low-Molecular-Weight Heparin with Unfractionated Heparin for Unstable Coronary Artery Disease. *N Engl J Med*. 1997;337(7):447-52.
261. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E. Assessment of the Treatment Effect of Enoxaparin for Unstable angina/non-Q-wave Myocardial Infarction. TIMI 11B-ESSENCE Meta-Analysis. *Circulation*. 1999;100(15), 1602-8.
262. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, et al. Enoxaparin VS unfractionated heparin in high risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292(1):45-54.
263. Collet JP, Montalescot G, Lison L, Choussat R, Ankri A, Drobinski G, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. *Circulation*. 2001;103(5):658-63.
264. Petitou M, Casu B, Lindahl U. 1976-1983, a critical period in the history of heparin: the discovery of the antithrombin binding site. *Biochimie*. 2003;85(12):83-9.
265. Holbrook A, Schulman S, Witt DM, Vandnick PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e152S-e184S.
266. Zhang Y, Zhang M, Tan L, Pan N, Zhang L. The clinical use of Fondaparinux: A synthetic heparin pentasaccharide. *Prog Mol Biol Transl Sci*. 2019;163:41-53.
267. Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, et al. Efficacy and Safety of Fondaparinux Versus Enoxaparin in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: Results From the OASIS-5 Trial. *J Am Coll Cardiol* 2007;50(18):1742-51
268. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Goose P, Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375(25):2423-34.
269. Cannon CP, Bhatt DL, Oldgren J, Thomas L, Ansell J, Fonarow GC, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(25):1513-24.
270. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehra R, et al. Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019;380(16):1509-24.
271. Vranckx P, Valgimigli M, Eckardt T, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based Versus Vitamin K Antagonist-Based Antithrombotic Regimen After Successful Coronary Stenting in Patients With Atrial Fibrillation (ENTRUST-AF PCI): A Randomised, Open-Label, Phase 3b Trial. *Lancet*. 2019;394 (10206), 1335-43.
272. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehra R, Cannon CP, et al. Optimal Antithrombotic Regimens for Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: an Updated Network Meta-analysis. *JAMA Cardiol*. 2020;5(5):582-589.
273. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. ESC Scientific Document Group, 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2020 Aug 20 ehaa575 [online]
274. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-15042.
275. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-9.
276. Heart Protection Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.
277. Dondo TB, Hall M, Timmis AD, Gilthorpe MS, Alabas AO, Batin PD, et al. Excess Mortality and Guideline-Indicated Care Following non-ST-elevation Myocardial Infarction. *Eur Heart J Acute Cardiovasc Care*, 2107;6 (5), 412-20.
278. Faludi AA, Izar MCO, Saraiva JFK, Bianco HT, Chacra APM, Bertoluci MC et al. Diretriz brasileira baseada em evidências sobre prevenção de doenças cardiovasculares em pacientes com diabetes: posicionamento da Sociedade Brasileira de Diabetes (SBD), da Sociedade Brasileira de Cardiologia (SBC) e da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM). *Arq Bras Cardiol*. 2017; 109(6 Supl.1):1-31
279. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387-97.
280. Berwanger O, Santucci EV, de Barros e Silva PGM, Jesuino IA, Damiani LP, Barbosa LM, et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome. *JAMA*. 2018;319(13):1331-40.
281. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342(3):145-53. Erratum in *N Engl J Med*. 2000;342(10):748 Erratum: *N Engl J Med*. 2000;342(18):1376.
282. Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003; 362(9386):782-8.
283. Hoedemaker NPG, Damman P, Ottervanger JP, Dambrink JHE, Gosselink ATM, Kedhi E, et al. Trends in Optimal Medical Therapy Prescription and Mortality After Admission for Acute Coronary Syndrome: A 9-year Experience in a Real-World Setting. *Eur Heart J Cardiovasc Pharmacother*, 2018; 4(2):102-10.
284. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003 Apr 3;348(14):1309-21. Erratum in: *N Engl J Med*. 2003; 348(22):2271.
285. Carillo S, Zhang Y, Fay R, Angioi M, Vincent J, Sutradhor SC, et al. Heart failure with systolic dysfunction complicating acute myocardial infarction - differential outcomes but similar eplerenone efficacy by ST-segment or non-ST-segment elevation: A post hoc substudy of the EPHEsus trial. *Arch Cardiovasc Dis*. 2014 Mar;107(3):149-57.

286. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999 Sep 2;341(10):709-17.
287. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106(14):1883-92.
288. Gibler WB, Cannon CP, Blomkalns AL, Char DM, Drew BJ, Hollander JE, et al; American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care); Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group; Society of Chest Pain Centers. Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: a scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Society of Chest Pain Centers. *Circulation*. 2005;111(20):2699-710.
289. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Early exercise testing in the management of low risk patients in chest pain centers. *Prog Cardiovasc Dis*. 2004;46(5):438-52.
290. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106(6):793-800.
291. Stein RA, Chaitman BR, Balady GJ, Fleg JL, Limacher MC, Pina IL, et al. Safety and utility of exercise testing in emergency room chest pain centers: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation*. 2000;102(12):1463-7.
292. Larsson H, Areskog M, Areskog NH, Nylander E, Nyman I, Swahn E, et al. Should the exercise test (ET) be performed at discharge or one month later after an episode of unstable angina or non-Q-wave myocardial infarction? *Int J Card Imaging*. 1991;7(1):7-14.
293. Hermann LK, Weingart SD, Duvall WL, Henzlova MJ. The limited utility of routine cardiac stress testing in emergency department chest pain patients younger than 40 years. *Ann Emerg Med*. 2009;54(1):12-6.
294. Natsui S, Sun BC, Shen E, Wu YL, Redberg RF, Lee MS, et al. Evaluation of Outpatient Cardiac Stress Testing After Emergency Department Encounters for Suspected Acute Coronary Syndrome. *Ann Emerg Med*. 2019 Aug;74(2):216-23.
295. Sabia P, Afrookteh A, Touchstone DA, Keller MW, Esquivel L, Kaul S. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction: a prospective study using two-dimensional echocardiography. *Circulation*. 1991;84(3 Suppl):185-92.
296. Stein JH, Neumann A, Preston LM, VandenBerg BJ, Parrillo JE, Calvin JE, et al. Improved risk stratification in unstable angina: identification of patients at low risk for in hospital cardiac events by admission echocardiography. *Clin Cardiol*. 1998;21(10):725-30.
297. Horowitz RS, Morganroth J, Parrotto C, Chen CC, Soffer J, Pauletto FJ. Immediate diagnosis of acute myocardial infarction by two-dimensional echocardiography. *Circulation*. 1982;65(2):323-9.
298. Kontos MC, Arrowood JA, Paulsen WH, Nixon JV. Early echocardiography can predict cardiac events in emergency department patients with chest pain. *Ann Emerg Med*. 1998;31(5):550-7.
299. Barberato SH, Romano MMD, Beck ALS, Rodrigues ACT, Almeida ALC, Assunção BMBL, et al. Position Statement on Indications of Echocardiography in Adults - 2019. *Arq Bras Cardiol*. 2019;113(1):135-81.
300. Campos FO, Zielinsky P, Ortiz J, Maciel BC, Andrade JL, Mathias WJr, et al; Brazilian Society of Cardiology. [Guideline for indication and utilization of echocardiography in clinical practice]. *Arq Bras Cardiol*. 2004;82(Suppl 2):11-34.
301. Atici A, Ali Barman H, Durmaz E, Demir K, Cakmak R, Tugrul S, et al. Predictive value of global and territorial longitudinal strain imaging in detecting significant coronary artery disease inpatients with myocardial infarction without persistent ST-segment elevation. *Echocardiography*. 2019; 36(3):425-622.
302. Solomon SD, Glynn RJ, Greaves S, Ajani U, Rouleau JL, Menapace RF, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: The healing and early after local therapy study. *Ann Intern Med*. 2001; 134(6): 451 -8.
303. Liou K, Negishi K, Ho S, Russell EA, Cranney G, Ooi SY. Detection of Obstructive Coronary Artery Disease Using Peak Systolic Global Longitudinal Strain Derived by Two-Dimensional Speckle-Tracking: A Systematic Review and Meta-Analysis. *J Am Soc Echocardiogr*. 2016;29(8):724-35 e4.
304. Marques-Alves P, Espirito-Santo N, Baptista R, Teixeira R, Martins R, Gonçalves F, et al. Two-dimensional speckle-tracking global longitudinal strain in high-sensitivity troponin-negative low-risk patients with unstable angina: a "resting ischemia test"? *Int J Cardiovasc Imaging*. 2017; 34(4):561-8.
305. Dahlslett T, Karlsen S, Grenne B, Eek C, Sjøli B, Skustad H, et al. Early assessment of strain echocardiography can accurately exclude significant coronary artery stenosis in suspected non-ST-segment elevation acute coronary syndrome. *J Am Soc Echocardiogr*. 2014;27(5):512-9.
306. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, et al. Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. *J Am Soc Echocardiogr*. 2018; 31(3):241-74.
307. Pellikka PA, Olson AA, Chaudhry FA, Chen MH, Marshall JE, Porter TR, Sawada SC, Guidelines for Performance, Interpretation, and Application of Stress Echocardiography in Ischemic Heart Disease: From the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33(1):1-41.
308. Sicari R, Landi P, Picano E, Pirelli S, Chiaranda G, Previtali M, et al. Exercise-electrocardiography and/or pharmacological stress echocardiography for non-invasive risk stratification early after uncomplicated myocardial infarction: a prospective international large scale multicentre study. *Eur Heart J*. 2002;23(13):1030-7.
309. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.
310. Picano E, Mathias WJr, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. *Echo Dobutamine International Cooperative Study Group*. *Lancet*. 1994;344(8931):1190-2.
311. Caldas MA, Tsutsui JM, Kowatsch I, Andrade JL, Nicolau JC, Ramires JF, et al. Value of myocardial contrast echocardiography for predicting left ventricular remodeling and segmental functional recovery after anterior wall acute myocardial infarction. *J Am Soc Echocardiogr*. 2004;17(9):923-32.
312. Mathias WJr, Arruda AL, Andrade JL, Filho OC, Porter TR. Endocardial borderline action during dobutamine infusion using contrast echocardiography. *Echocardiography*. 2002;19(2):109-14.
313. Porter TR, Abdelmoneim S, Belcik JT, McCulloch ML, Mulvagh SL, Olson JJ, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2014;27(8):797-810.
314. Tsutsui JM, Elhendy A, Xie F, O'Leary EL, McGrain AC, Porter TR. Safety of dobutamine stress real-time myocardial contrast echocardiography. *J Am Coll Cardiol*. 2005;45(8):1235-42.

Guidelines

315. Tsutsui JM, Xie F, O'Leary EL, Elhendy A, Anderson JR, McGrain AC, et al. Diagnostic accuracy and prognostic value of dobutamine stress myocardial contrast echocardiography in patients with suspected acute coronary syndromes. *Echocardiography*. 2005;22(6):487-95.
316. Brown KA. Evaluation of the unstable angina patient in 2005: is there still a role for non invasive risk stratification? *J Nucl Cardiol*. 2005;12(1):9-11.
317. Amanullah AM. Noninvasive testing in the diagnosis and management of unstable angina. *Int J Cardiol*. 1994;47(2):95-103.
318. Miller DD. Risk stratification in unstable angina pectoris. In: Zaret BL, Beller GA. (eds) *Nuclear cardiology: stateofheartand future directions*. Saint Louis: Mosby Inc; 1999. p. 490-9.
319. Stratmann HG, Younis LT, Wittry MD, Amato M, Miller DD. Exercise technetium-99m myocardial tomography for the risk stratification of men with medically treated unstable angina pectoris. *Am J Cardiol*. 1995;76(4):236-40.
320. Freeman MR, Chisholm RJ, Armstrong PW. Usefulness of exercise electrocardiography and thallium scintigraphy in unstable angina pectoris in predicting the extent and severity of coronary artery disease. *Am J Cardiol*. 1988;62(17):1164-70. Erratum in: *Am J Cardiol* 1989;63(5):392.
321. Zhu YY, Chung WS, Botvinick EH, Dae MW, Lim AD, Ports TA, et al. Dipyridamole perfusion scintigraphy: the experience with its application in one hundred seventy patients with known or suspected unstable angina. *Am Heart J*. 1991;121(1 Pt 1):33-43.
322. Brown KA. Prognosticvalueof thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. *J Am Coll Cardiol*. 1991;17(5):1053-7.
323. Madsen JK, Stubgaard M, Utne HE, Hansen JF, van Duijvendijk K, Reiber JH, et al. Prognosis and thallium-201 scintigraphy in patients admitted with chest pain without confirmed acute myocardial infarction. *Br Heart J*. 1988;59(2):184-9.
324. Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, et al. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: A randomized, controlled trial (PARR-2). *J Am Coll Cardiol*. 2007;50(2):2002-12.
325. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, Renaud JM, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol*. 2011;58(7):740-8.
326. de Souza ACDAH, Gonçalves BKD, Tedeschi AL, Lima RSL. Quantification of Myocardial Flow Reserve Using aGamma Camera With Solid-State Cadmium-Zinc-Telluride Detectors: Relation to Angiographic Coronary Artery Disease. *J Nucl Cardiol*. 2019; Jun 20. Doi 10.1007/s12350-019-01775-z. ahead of print
327. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus documenton cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;121(22):2462-508.
328. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, et al. Non invasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation*. 1999;99(6):763-70.
329. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2012;59(19):1719-28.
330. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettler K, et al; MR-IMPACT Investigators. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2013;34(10):775-81.
331. Watkins S, McGeoch R, Lyne J, Steedman T, Good R, McLaughlin MJ, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation*. 2009;120(22):2207-13.
332. Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, et al. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circulation*. 2009;120(14):1390-400.
333. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343(20):1445-53.
334. Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. *Circulation*. 2001;104(10):1101-7.
335. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial Myocardial infarcts: an imaging study. *Lancet*. 2003;361(9355):374-9.
336. Cheong BY, Muthupillai R, Wilson JM, Sung A, Huber S, Amin S, et al. Prognostic significance of delayed-enhancement magnetic resonance imaging: survival of 857 patients with and without left ventricular dysfunction. *Circulation*. 2009;120(21):2069-76.
337. Wu E, Judd RM, Vargas JD, Klocke FJ, Bonow RO, Kim RJ. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q wave myocardial infarction. *Lancet*. 2001;357(9249):21-8.
338. Kim RJ, Albert TS, Wible JH, Elliott MD, Allen JC, Lee JC, et al. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: na international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117(5):629-37.
339. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magneticresonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol*. 2009;55(1):1-16.
340. Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2014 Sep 23;64(12):1217-26.
341. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *JAMA*. 2012;308(9):890-6.
342. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or Symptoms of coronary artery disease. *Circulation*. 2006;113(23):2733-43. Erratum in *Circulation*. 2006;114(8):e365.
343. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation*. 1998;97(8):765-72.
344. Kelle S, Roes SD, Klein C, Kokocinski T, de Roos A, Fleck E, et al. Prognostic value of myocardial infarct size and contractile reserve using magnetic resonance imaging. *J Am Coll Cardiol*. 2009;54(19):1770-7.
345. Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. *PLoS One*. 2020 Feb 13;15(2):e0228736.

346. Rochitte CE. Microvascular obstruction the final frontier for a complete myocardial reperfusion. *J Am Coll Cardiol*. 2008;51(23):2239-40.
347. Klug G, Mayr A, Schenk S, Esterhammer R, Schocke M, Nocker M, et al. Prognostic value at 5 years of microvascular obstruction after acute myocardial infarction assessed by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2012;14(1):46.
348. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non ischaemic cardiomyopathies. *Eur Heart J*. 2005;26(15):1461-74.
349. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;53(17):1475-87.
350. Gannon MP, Schaub E, Grines CL, Saba SG. State of the Art: Evaluation and Prognostication of Myocarditis Using Cardiac MRI. *J Magn Reson Imaging*. 2019;49 (7), e122-e131
351. Athanasiadis A, Schneider B, Sechtem U. Role of cardiovascular magnetic resonance in takotsubo cardiomyopathy. *Heart Fail Clin*. 2013;9(2):167-76.
352. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, et al. Myocardial and Systemic Inflammation in Acute Stress-Induced (Takotsubo) Cardiomyopathy. *Circulation*. 2019;139 (13):1581-92.
353. Vidal-Perez R, Abou Jokh Casas C, Agra-Bermejo RM, Alvarez-Alvarez B, Grapsa J, Fontes-Carvalho R, et al. Myocardial infarction with non-obstructive coronary arteries: A comprehensive review and future research directions. *World J Cardiol*. 2019 Dec 26;11(12):305-15.
354. Perazzolo Marra M, Lima JA, Iliceto S. MRI in acute myocardial infarction. *Eur Heart J*. 2011;32(3):284-93.
355. Sandoval Y, Jaffe AS. Type 2 Myocardial Infarction: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019 Apr 16;73(14):1846-60.
356. Barbarawi, M, Kheiri, B, Zayed, Y, Barbarawi O, Chahine A, Haykal T, et al. Meta - analysis of optimal timing of coronary intervention in nonST - elevation acute coronary syndrome. *Catheter Cardiovasc Interv*. 2020; 95(2): 185– 93.
357. Lindholm D, Alfredsson J, Angerås O, Bohm F, Calais F, Koul S, et al. Timing of percutaneous coronary intervention in patients with non-ST-elevation myocardial infarction: a SWEDEHEART study. *Eur Heart J Qual Care Clin Outcomes*. 2017;3(1):53 - 60.
358. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2): 87-165.
359. Götzberg M, Christiansen EH, Gudmundsdottir JJ, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376(19):1813-23.
360. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376(19), 1824-34.
361. Matsuo Y, Kubo T, Akasaka T. The use of optical coherence tomography in acute coronary syndrome. *Expert Rev Cardiovasc Ther*. 2016;14(5):649-57.
362. Ali ZA, Galougahi, KK, Maehara A, Shlofmitz RA, Ben-Yehuda O, Mintz GS, Stone GW. Intracoronary Optical Coherence Tomography 2018. *JACC: Cardiovasc Interv*. 2017;10(24), 2473–87.
363. Meneveau N, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, et al. Optical Coherence Tomography to Optimize Results of Percutaneous Coronary Intervention in Patients with Non-ST-Elevation Acute Coronary Syndrome: Results of the Multicenter, Randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation*. 2016;134(13):906 - 17.
364. Chowdhury M, Osborn EA. Physiological assessment of coronary lesions in 2020. *Curr Treat Options Cardiovasc Med*. 2020; 22(1):2.
365. Choudhry NK, Singh JM, Barolet A, Tomlinson GA, Detsky AS. How should patients with unstable angina and non-ST-segment elevation myocardial infarction be managed? A meta-analysis of randomized trials. *Am J Med*. 2005;118(5):465-74.
366. Damman P, van Geloven N, Wallentin L, Lagerqvist B, Fox KA, Clayton T, et al. Timing of angiography with a routine invasive strategy and long-term outcomes in non-ST-segment elevation acute coronary syndrome: a collaborative analysis of individual patient data from the FRISC II (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease), ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes), and RITA-3 (Intervention Versus Conservative Treatment Strategy in Patients With Unstable Angina or Non-ST Elevation Myocardial Infarction) Trials. *JACC Cardiovasc Interv*. 2012;5(2):191-9.
367. Zimarino M, Curzen N, Cicchitti V, De Caterina R. The adequacy of myocardial revascularization in patients with multivessel coronary artery disease. *Int J Cardiol*. 2013;168(3):1748-57.
368. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med* 2003;163:2345–53138.
369. Judd E, Hollander JE, Than M, Mueller C. State-of-the-Art Evaluation of Emergency Department Patients Presenting With Potential Acute Coronary Syndromes. *Circulation* 2016;134:547–564.
370. Damman P, Hirsch A, Windhausen F, Tijssen JGP, Winter RJ, ICTUS Investigators. 5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial a randomized comparison of an early invasive versus selective invasive management in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol*. 2010;55:858–64.
371. Mahmoud AN, Elgendy IY, Mansoor H, Xuerong W, Mojaddid MK, Bavry AA, et al. Early invasive strategy and in-hospital survival of diabetics with non-ST-elevation Myocardial infarction: a contemporary national insight. *JACC*. 2017;(69):182.
372. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1(2):219-27.
373. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stähle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381(9867):629-38.
374. Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR Jr, Riechwald N. Importance of complete revascularization in performance of the coronary bypass operation. *Am J Cardiol*. 1983;51(1):7-12.
375. Bundhun PK, Sookharee Y, Bholee A, Huang F. Application of the SYNTAX score in interventional cardiology: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(28):e7410.
376. Ranasinghe I, Alprandi-Costa B, Chow V, Elliott JM, Waites J, Counsell JT, et al. Risk stratification in the setting of non-ST elevation acute coronary syndromes 1999-2007. *Am J Cardiol* 2011;108:617–624.
377. Fukui T, Tabata M, Morita S, Takanashi S. Early and long-term outcomes of coronary artery bypass grafting in patients with acute coronary syndrome versus stable angina pectoris. *J Thorac Cardiovasc Surg* 2013;145:1577–1583.
378. Malm CJ, Hansson EC, Akesson J, Andersson M, Hesse C, Shams Hakimi C, et al. Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: A prospective observational study. *Br J Anaesth* 2016;117:309–315.
379. Nichols EL, McCullough JN, Ross CS, Kramer RS, Westbrook BM, Klemperer JD, et al. Optimal Timing From Myocardial Infarction to Coronary Artery Bypass Grafting on Hospital Mortality. *Ann of Thorac Surg*. 2017;103(1):162–171.

Guidelines

380. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, et al. After Eighty study investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. *Lancet*. 2016;387(10023):1057–1065.
381. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TRD, Wheatley DJ, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet*. 2005;366(9489):914–20.
382. Fanning JP, Nyong J, Scott IA, Aroney CN, Walters DL. Routine Invasive Strategies Versus Selective Invasive Strategies for Unstable Angina and non-ST Elevation Myocardial Infarction in the Stent Era. *Cochrane Database Syst Rev*. 2016;(5):CD004815.
383. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lundelund K, Schotborgh CE, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376(13):1234–44.
384. Choi KH, Song YB, Lee JM, Lee SY, Park TK, Yang JH, et al. Impact of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention on Long-Term Clinical Outcomes in Patients Undergoing Complex Procedures. *JACC Cardiovasc Interv*. 2019;12(7):607–20.
385. Gao XF, Wang ZM, Wang F, Gu Y, Ge Y, et al. Intravascular Ultrasound Guidance Reduces Cardiac Death and Coronary Revascularization in Patients Undergoing Drug-Eluting Stent Implantation: Results From a Meta-Analysis of 9 Randomized Trials and 4724 Patients. *Int J Cardiovasc Imaging*. 2019;35(2):239–47.
386. Nicolau JC, Franken M, Lotufo PA, Carvalho AC, Marin-Neto JA, Gallego F, et al. Use of demonstrably effective therapies in the treatment of acute coronary syndromes: comparison between different Brazilian regions. Analysis of the Brazilian Registry on Acute Coronary Syndromes (BRACE). *Arq Bras Cardiol*. 2012;98(4):282–9.
387. Coleman EA. Falling through the cracks: challenges and opportunities for improving transitional care for persons with continuous complex care needs. *J Am Geriatr Soc*. 2003;51(4):549–55.
388. Coleman EA, Boulton C, American Geriatrics Society Health Care Systems Committee. Improving the quality of transitional care for persons with complex care needs. *J Am Geriatr Soc*. 2003;51(4):556–7.
389. Coleman EA, Mahoney E, Parry C. Assessing the quality of preparation for posthospital care from the patient's perspective: the care transitions measure. *Med Care*. 2005;43(3):246–55.
390. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458–73.
391. Bernheim SM, Spertus JA, Reid KJ, Bradley E, Desai RA, Peterson ED, et al. Socioeconomic disparities in outcomes after acute myocardial infarction. *Am Heart J*. 2007;153(2):313–9.
392. Rahimi AR, Spertus JA, Reid KJ, Bernheim SM, Krumholz HM. Financial barriers to health care and outcomes after acute myocardial infarction. *JAMA*. 2007;297(10):1063–72.
393. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2(4):328–37.
394. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Becky KR, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116(10):682–92.
395. Leon AS, Franklin BA, Costa F, Balady GB, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2005;111(3):369–76.
396. Suaya JA, Stason WB, Ades PA, Normand ST, Shepard DS, et al. Cardiac rehabilitation and survival in older coronary patients. *J Am Coll Cardiol*. 2009;54(1):25–33.
397. Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. *Circulation*. 2005;112(6):924–34.
398. Anderson L1, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2016 Jan 5;67(1):1–12.
399. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA*. 2003;290(1):86–97.
400. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention, (US); 2014.
401. Kalkhoran S, Benowitz N, Rigotti N. Prevention and Treatment of Tobacco Use. *JACC Health Promotion Series*. *J Am Coll Cardiol*. 2018;72(9):1030–45.
402. Goldenberg I, Jonas M, Tenenbaum A, Boyoko V, Matetzky S, Shotan A, et al. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Arch Intern Med*. 2003;163(19):2301–5.
403. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol*. 2014;34(3):509–15.
404. Chamberlain AM, Agarwal SK, Folsom AR, et al. (2011) Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. *Heart Rhythm*. 2011;8(8):1160–6.
405. Daly LE, Mulcahy R, Graham IM, Hickey N. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J (Clin Res Ed)*. 1983;287(6388):324–6.
406. Parasuraman S, Zaman AG, Egred M, Bagnall A, Broadhurst PA, Ahmed J, et al. Smoking status and mortality outcomes following percutaneous coronary intervention. *Eur J Prev Cardiol*. 2020 Feb 3;2047487320902325.
407. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med*. 2006;145(11):845–56.
408. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356(23):2388–98.
409. Lindson N, Klemperer E, Hong B, Ordóñez-Mena JM, Aveyard P. Smoking reduction interventions for smoking cessation. *Cochrane Database Syst Rev*. 2019 Sep 30;9(9):CD013183.
410. Eisenberg MJ, Grandi SM, Gervais A, O'Loughlin J, Paradis G, Rinfret S, et al. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: a randomized, placebo-controlled trial. *J Am Coll Cardiol*. 2013;61(5):524–32.
411. Planer D, Lev I, Elitzur Y, Sharon N, Ouzan E, Pugatsch T, et al. Bupropion for smoking cessation in patients with acute coronary syndrome. *Arch Intern Med*. 2011;171(12):1055–60.
412. Stead LF, Perera R, Bullen C, Mant D, Hartman-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2018;5(5):CD000146.

413. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Arch Intern Med.* 2000;160(7):939-44.
414. Agency for Health Care Research and Quality. (AHRQ). Clinical Practice Guidelines: Smoking Cessation. No 18. AHCPR Publication No.96-0692; 1996.
415. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):56-63. Erratum in *JAMA.* 2006;296(11):1355.
416. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):47-55.
417. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Sao Paulo Med J.* 2012;130(5):346-7. (Cochrane Highlights)
418. Anthenelli RM, Benowitz NL, West R, Russ C, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016; 387(10037):P2507-20.
419. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation.* 2010; 121(2):221-9.
420. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation.* 2016; 133(1):21-30.
421. Windle SB, Dehghani P, Roy N, Old W, Grondin FR, Bhatta I, et al. Smoking abstinence 1 year after acute coronary syndrome: follow-up from a randomized controlled trial of varenicline in patients admitted to hospital. *CMAJ.* 2018;190(12):E347-E354.
422. Zhong Z, Zhao S, Zhao Y, Xia S. Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. *Compr Psychiatry.* 2019; 95:152125.
423. Kalkhoran S, Benowitz NL, Rigotti N. Prevention and Treatment of Tobacco Use. *J Am Coll Cardiol.* 2018;72(23):2964-979.
424. Benowitz NL, Donny EC, Hatsukami DK. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. *Addiction.* 2017; 112(1):6-7.
425. Hatsukami DK, Donny EC, Koopmeiners JS, Benowitz NL. Compensatory smoking from gradual and immediate reduction in cigarette nicotine content. *Cancer Epidemiol Biomarkers Prev.* 2015; 24(2):472-6.
426. MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? *Vasc Health Risk Manag.* 2019 Jun 21;15:159-74.
427. Baigent C, Blackwell L, Emberson J. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376: 1670-81.
428. Collins R, Reith C, Emberson J, Bhatta N, Peto R, Barnes EH, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet.* 2016;388(9753):2532-61.
429. Amarencu P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355(6):549-59.
430. Athyros VG, Papageorgiou AA, Mercouris BR, Athyros VV, Symeonidis AN, Basayannis EO, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin.* 2002;18(4):220-8.
431. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248-61.
432. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008; 372(9645):1231-9.
433. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S76-99.
434. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 2014;63(25 Pt B):2985-3023.
435. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* 2018 Jun 21;378(25):e34.
436. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA.* 2007; 297(8):842-57.
437. Carvalho T, Milani M, Ferraz AS, Silveira AD, Herdy AH, Hossri CAC, et al. Diretriz Brasileira de Reabilitação Cardiovascular – 2020. *Arq Bras Cardiol.* 2020; 114(5):943-87.
438. Kureshi F, Kennedy KF, Jones PG, Thomas RJ, Arnold S V., Sharma P, et al. Association between cardiac rehabilitation participation and health status outcomes after acute myocardial infarction. *JAMA Cardiol.* 2016;1(9):980-8.
439. Suaya JA, Shepard DS, Normand S-LT, Ades PA, Prottas J, Stason WB. Use of Cardiac Rehabilitation by Medicare Beneficiaries After Myocardial Infarction or Coronary Bypass Surgery. *Circulation.* 2007 Oct 9;116(15):1653 LP – 1662.
440. Sunamura M, Ter Hoeve N, van den Berg-Emons RJG, Boersma E, van Domburg RT, Geleijnse ML. Cardiac rehabilitation in patients with acute coronary syndrome with primary percutaneous coronary intervention is associated with improved 10-year survival. *Eur Heart J Qual Care Clin Outcomes.* 2018 Jul;4(3):168-72.
441. Ades PA, Keteyian SJ, Wright JS, Hamm LF, Lui K, Newlin K, et al. Increasing Cardiac Rehabilitation Participation From 20% to 70%: A Road Map From the Million Hearts Cardiac Rehabilitation Collaborative. *Mayo Clin Proc.* 2017;92(2):234-42.
442. Correia LC, Garcia G, Kalil F, Ferreira F, Carvalhal M, Oliveira R, et al. Prognostic value of TIMI score versus GRACE score in ST-segment elevation myocardial infarction. *Arq Bras Cardiol.* 2014 Aug;103(2):98-106.
443. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American heart association. *Circulation.* 2013;128(8):873-934.
444. Costa RVC, Braga AMW, Carlos A. Arquivos Brasileiros de Cardiologia I CONSENSO NACIONAL DE REABILITAÇÃO CARDIOVASCULAR. *Arq Bras Cardiol.* 1997;69(4):267-91.
445. Loh JP, Pendyala LK, Kitabata H, Torguson R, Chen F, Kent KM, et al. Safety of reloading prasugrel in addition to clopidogrel loading in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Cardiol.* 2013;111(6):841-5.

Guidelines

446. Zettler ME, Peterson ED, McCoy LA, Effron MB, Anstrom KJ, Henry TD, et al. Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: Insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after. *Am Heart J*. 2017;183:62-8.
447. Angiolillo DJ, Curzen N, Gurbel P, Vaitkus P, Lipkin F, Li W, et al. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: Results of the swap-2 study (switching anti platelet-2). *J Am Coll Cardiol*. 2014;63(15):1500-9.
448. Pourdjabbar A, Hibbert B, Chong AY, Le May MR, Labinaz M, Simard T, et al. A randomised study for optimising crossover from ticagrelor to clopidogrel in patients with acute coronary syndrome. *Thromb Haemost*. 2017;117(2):303-10.
449. Franchi F, Rollini F, Rios JR, Rivas A, Agarwal M, Kureti M, et al. Pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease results of the SWAP-4 study. *Circulation*. 2018;137(23):2450-62.
450. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation*. 2017;136(20):1955-75.
451. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J*. 2017;38(1):213-54.
452. Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367(14):1297-309.
453. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-800.
454. Furtado RHM, Nicolau JC, Magnani G, Im K, Bhatt DL, Storey RF, et al. Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54. *Eur Heart J*. 2020;41(17):1625-32.
455. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371(23):2155-66.
456. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015 Apr 7;65(13):1298-310.
457. Bonaca MP, Sabatine MS. Antiplatelet Therapy for Long-term Secondary Prevention After Myocardial Infarction. *JAMA Cardiol*. 2016 Sep 1;1(6):627-8.
458. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389(10073):1025-34.
459. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SLT, Gershlick AH, Cohen DJ, et al. Development and validation of a prediction rule for benefit and harm of Dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA - J Am Med Assoc* 2016;315(16):1735-49.
460. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017 Oct 5;377(14):1319-30.
461. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanus F, et al; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018 Jan 20;391(10117):205-18.
462. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label. *Lancet*. 2018;392(10151):940-9.
463. Takahashi K, Serruys PW, Chichareon P, Chang CC, Tomaniak M, Modolo R, et al. Efficacy and Safety of Ticagrelor Monotherapy in Patients Undergoing Multivessel PCI. *J Am Coll Cardiol*. 2019 Oct 22;74(16):2015-27.
464. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019;381(21):2032-42.
465. O'Donoghue ML, Murphy SA, Sabatine MS. The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y12 Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. *Circulation*. 2020 Aug 11;142(6):538-45.
466. Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: The clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) trial. *Circulation* 2004;110(10):1202-8.
467. Lopes RD, Pieper KS, Horton JR, Al-Khatib SM, Newby LK, Mehta RH, et al. Short- and long-term outcomes following atrial fibrillation in patients with acute coronary syndromes with or without ST-segment elevation. *Heart*. 2008;94(7):867-73.
468. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. *Lancet* 2013;381(9872):1107-15.
469. Nicolau JC, Bhatt DL, Hohnloser SH, Kimura T, Lip GYH, Miede C, et al. RE-DUAL PCI Steering Committee and Investigators. Dabigatran Dual Therapy vs Warfarin Triple Therapy Post-Percutaneous Coronary Intervention in Patients with Atrial Fibrillation With/Without a Proton Pump Inhibitor: A Pre-Specified Analysis of the RE-DUAL PCI Trial. *Drugs*. 2020 Jul;80(10):995-1005.
470. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, Oldgren J, Ten Berg JM, Kimura T, Hohnloser SH, Lip GYH, Bhatt DL. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2018; 39(19):1726-1735.
471. Lopes RD, Hong H, Alexander JH. Antithrombotic therapy after acute coronary syndrome and/or percutaneous coronary intervention in atrial fibrillation: finding the sweet spot. *Eur Heart J*. 2019 Dec 7;40(46):3768-70.
472. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019 Dec 7;40(46):3757-67.
473. Malachias MVB, Souza WKS, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT, et al, Sociedade Brasileira de Cardiologia. 7ª Diretriz Brasileira de Hipertensão Arterial. *Arq Bras Cardiol* 2016; 107(3Supl.3):1-83.
474. Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, et al. ONTARGET investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens*. 2009;27(7):1360-9.
475. Banach M, Michalska M, Kjeldsen SE, Małyszko J, Mikhailidis DP, Rysz J. What should be the optimal levels of blood pressure: Does the J-curve phenomenon really exist? *Expert Opin Pharmacother*. 2011;12(12):1835-44.

476. Bangalore S, Messerli FH, Wun C, Zuckerman AL, DeMicco D, Kostis JB, et al. J-curve revisited: an analysis of the Treating to New Targets (TNT) Trial. *Eur Heart J*. 2010; 31(23):2897–908.
477. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015 Nov 26;373(22):2103–16. Erratum in: *N Engl J Med*. 2017 Dec 21;377(25):2506.
478. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247(12):1707–14.
479. Hjalmarson Å, Herlitz J, Målek I, Rydén L, Vedin A, Waldenström A, et al. Effect On Mortality of Metoprolol In Acute Myocardial Infarction. A Double-blind Randomised Trial. *Lancet*. 1981;318(8251):823–7.
480. Goldberger JJ, Bonow RO, Cuffe M, Liu L, Rosenberg Y, Shah PK, et al. Effect of Beta-Blocker Dose on Survival after Acute Myocardial Infarction. *J Am Coll Cardiol*. 2015;66(13):1431–41.
481. Bangalore S, Steg G, Deedwania P, Crowley K. B-Blocker Use and Clinical Outcomes in Stable Outpatients With and Without Coronary Artery Disease. *J Am Med Assoc*. *JAMA*. 2012;308(13):1340–9.
482. Piva e Mattos LA, Berwanger O, Santos ES, Reis HJ, Romano ER, Petriz JL, et al. Clinical outcomes at 30 days in the Brazilian Registry of Acute Coronary Syndromes (ACCEPT). *Arq Bras Cardiol*. 2013 Jan;100(1):6–13.
483. Lachin JM, Genuth S, Cleary P. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive insulin therapy. *N Engl J Med*. 2000;342(6):381–9.
484. Holman RR, Paul SK, Bethel MA. Follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577–89.
485. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging study). *Diabetes Care*. 2019;42(3):416–26.
486. Gerstein C, Miller M, Byington R. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *N Engl J Med*. 2008;358(24):2545–59.
487. American Diabetes Association. Standards of Medical Care in Diabetes — 2020. *Diabetes Care*. 2020 Jan;43(Suppl 1):S14–S31.
488. U.S. Food and Drug Administration. FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. [Internet]. [Cited in 2019 Apr 12] Available from: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf>
489. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. *J Clin Endocrinol Metab*. 2016;101(4):1754–61.
490. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus: Systematic review and meta-analysis of cardio. *Circulation*. 2019;139(17):2022–31.
491. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. *Circulation*. 2019;139(22):2516–27.
492. McMurray JJ V, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381:1995–2008.
493. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380(24):2295–306.
494. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369(14):1317–26.
495. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;376(18):1713–22.
496. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379(22):2097–107.
497. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11–22.
498. Chang CH, Tseng PT, Chen NY, Lin PC, Lin PY, Chang JPC, et al. Safety and tolerability of prescription omega-3 fatty acids: A systematic review and meta-analysis of randomized controlled trials. *Prostaglandins Leukot Essent Fat Acids*. 2018 Feb;129:1–12.
499. Moukarbel G V, Signorovitch JE, Pfeffer MA, McMurray JJ V, White HD, Maggioni AP, et al. Gastrointestinal bleeding in high risk survivors of myocardial infarction: the VALIANT Trial. *Eur Heart J*. 2009;30(18):2226–32.
500. Lin KJ, Hernandez-Diaz S, Garcia Rodriguez LA. Acid suppressants reduce risk of gastrointestinal bleeding in patients on antithrombotic or anti-inflammatory therapy. *Gastroenterology*. 2011;141(1):71–9.
501. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348(14):1322–32.
502. Brasil. Ministério da Saúde. Manual de Normas e Procedimentos para Vacinação [Internet]. [Citado em 2020 Jan 12]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/manual_procedimentos_vacinacao.pdf
503. Ridker PM, Everett B, Thuren T, Mac Fadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017; 377(12): 1119–31.
504. Tardif JC, Kouz S, Waters DD, Bertrand D, Diaz R, Maggioni A, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*. 2019;381(26):2497–505.
505. Nicolau, JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al. Diretrizes da Sociedade Brasileira de Cardiologia sobre Angina Instável e Infarto Agudo do Miocárdio sem Supradesnível do Segmento ST (II Edição, 2007) - Atualização 2013/2014. *Arq Bras Cardiol*. 2014;102(3 supl 1):1–61.
506. Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, et al. Euro Heart Survey Investigators. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. *BMJ*. 2006;332(7536):262–7.
507. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277–314.
508. Steeds RP, Garbi M, Cardim N, Kasprzak JD, Sade E, Nihoyannopoulos P, et al. 2014 EACVI Scientific Documents Committee. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: a report of literature and current practice review. *Eur Heart J Cardiovasc Imaging*. 2017;18(11):1191–204.
509. Knuuti J, Wijins W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–77.
510. van Holten TC, Waanders LF, de Groot PG, Vissers J, Hoefer IE, Pasterkamp G, et al. Circulating biomarkers for predicting cardiovascular disease risk: a systematic review and comprehensive overview of meta-analyses. *PLoS One*. 2013;8(4):e62080.

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511. Lindholm D, Lindback J, Armstrong PW, Budaj A, Cannon CP, Granger CB, et al. Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. *J Am Coll Cardiol*. 2017;70(7):813-26.
512. Eapen DJ, Manocha P, Patel RS, Hammadah M, Veledar E, Wassel C, et al. Aggregate risk score based on markers of inflammation, cell stress, and coagulation is an independent predictor of adverse cardiovascular outcomes. *J Am Coll Cardiol*. 2013;62(4):329-37.
513. Harb SC, Marwick TH. Prognostic value of stress imaging after revascularization: a systematic review of stress echocardiography and stress nuclear imaging *Am Heart J*. 2014;167(1):7-85.

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March 2021 Issue, vol. 116 (3), pages 383-392

In Original Article "Prognostic Value of Lung Ultrasound for Clinical Outcomes in Heart Failure Patients: A Systematic Review and Meta-Analysis", with DOI number: <https://doi.org/10.36660/abc.20190662>, published in the Journal Arquivos Brasileiros de Cardiologia, 116(3):383-392, on page 383, correct the name of the institution Chengdu City First People's Hospital to: Department of Cardiology, Chengdu First People's Hospital; correct the name of the institution Chengdu Sixth People's Hospital to: Department of Cardiology, The Sixth People's Hospital of Chengdu. And correct Dr. Min Ma's affiliation to: Department of Cardiology, The Sixth People's Hospital of Chengdu.

April 2021 Issue, vol. 116 (4), págs. 806-811

In Original Article "Increased Pulmonary Arterial Stiffness and Impaired Right Ventricle-Pulmonary Artery Coupling In PCOS", with DOI number: <https://doi.org/10.36660/abc.20190762>, published in the Journal Arquivos Brasileiros de Cardiologia, 116(4):806-811, on page 806, corrigir o nome do autor Hilmi Sumbul para: Hilmi Erdem Sumbul.

April 2021 Issue, vol. 116 (4), págs. 844-849

In Brief Communication "Pacientes Naïve Infectados por HIV Apresentam Disfunção Concomitante com Diminuição de Anticorpos Naturais contra Autoantígenos Derivados da Apolipoproteína B Definidos", with DOI number: <https://doi.org/10.36660/abc.20200062>, published in the Journal Arquivos Brasileiros de Cardiologia, on page 844, correct the title of the article in Portuguese "Pacientes Naïve Infectados por HIV Apresentam Disfunção Concomitante com Diminuição de Anticorpos Naturais contra Autoantígenos Derivados da Apolipoproteína B Definidos" to: "Os Pacientes Naïve Infectados pelo HIV Apresentam Disfunção Endotelial Concomitante com a Diminuição de Anticorpos Naturais contra Definidos Autoantígenos Derivados da Apolipoproteína B".

DOI: <https://doi.org/10.36660/abc.20210556>



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