ABC Cardiol
Arquivos Brasileiros de Cardiologia

Volume 118 | Number 6
June 2022

Brazilian Society of Cardiology
ISSN-0066-782X

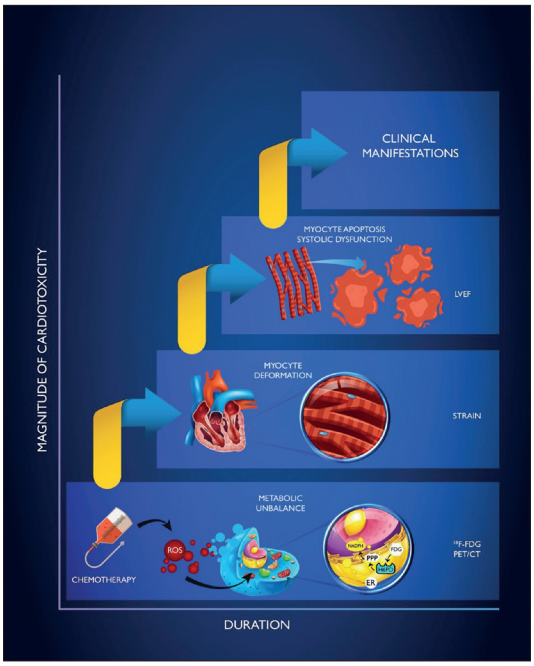


Figure 4, page 1055

ABC Cardiol
Arquivos Brasileiros de Cardiologia
JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Contents

Short Editorial

Review Article

Research Letter

Image

Erratum

ABC Cardiol
Arquivos Brasileiros de Cardiologia
REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

Editorial Board

Editorial Board

Administrative Council – Mandate 2022 (Brazilian Society of Cardiology)

North/Northeast Region
Nivaldo Menezes Filgueiras Filho (BA)
Sérgio Tavares Montenegro (PE)

Eastern Region
Denilson Campos de Albuquerque (RJ)
Andréa Araujo Brandão (RJ) – Vice-presidente do Conselho Administrativo

Região Paulista
Celso Amodeo (SP)
João Fernando Monteiro Ferreira (SP) – Presidente do Conselho Administrativo

Central Region
Carlos Eduardo de Souza Miranda (MG)
Weimar Kunz Sebba Barroso de Souza (GO)

South Region
Paulo Ricardo Avancini Caramori (RS)
Gerson Luiz Bredt Júnior (PR)

Scientific Committee
Denilson Campos de Albuquerque (RJ)
Paulo Ricardo Avancini Caramori (RS)
Weimar Kunz Sebba Barroso de Souza (GO)

Presidents of State and Regional Brazilian Societies of Cardiology

SBC/AL – Pedro Henrique Oliveira de Albuquerque

SBC/BA – Joberto Pinheiro Sena

SBC/DF – Fausto Stauffer Junqueira de Souza

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Humberto Graner Moreira

SBC/MA – Francisco de Assis Amorim de Aguiar Filho

SBC/MG – Antônio Fernandino de Castro Bahia Neto

SBC/MS – Mauro Rogério de Barros Wanderley Júnior

SBC/NNE – José Albuquerque de Figueiredo Neto

SBC/PB – Guilherme Veras Mascena

SBC/PE – Carlos Japhet Da Matta Albuquerque

SBC/PI – Jônatas Melo Neto

SBC/PR – Olímpio R. França Neto

SOCERJ – Ronaldo de Souza Leão Lima

SBC/RN – Antônio Amorim de Araújo Filho

SOCERGS – Fábio Cañellas Moreira

SOCESP – Ieda Biscegli Jatene

Presidents of the Specialized Departaments and Study Groups

SBC/DA – Marcelo Heitor Vieira Assad

SBC/DCC – Bruno Caramelli

SBC/DCC/CP – Cristiane Nunes Martins

SBC/DCM – Maria Cristina Costa de Almeida

SBC/DECAGE – José Carlos da Costa Zanon

SBC/DEIC – Mucio Tavares de Oliveira Junior

SBC/DEMCA – Álvaro Avezum Junior

SBC/DERC – Ricardo Quental Coutinho

SBC/DFCVR – Elmiro Santos Resende

SBC/DHA – Lucélia Batista Neves Cunha Magalhães

SBC/DIC – André Luiz Cerqueira de Almeida

SBCCV – João Carlos Ferreira Leal

SOBRAC – Fatima Dumas Cintra

SBHCI – Ricardo Alves da Costa

DCC/GECIP – Marcelo Luiz da Silva Bandeira

DCC/GECOP – Maria Verônica Câmara dos Santos

DCC/GEPREVIA – Isabel Cristina Britto Guimarães

DCC/GAPO – Luciana Savoy Fornari

DCC/GEAT – Carlos Vicente Serrano Junior

DCC/GECETI – João Luiz Fernandes Petriz

DCC/GEDORAC – Sandra Marques e Silva

DCC/GEECG – Nelson Samesima

DCC/GERTC – Adriano Camargo de Castro Carneiro

DEIC/GEICPED – Estela Azeka

DEIC/GEMIC – Marcus Vinicius Simões

DEIC/GETAC – Silvia Moreira Ayub Ferreira

DERC/GECESP – Marconi Gomes da Silva

DERC/GECN – Lara Cristiane Terra Ferreira Carreira

DERC/GERCPM – Pablo Marino Corrêa Nascimento

Arquivos Brasileiros de Cardiologia

Volume 118, Nº 6, June 2022

Indexing: ISI (Thomson Scientific), Cumulated Index Medicus (NLM), SCOPUS, MEDLINE, EMBASE, LILACS, SciELO, PubMed

Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
http://abccardiol.org//
SciELO: www.scielo.br

Commercial Department
TPhone: (11) 3411-5500
E-mail: comercialsp@cardiol.br

Editorial Production
SBC - Scientific Department

Graphic Design and Diagramming
SBC - Communication and Events Department

Universal Definition of Myocardial Infarction 99th Percentile versus Diagnostic Cut-off Value of Troponin I for Acute Coronary Syndromes

Antonio Haddad Tapias Filho,[1] *Gustavo Bernardes de Figueiredo Oliveira,*[1] *João Italo Dias França,*[1] *Rui Fernando Ramos*[1]

Instituto Dante Pazzanese de Cardiologia,[1] *São Paulo, SP – Brazil*

Abstract

Background: **Contemporary diagnosis of ACS and risk stratification are essential for appropriate management and reduction of mortality and recurrent ischemic events, in the acute phase of disease and after hospitalization. The Universal Definition of Myocardial Infarction recommends the detection of troponin levels above the 99th percentile.**

Objectives: **To evaluate the occurrence of early death and acute myocardial infarction (AMI) in patients without elevation of troponin (<0.034 ng/mL), patients with mild elevation (above the 99th percentile [>0.034 ng/mL and <0.12 ng/mL)], and patients with significant elevation of troponin (above the diagnostic cutoff for AMI defined by the troponin kit (≥0.12 ng/mL)]; and to analyze the impact of troponin on the indication for invasive strategy and myocardial revascularization.**

Methods: **Cross-sectional cohort study of patients with ACS with assessment of peak troponin I, risk score, prospective analysis of 30-day clinical outcomes and two-sided statistical tests, with statistical significance set at p<0.05.**

Results: **A total of 494 patients with ACS were evaluated. Troponin > 99th percentile and below the cutoff point, as well as values above the cutoff, were associated with higher incidence of composite endpoint (p<0.01) and higher rates of percutaneous or surgical revascularization procedures (p<0.01), without significative difference in 30-day mortality.**

Conclusions: **Troponin levels above the 99th percentile defined by the universal definition of AMI play a prognostic role and add useful information to the clinical diagnosis and risk scores by identifying those patients who would most benefit from invasive risk stratification and coronary revascularization procedures.**

Keywords: **Troponin I; Acute Coronary Syndrome; Myocardial Revascularization.**

Introduction

Cardiovascular diseases are the main cause of death among people older than 60 years in Brazil,[1] and important causes of disability, hospitalizations and death, mainly in low per capita income countries.[2,3]

In acute coronary syndromes (ACS), serial electrocardiography (ECG) and troponin measurements, associated with clinical examination, are essential for the correct diagnosis and appropriate management of disease.[4] In the context of acute myocardial ischemia, in addition to establishing the diagnosis of acute myocardial infarction (AMI), the measurement of troponin is useful for risk stratification in invasive strategies.[5] Besides, peak troponin levels are correlated with the extension of necrosis and left ventricular ejection fraction (LVEF), which are important determinants of post-AMI mortality.[6,7] In addition, elevated troponin levels have been correlated with multivessel coronary artery disease (CAD) and greater severity of stenosis in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS),[8,9] in addition to a directly proportional relationship with rates of clinical outcomes[10-13] in patients undergoing early revascularization procedures.[14]

Factors including severity and complexity of CAD, previous use of acetylsalicylic acid and early coronary angiography are associated with peak troponin in NSTE-ACS.[15] Among patients stabilized after an ACS, increased troponin is associated with higher all-cause cardiovascular mortality, regardless of covariables.[16] Individuals with very high levels of troponin have more complex CAD and, based on pathophysiological plausibility, revascularization may be more often indicated in this group as compared with patients without troponin elevation. On the other hand, some authors have not found an association between high troponin levels and worse clinical outcomes.[17,18]

Troponin levels proposed for the diagnosis of ACS

According to the International Federation of Clinical Chemistry and the National Academy of Clinical Biochemistry, increased troponin levels are defined as those above the 99th percentile of a healthy population, and an intra-assay coefficient of variation (CV) <10%,[19] although many troponin test kits have poor accuracy based on this percentile.[20-22] Therefore, for the use of troponin in the diagnosis of AMI, it is necessary an ascending or descending curve of the biomarker,

Mailing Address: Antonio Haddad Tapias Filho •
Instituto Dante Pazzanese de Cardiologia - Avenida Doutor Dante Pazzanese, 500. Postal Code 04012-909, Vila Mariana, São Paulo, SP – Brazil
E-mail: ahtfilho@hotmail.com
Manuscript received March 31, 2021, revised manuscript August 18, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210191

including at least one value above the 99th percentile of the reference population, according to sex, ethnics and other factors.[23,24] Some studies have pointed out the importance of using standard levels for the diagnosis of AMI in hospital laboratories to improve clinical decisions, to tailor diagnostic thresholds to the population seen in each institution, and facilitate reporting in clinical trials.[25,26]

Therefore, the present study aimed to evaluate the occurrence of clinically relevant outcomes (death, AMI, and composite endpoint) in patients at the early stage of NSTE-ACS; to compare three groups formed according to the ranges of troponin I values – without elevation (<0.034 ng/mL, i.e., below the 99th percentile), mild increase (Universal Definition of AMI, above the 99th percentile [>0.034 ng/mL and <0.12 ng/mL]), and significant increase (the most accurate diagnostic cut-off defined by local troponin kit [≥0.12 ng/mL]; and to assess the association between these groups and requirement of an invasive strategy or myocardial revascularization procedures during hospital stay. The hypothesis is that the 99th percentile value of troponin, even if lower than the cut-off point for troponin I defined by the commercial kit, is associated with clinical impact and indication for invasive stratification and myocardial revascularization, in comparison with negative levels, corroborating the values proposed by the Universal Definition of AMI.

Methods

Characteristics of the study and ethical aspects

Observational, cross-sectional study, with follow-up of up to 30 days for evaluation of death and infarction rates, and composite endpoint in patients with NSTE-ACS admitted to a coronary care unit (CCU), divided into groups according to troponin levels. All clinical events were pre-defined and assessed following a systematic collection of data from databases. Indication for invasive or non-invasive risk stratification, in-hospital treatments, and routine laboratory tests were also evaluated. All participants signed an informed consent form. The study was approved by local ethics committee in April 2019. Recruitment of patients was carried out from May 2019 to January 2020.

Inclusion criteria

- Age ≥ 18 years
- Admission to a CCU
- Diagnosis of NSTE-ACS
- The diagnosis of NSTE-ACS was made based on two of the following criteria:

- Clinical presentation suggestive of ACS;

- ECG showing depression of the ST segment, T-wave inversion or non-specific findings;

- Ascending or descending troponin curves, including at least one value above 0.12 ng/mL (diagnostic value for AMI in the troponin I kit used at Dante Pazzanese Institute of Cardiology).

Reinfarction was defined following the recommendations of the fourth universal definition of AMI, and considered suspected in the presence of signs or symptoms of infarction, requiring another troponin measurement in this case. Diagnosis is confirmed by a 20% increase in troponin levels in patients with already elevated values, or a new increase in those with previously normal levels.

- The diagnosis of unstable angina was made based on two of the following criteria:

- Clinical presentation suggestive of ACS;

- ECG showing depression of the ST segment, T-wave inversion or non-specific findings;

- Absence of troponin levels above 0.034 ng/mL (according to troponin levels for the diagnosis of AMI proposed by the universal definition of AMI[27] and the European Society of Cardiology guidelines[28]).

Exclusion criteria

- Absence of consent to participate in the study
- Patients referred for invasive management 48 hours after the first episode of ACS.

Variables analyzed

Demographic data, cardiovascular risk factors, comorbidities, previous use of medications, non-invasive hemodynamic parameters, coronary angiographic findings (of patients referred for invasive strategy), GRACE and CRUSADE scores were analyzed. Laboratory tests, therapeutic procedures and approaches during hospital stay were performed according to institutional protocols.

Cardiac troponin test

The VITROS® high-sensitivity troponin I assay (Ortho Clinical Diagnostics) was used for measurements of cardiac troponin I, with a 99th percentile value of 0.034 ng/mL, diagnostic cut off point of 0.12 ng/mL for AMI, sensitivity of 95% and specificity of 93% (Figure 1). The CV of the kit at the 99th percentile was <10%, according to current recommendations.[20-22] Blood collection was performed at admission to the emergency department and at the CCU.

Study design and statistical analysis

We used the mortality and AMI data described on a Masters thesis of a study conducted at the same CCU (available at: https://doi.org/10.11606/D.98.2020.tde-27122019-080250), and estimated a relative difference of 50% in the rate of events between the groups with negative and positive troponin. Using a power of 90% and alpha of 5%, we estimated a minimum sample size of 273 patients for the objectives of the study. Two-sided significance tests were used, with significance level at 0.05. Continuous variables were expressed as mean and standard deviation or median and interquartile range, according to normality of distributions, which was tested using the Shapiro-Wilk test. Between-group comparisons were assessed by the one-way ANOVA or by the non-parametric Kruskal-Wallis test. Categorical variables were expressed as frequency and percentages and compared by the chi-square test or Fisher exact test. Analysis of outcomes was conducted

		Hours Post Admission		
		0-6 hrs	6-12 hrs	12-24 hrs
VITROS Troponin I ES Assay (AMI cutoff = 0.120 ng/mL)	% sensitivity	70 (86/123)	89 (78/88)	90 (43/48)
	% Specificity	96 (683/711)	94 (420/447)	94 (206/220)

Figure 1 – *Specifications of the VITROS® high-sensitivity troponin I assay. Fonte:TropIES_GEM1309_WW_PT_I_10.pdf. Acessado em http://www.OrthoClinicalDiagnostics.com.*

according to the time to the first event since the onset of NSTE-ACS by the Kaplan-Meier method and the log-rank test for statistical significance between survival curves for the events (death, infarction, and composite endpoint). Statistical analysis was performed using the R system and the SPSS statistics, version 19.0.

Results

Patients' characteristics and clinical course

A total of 494 patients with diagnosis of NSTE-ACS were evaluated. Table 1 presents the results of the descriptive analysis of the groups. The group of patients with significant increase in troponin levels had a higher proportion of older people, longer duration of chest pain, higher GRACE and CRUSADE scores, lower creatinine clearance levels, lower LVEF, and higher rates of acute kidney injury during hospitalization (Table 1).

Comparison of management strategies, clinical outcomes, and revascularization according to troponin levels

A greater number of patients with significant increase in troponin levels underwent functional studies, invasive approach, and myocardial revascularization procedures. All patients were treated with benefit-proven medications recommended by guidelines (100% of patients received acetylsalicylic acid and statins) (Table 1).

Overall mortality was 3.4%, with no statistically significant difference between the groups, although the incidence of AMI (or reinfarction) was 2-4 times higher in the group with troponin elevation (Table 2). Kaplan–Meier plots depicting overall survival, AMI and composite endpoint are illustrated in Figures 2, 3 and 4, respectively.

Discussion

CAD is one of the main causes of death, especially in the context of ACS.[29,30] Despite therapeutic advances, morbidity and mortality of CAD in the early stages of disease and after hospital discharge are high, varying from 5-10% within 30 days to 20% in six months after the acute event.[31] In this context, guidelines have recommended the use of troponin as a biomarker for risk stratification.[32,33] Patients with increased troponin may have a 20% rate of AMI and death in 30 days, and a 25% rate in six months of follow-up.[34,35] However, differential diagnosis by increased troponin is crucial and should be analyzed together with clinical data and complementary tests.[28]

In the present study, we observed an association between mild elevations of troponin and higher rates of coronary angiography and revascularization procedures. This may be explained by the fact that these patients had higher risk scores, which increases the likelihood of referral for invasive procedures during hospitalization. Also, higher rates of AMI were found in patients with increased troponin. This is in agreement with previous studies showing that peak troponin values are associated with higher rates of adverse events.[10-13] It is worth mentioning the considerably higher number of cases of AMI among patients with troponin levels ≥0.12 ng/mL, even as compared with those with troponin > 0.034 ng/mL.

Regarding mortality rates, although we have not detected statistically significant difference, a higher number of deaths was found among patients with elevated troponin, corroborating other studies that showed a relationship between peak troponin values and mortality in ACS.[10] These data may be explained by some factors. First, despite the higher risk of death estimated by higher GRACE score, troponin elevation, severity of CAD, and lower LVEF, most patients of the three groups were referred for invasive risk stratification. Therefore, there was not a linear association between increased risk and elevated troponin, although a larger number of patients with a marked increase in troponin levels underwent revascularization. Combined with the use of medications with proven benefits in reducing ischemic events and death, this "more invasive" approach, based not only on significant elevations but also on mild elevations in troponin levels, may have mitigated the occurrence of composite events that would be expected due to high risk score at admission. Therefore, the invasive strategy was important to reduce cardiovascular events despite increased initial risk. This is clearly corroborated by the reduction in GRACE score from hospital admission to discharge.

Another important finding is the association between the two groups of patients with elevated troponin in comparison with patients with normal levels regarding myocardial revascularization. Higher troponin levels were associated with multiple stent implantation and higher number of surgically treated vessels, which reinforces the biological plausibility linking increased troponin levels with complexity of coronary anatomy.[8,9]

On the other hand, although the universal definition of AMI recommends the use of the 99th percentile for the

Table 1 – Clinical characteristics, diagnostic tests and clinical events of the study population divided into three groups by troponin levels

Variable	Troponin			p-value
	< 0.034 ng/mL	0.034-0.12 ng/mL	> 0.12 ng/mL	
Population	122 (24.6%)	63 (12.7%)	309 (62.4%)	-
Male sex	81 (66.4%)	47 (74.6%)	215 (69.6%)	0.47
Age	63.5 (55-70)	64 (59-71)	66 (59-74)	0.003
Weight	78.5 (69-87.1)	78 (68-87)	75 (66-85)	0.19
Duration of symptoms	60 (10-292)	80 (15-741)	134 (30-489)	0.019
GRACE at admission	99 (83-111)	102 (86-122)	120 (103-140)	<0.001
GRACE at discharge	84 (70-97)	85 (70-108)	103 (88-120)	<0.001
CRUSADE	26 (19-34)	24 (19-35)	29 (19-40)	0.033
Creat. Clear. (mL/min)	77.5 (69-87)	77 (62-91)	72 (58-87)	0.024
LVEF	59 (50-62)	56 (45-63)	55 (41-60)	0.006
Clinical history				
Ischemic stroke	2 (1.6%)	0	4 (1.3%)	0.42
Hemorrhagic stroke	1 (0.8%)	0	0	0.42
CABG	14 (11.4%)	9 (14.2%)	66 (21.3%)	0.03
Dyslipidemia	84 (68.8%)	49 (77.7%)	194 (62.7%)	0.05
PAD	3 (2.4%)	4 (6.3%)	20 (6.5%)	0.20
Hypertension	97 (79.5%)	55 (87.3%)	258 (83.5%)	0.33
CRF	11 (9%)	12 (19%)	69 (22.3%)	<0.01
AMI	60 (49.2%)	28 (44.4%)	172 (55.7%)	0.16
HF	14 (11.4%)	10 (15.8%)	45 (14.6%)	0.61
PCI	43 (35.2%)	20 (31.7%)	103 (33.3%)	0.91
Obesity	35 (28.6%)	15 (23.8%)	75 (24.3%)	0.65
DM	63 (51.6%)	22 (34.9%)	142 (46%)	0.10
Smoker	19 (15.5%)	14 (22.2%)	53 (17.2%)	0.71
Former smoker	44 (36%)	24 (38.1%)	119 (38.5%)	0.71
Physical activity	16 (13.1%)	4 (6.3%)	29 (9.4%)	0.34
Previous medications				
ASA	96 (78.7%)	51 (80.9%)	218 (70.6%)	0.10
Clopidogrel	38 (31.1%)	12 (19%)	89 (28.8%)	0.20
Amiodarone	1 (0.8%)	4 (6.3%)	7 (2.3%)	0.07
CCB	31 (25.4%)	15 (23.8%)	76 (24.6%)	0.98
ARB	50 (40.9%)	28 (44.5%)	109 (35.3%)	0.29
Oral BB	80 (65.5%)	40 (63.5%)	208 (67.3%)	0.77
Diuretics	39 (31.9%)	26 (41.3%)	112 (36.2%)	0.40
Statin	92 (75.4%)	48 (76.2%)	218 (70.6%)	0.55
ACEi	33 (27%)	18 (28.6%)	111 (35.9%)	0.14
Nitrates	44 (36%)	17 (27%)	101 (32.7%)	0.49
Warfarin	1 (0.8%)	1 (1.6%)	10 (3.2%)	0.36
OADs	53 (43.4%)	16 (25.4%)	120 (38.8%)	0.05
Insulin	22 (18%)	6 (9.5%)	49 (15.9%)	0.33
Medications during hospitalization				
ASA	122 (100%)	63 (100%)	309 (100%)	0.37
Clopidogrel	94 (77%)	50 (79.4%)	272 (88%)	<0.01

ACEi	61 (50%)	28 (44.4%)	177 (57.3%)	0.09
ARB	49 (40.1%)	24 (38.1%)	89 (28.8%)	0.05
Oral BB	112 (91.8%)	55 (87.3%)	290 (93.9%)	0.15
Statin	122 (100%)	63 (100%)	309 (100%)	0.19
Killip class				**0.08**
I	117 (95.9%)	60 (95.2%)	265 (85.7%)	
II	5 (4.1%)	2 (3.2%)	32 (10.3%)	
III	0	0	5 (1.6%)	
IV	1 (0.8%)	1 (1.6%)	6 (1.9%)	
Diagnostic tests				
Cardiac MRI	4 (3.2%)	2 (3.2%)	7 (2.3%)	0.70
CCTA	2 (1.6%)	2 (3.2%)	3 (1%)	0.25
Echocardiography	102 (83.6%)	51 (81%)	262 (84.8%)	0.61
Complications				
Second degree-AVB	0	1 (1.6%)	2 (0.6%)	0.46
Pacemaker	0	2 (3.2%)	4 (1.3%)	0.14
IAB	2 (1.6%)	1 (1.6%)	4 (1.3%)	1.0
Cardiogenic shock	2 (1.6%)	2 (3.2%)	10 (3.2%)	0.71
AKI	9 (7.4%)	6 (9.5%)	52 (16.8%)	0.01
Hemodialysis	1 (0.8%)	2 (3.2%)	4 (7.5%)	0.10
APE	1 (0.8%)	0	8 (2.6%)	0.40
AF	6 (4.9%)	3 (4.7%)	20 (6.8%)	0.82
CRA	3 (2.4%)	1 (1.6%)	14 (4.5%)	0.51
Second surgical approach	0	0	2 (0.6%)	1.0
Sepsis	2 (1.6%)	3 (4.7%)	18 (5.8%)	0.18
SVT	1 (0.8%)	1 (1.6%)	7 (2.3%)	0.78
VF	3 (2.4%)	1 (1.6%)	4 (1.3%)	0.66
Punction-site bleeding	7 (5.7%)	7 (11.2%)	40 (13%)	0.08

GRACE: Global Registry of Acute Coronary Events; CC: creatinine clearance; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; PAD: peripheral arterial disease; CRF: chronic renal failure; AMI: acute myocardial infarction; HF: heart failure; PCI: percutaneous coronary intervention; DM: diabetes mellitus; ASA: acetylsalicylic acid; CCB: calcium channel blockers; ARB: angiotensin II receptor blocker; BB: beta-blocker; ACEI: angiotensin converting enzyme inhibitors; OAD: oral antidiabetics; MRI: magnetic resonance imaging; CCTA: coronary computed tomography angiography; AVB: atrioventricular block; IAB: intra-aortic balloon; AKI: acute kidney injury; APE: acute pulmonary edema; AF: atrial fibrillation; CRA: cardiorespiratory arrest; SVT: sustained ventricular tachycardia; VF: ventricular fibrillation.

diagnosis of AMI, its widespread implementation is still hampered by between-kit variability and variation of troponin I reference values between hospitals, which may influence the comparability between clinical trials and standardization of protocols.[25]

In the comparison between the groups, although the number of patients who underwent coronary angiography was not different, the proportion of patients was significantly higher in those with greater elevation of troponin (86% vs 92% vs 96%, respectively; $p<0.01$). As we pointed out, the high proportion of anatomic diagnosis made by angiography may have influenced the decision to perform percutaneous or surgical myocardial revascularization, even in patients with mild increase of troponin, with no statistical difference regarding mortality, despite numerical difference in survival.

This study emphasizes the importance of using the diagnostic criteria of AMI proposed by the universal definition of AMI, particularly with respect to three aspects – prediction of major cardiovascular outcomes, indication of invasive strategy, and performance of myocardial revascularization procedures in the comparison of groups of patients with different troponin levels.

The rationale of the analysis of troponin cutoff points is the high variability of the diagnostic value between the hospitals, with nearly 30% of hospital laboratories following the recommendations by the universal definition of AMI.[14]

In the present study, we did not evaluate the use of high-sensitivity troponin since our objective was not to analyze the usefulness of this biomarker in rule-in or rule-out protocols for AMI in the emergency room in cases of chest pain, in patients

Table 2 – Comparison of risk stratification, revascularization procedures and clinical outcomes between the groups of patients by troponin levels

Variables	Troponin			p-value
	< 0.034	0.034-0.12	> 0.12	
Population	122 (24.6%)	63 (12.7%)	309 (62.4%)	-
Myocardial scintigraphy	27 (22.1%)	8 (12.7%)	8 (2.6%)	< 0.01
Coronary angiography	105 (86%)	58 (92.1%)	298 (96.4%)	< 0.01
PCI	35 (28.7%)	29 (46%)	180 (58.3%)	< 0.01
CABG	36 (29.5%)	20 (31.7%)	54 (17.5%)	< 0.01
Number of coronary grafts:				< 0.01
1	0	0	3 (1%)	
2	10 (8.2%)	6 (9.5%)	18 (5.8%)	
3	21 (17.2%)	14 (22.3%)	25 (8.1%)	
4	8 (6.5%)	0	8 (2.6%)	
Number of stents:				
1 stent	25 (20.5%)	25 (39.7%)	118 (38.1%)	0.06
> 1 stent	10 (8.2%)	4 (6.3%)	61 (19.7%)	0.07
Death	3 (2.4%)	2 (3.2%)	12 (3.9%)	0.87
AMI (or reinfarction)	7 (5.7%)	3 (4.8%)	50 (16.2%)	<0.01

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; AMI: acute myocardial infarction

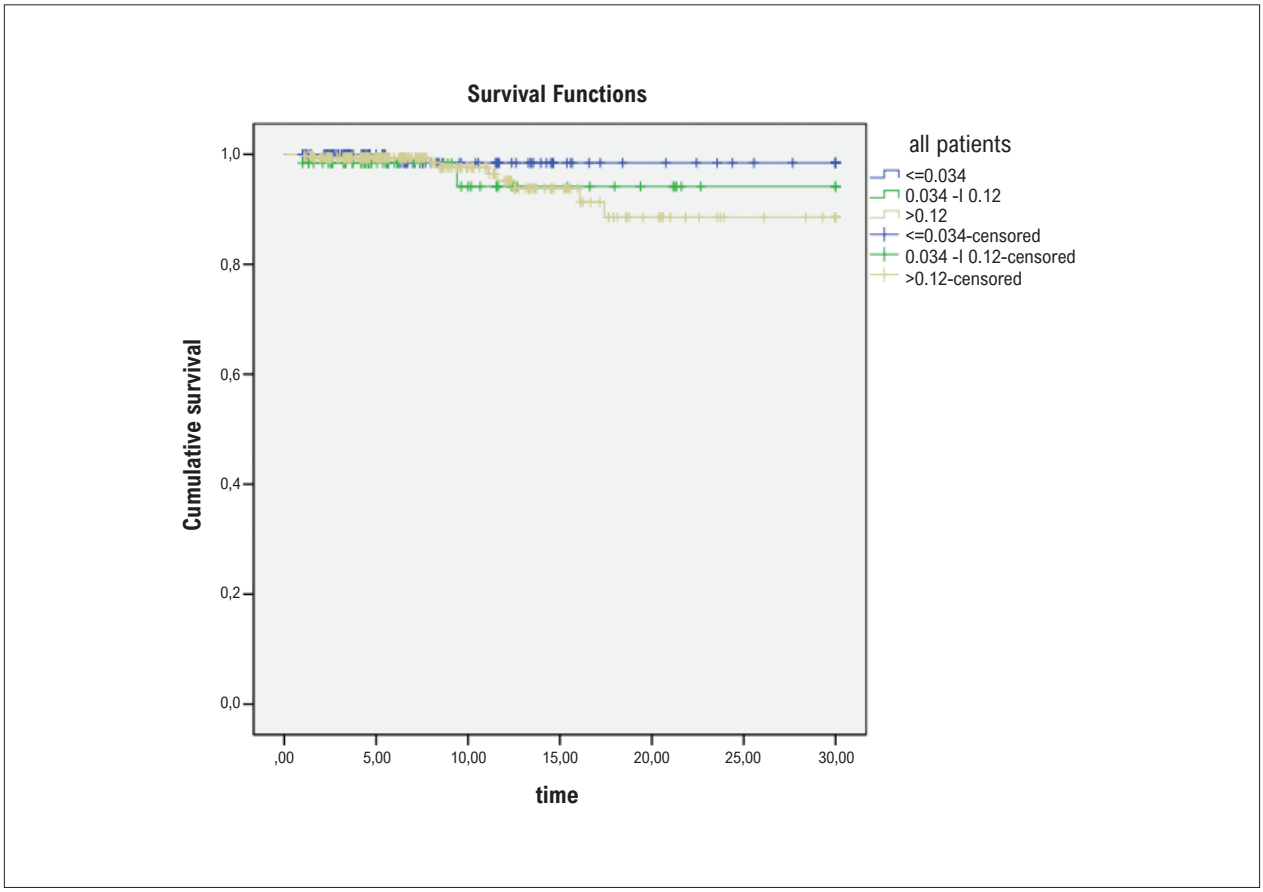


Figure 2 – *Kaplan Meier curves illustrating event-free survival after acute myocardial infarction (or reinfarction) by troponin range groups (log-rank test, p=0.002).*

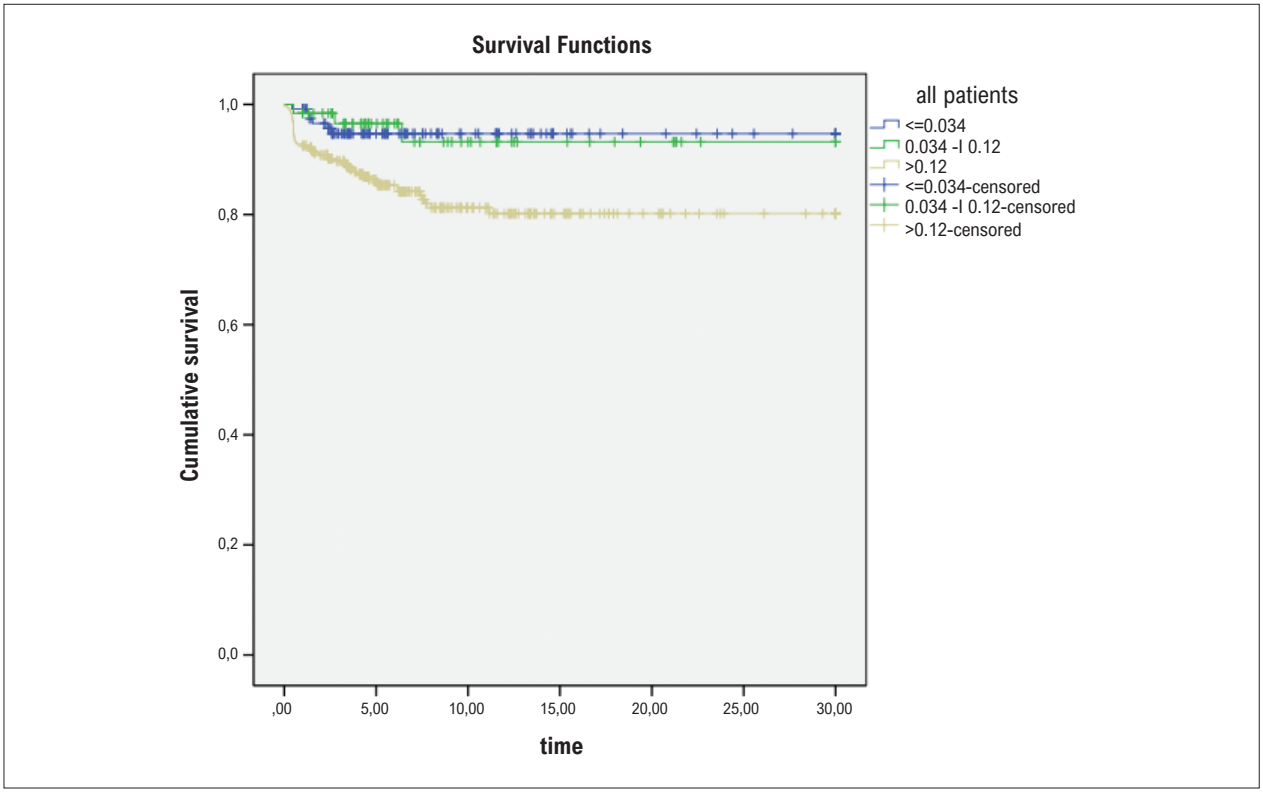


Figure 3 – *Kaplan Meier curves illustrating event-free survival after acute myocardial infarction (or reinfarction) by troponin range groups (log-rank test, p=0.002).*

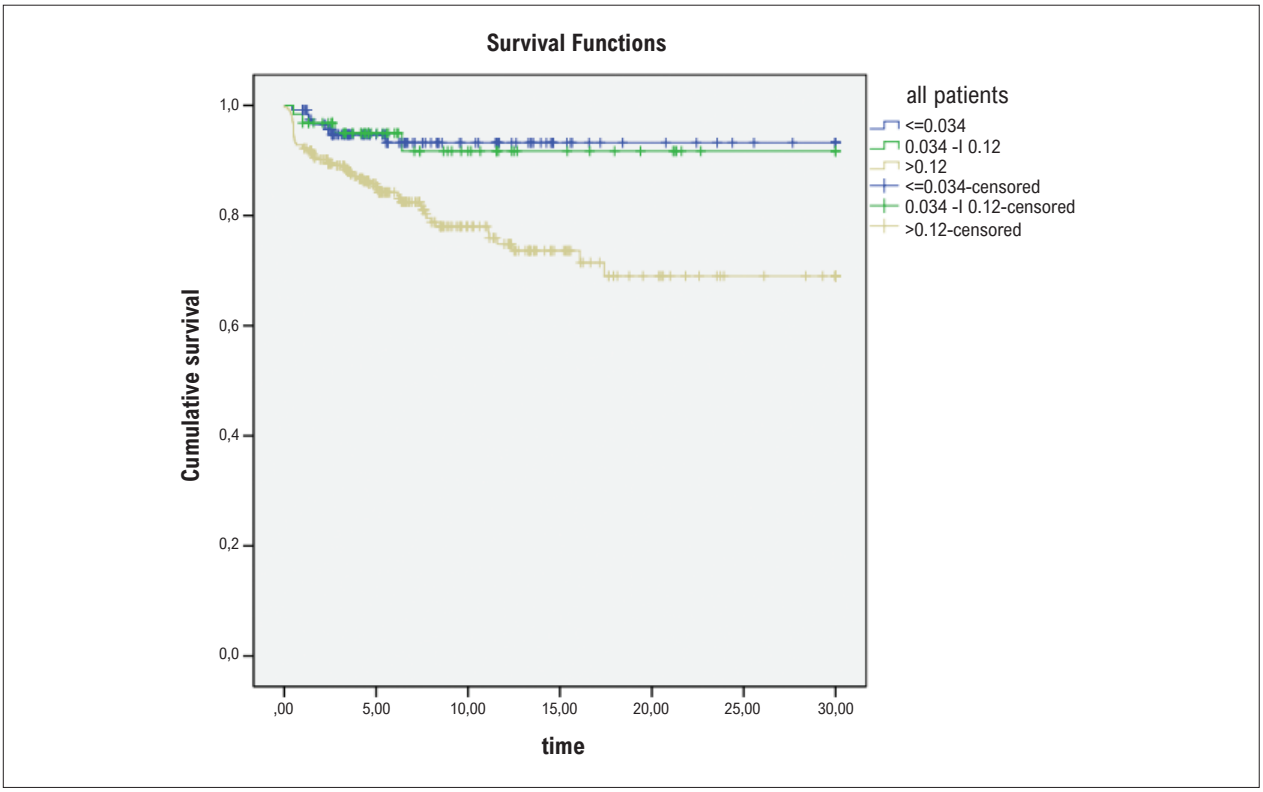


Figure 4 – *Kaplan-Meier curves of composite endpoint (death or acute myocardial infarction/reinfarction) by troponin range groups (log-rank test p<0.001).*

with very early presentation. However, we did analyze the prognostic role and the possible influence of troponin cutoff values on the decision making in the management of NSTE-ACS in intensive care unit as well as the potential effect of attenuating the early risk (estimated by scores), even in patients without troponin elevation, as compared with patients with slight elevation, by an "aggressive" invasive risk stratification and appropriate revascularization. Indeed, our data reinforce the use of the 99th percentile concentration of cardiac troponin proposed by the universal definition of AMI, avoiding unnecessary dismissal of patients without troponin elevations compatible with AMI when adopting a more accurate cutoff instead of the 99th percentile.

Limitations

The number of events observed may have reduced the statistical power to detect significant differences in terms of mortality. However, the high rate of coronary angiography, even among patients with no or minimal elevation of troponin, and subsequent early coronary revascularization may have reduced the estimated acute risk. Therefore, the hypothesis of a difference in mortality cannot be excluded, as this was not a random situation. Second, our data derived from a single center and reflected the reality of a research and education institution, with historical experience, and where invasive and non-invasive tests, indicators of performance such as drug prescription, coronary stent implantation (100% drug-eluting stents) with use of the left internal thoracic artery are highly available, and a large volume of percutaneous intervention and surgical revascularization has been performed. These factors could probably explain the low number of deaths and AMI even after highly complex invasive procedures, which may not be applied to other centers with different characteristics and infrastructures. Also, these aspects may have influenced the indication for coronary angiography in the majority of patients, without an isolated and linear association with troponin levels, and not necessarily dependent on more elevated risk scores. Thus, the association of troponin with outcomes, risk stratification and indication of revascularization may be different in institutions where hemodynamic laboratories and cardiac surgery are not available. Considering the scope of the study, the high variability of troponin I kits may influence local decisions and produce divergent results. Finally, due to the exploratory nature of observational studies, variability inherent to the selection of patients, and unmeasured confounding factors, we emphasize that the results and conclusions obtained in this study should be considered just an indication and be used as a support to their applicability in Brazilian populations.

Conclusions

Cardiac troponin values above the 99th percentile, proposed by the universal definition of AMI, or above the most accurate diagnostic cut-off point for AMI, defined by specific kit, have prognostic value in terms of the occurrence of composite endpoint of death and AMI within 30 days after NSTE-ACS. More importantly, mild elevations of troponin add useful information to the clinical diagnosis and risk scores in the decision-making process, by identifying those patients who would most benefit from invasive risk stratification and coronary revascularization procedures, which could explain the attenuation of early mortality risk associated with the increase in this biomarker.

Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Tapias Filho AH, Oliveira G; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Tapias Filho AH, Oliveira G, Ramos RF; Statistical analysis: França JID.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the Masters thesis submitted by Antonio Haddad Tapias Filho, from Universidade de São Paulo and Instituto Dante Pazzanese de Cardiologia.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Dante Pazzanese de Cardiologia under the protocol number 3287541. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Schmidt MI, Duncan BB, Silva GA, Menezes AM, Monteiro CA, Barreto SM, et al. Chronic Non-communicable Diseases in Brazil: Burden and Current Challenges. Lancet. 2011;377(9781):1949-61. doi: 10.1016/S0140-6736(11)60135-9.
2. World Health Organization. The World Health Report 2002: Reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.
3. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al. Variations in Common Diseases, Hospital Admissions, and Deaths in Middle-aged Adults in 21 Countries from Five Continents (PURE): A Prospective Cohort Study. Lancet. 2020;395(10226):785-94. doi: 10.1016/S0140-6736(19)32007-0.
4. Badertscher P, Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Sabti Z, et al. Effect of Acute Coronary Syndrome Probability on Diagnostic and Prognostic Performance of High-Sensitivity Cardiac Troponin. Clin Chem. 2018;64(3):515-25. doi: 10.1373/clinchem.2017.279513.
5. Morrow DA, Cannon CP, Rifai N, Frey MJ, Vicari R, Lakkis N, et al. Ability of Minor Elevations of Troponins I and T to Predict Benefit from an Early Invasive Strategy in Patients with Unstable Angina and non-ST Elevation Myocardial Infarction: Results from a Randomized Trial. JAMA. 2001;286(19):2405-12. doi: 10.1001/jama.286.19.2405.

6. Rao AC, Collinson PO, Canepa-Anson R, Joseph SP. Troponin T Measurement After Myocardial Infarction can Identify Left Ventricular Ejection of Less Than 40%. Heart. 1998;80(3):223-5. doi: 10.1136/hrt.80.3.223.

7. Sutton MJ, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, et al. Quantitative Two-dimensional Echocardiographic Measurements are Major Predictors of Adverse Cardiovascular Events After Acute Myocardial Infarction. The Protective Effects of Captopril. Circulation. 1994;89(1):68-75. doi: 10.1161/01.cir.89.1.68.

8. Frey N, Dietz A, Kurowski V, Giannitsis E, Tölg R, Wiegand U, et al. Angiographic Correlates of a Positive Troponin T Test in Patients with Unstable Angina. Crit Care Med. 2001;29(6):1130-6. doi: 10.1097/00003246-200106000-00006.

9. Jurlander B, Farhi ER, Banas JJ Jr, Keany CM, Balu D, Grande P, et al. Coronary Angiographic Findings and Troponin T in Patients with Unstable Angina Pectoris. Am J Cardiol. 2000;85(7):810-4. doi: 10.1016/s0002-9149(99)00872-3.

10. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes. N Engl J Med. 1996;335(18):1342-9. doi: 10.1056/NEJM199610313351802.

11. Chin CT, Wang TY, Li S, Wiviott SD, deLemos JA, Kontos MC, et al. Comparison of the Prognostic Value of Peak Creatine Kinase-MB and Troponin Levels among Patients with Acute Myocardial Infarction: A Report from the Acute Coronary Treatment and Intervention Outcomes Network Registry-get with the Guidelines. Clin Cardiol. 2012;35(7):424-9. doi: 10.1002/clc.21980.

12. Kontos MC, Shah R, Fritz LM, Anderson FP, Tatum JL, Ornato JP, et al. Implication of Different Cardiac Troponin I Levels for Clinical Outcomes and Prognosis of Acute Chest Pain Patients. J Am Coll Cardiol. 2004;43(6):958-65. doi: 10.1016/j.jacc.2003.10.036.

13. Diderholm E, Andrén B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, et al. The prognostic and therapeutic implications of increased troponin T levels and ST depression in unstable coronary artery disease: the FRISC II invasive troponin T electrocardiogram substudy. Am Heart J. 2002;143(5):760-7. doi: 10.1067/mhj.2002.121733.

14. Bagai A, Huang Z, Lokhnygina Y, Harrington RA, Armstrong PW, Strony J, et al. Magnitude of Troponin Elevation and Long-term Clinical Outcomes in Acute Coronary Syndrome Patients Treated with and without Revascularization. Circ Cardiovasc Interv. 2015;8(6):e002314. doi: 10.1161/CIRCINTERVENTIONS.115.002314.

15. Bhatt HA, Sanghani DR, Lee D, Julliard KN, Fernaine GA. Predictors of Peak Troponin Level in Acute Coronary Syndromes: Prior Aspirin Use and SYNTAX Score. Int J Angiol. 2016;25(1):54-63. doi: 10.1055/s-0035-1547396.

16. Castro LT, Santos IS, Goulart AC, Pereira ADC, Staniak HL, Bittencourt MS, et al. Elevated High-Sensitivity Troponin I in the Stabilized Phase after an Acute Coronary Syndrome Predicts All-Cause and Cardiovascular Mortality in a Highly Admixed Population: A 7-Year Cohort. Arq Bras Cardiol. 2019;112(3):230-7. doi: 10.5935/abc.20180268.

17. 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;344(25):1879-87. doi: 10.1056/NEJM200106213442501.

18. Fuchs S, Kornowski R, Mehran R, Satler LF, Pichard AD, Kent KM, et al. Cardiac Troponin I Levels and Clinical Outcomes in Patients with Acute Coronary Syndromes: The Potential Role of Early Percutaneous Revascularization. J Am Coll Cardiol. 1999;34(6):1704-10. doi: 10.1016/s0735-1097(99)00434-9.

19. Romano ER. Elaboração de um Escore de Risco para Síndrome Coronária Aguda em Hospital Terciário Privado [dissertation]. São Paulo: Instituto Dante Pazzanese de Cardiologia; 2013.

20. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical issues for biochemical markers of acute coronary syndromes. Circulation. 2007;115(13):352-5. doi: 10.1161/CIRCULATIONAHA.107.182881.

21. Apple FS. A New Season for Cardiac Troponin Assays: It's Time to Keep a Scorecard. Clin Chem. 2009;55(7):1303-6. doi: 10.1373/clinchem.2009.128363.

22. Apple FS, Parvin CA, Buechler KF, Christenson RH, Wu AH, Jaffe AS. Validation of the 99th Percentile Cutoff Independent of Assay Imprecision (CV) for Cardiac Troponin Monitoring for Ruling out Myocardial Infarction. Clin Chem. 2005;51(11):2198-200. doi: 10.1373/clinchem.2005.052886.

23. Agirbasli M. Universal Definition of MI: Above 99 Percentile of Upper Reference Limit (URL) for hs-cTn: Yes, but Which URL? Am J Emerg Med. 2019;37(3):510. doi: 10.1016/j.ajem.2018.12.052.

24. Sandoval Y, Apple FS. The Global Need to Define Normality: The 99th Percentile Value of Cardiac Troponin. Clin Chem. 2014;60(3):455-62. doi: 10.1373/clinchem.2013.211706.

25. Bagai A, Alexander KP, Berger JS, Senior R, Sajeev C, Pracon R, et al. Use of Troponin Assay 99th Percentile as the Decision Level for Myocardial Infarction Diagnosis. Am Heart J. 2017;190:135-9. doi: 10.1016/j.ahj.2017.04.016.

26. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J. Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care. Clin Chem. 2017;63(1):73-81. doi: 10.1373/clinchem.2016.255109.

27. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal Definition of Myocardial Infarction. Circulation. 2007;116(22):2634-53. doi: 10.1161/CIRCULATIONAHA.107.187397.

28. 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. doi: 10.1093/eurheartj/ehv320.

29. Bassan R, Pimenta L, Leães PE, Timerman A, Volschan A, Polanczyk C, et al. I Diretriz de Dor Torácica na Sala de Emergência. Arq. Bras. Cardiol. 2002;79(Suppl 2):1-22. doi: 10.1590/S0066-782X2002001700001.

30. Tabnet. DataSUS. Sistema de Informações Hospitalares do SUS (SIH/SUS). Brasília: Ministério da Saúde; c2022 [cited 2022 Feb 02]. Available from: http://tabnet.datasus.gov.br.2004.

31. Grech ED, Ramsdale DR. Acute Coronary Syndrome: Unstable Angina and non-ST Segment Elevation Myocardial Infarction. BMJ. 2003;326(7401):1259-61. doi: 10.1136/bmj.326.7401.1259.

32. 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;102(11):1216-20. doi: 10.1161/01.cir.102.11.1216.

33. 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;335(18):1333-41. doi: 10.1056/NEJM199610313351801.

34. Zimmerman J, Fromm R, Meyer D, Boudreaux A, Wun CC, Smalling R, et al. Diagnostic Marker Cooperative Study for the Diagnosis of Myocardial Infarction. Circulation. 1999;99(13):1671-7. doi: 10.1161/01.cir.99.13.1671.

35. Polanczyk CA, Lee TH, Cook EF, Walls R, Wybenga D, Printy-Klein G, et al. Cardiac Troponin I as a Predictor of Major Cardiac Events in Emergency Department Patients with Acute Chest Pain. J Am Coll Cardiol. 1998;32(1):8-14. doi: 10.1016/s0735-1097(98)00176-4.

Troponin – Use it wisely. And as Another Instrument in the Clinic

Ricardo Wang[1] *and Estevão Lanna Figueiredo*[1]

Instituto Orizonti Hospital das Clínicas da Universidade Federal e Minhas Gerais,[1] *Belo Horizonte, MG – Brazil*

Short Editorial related to the article: Universal Definition of Myocardial Infarction 99th Percentile versus Diagnostic Cut-off Value of Troponin I for Acute Coronary Syndromes

Acute myocardial infarction (AMI) and stable chronic coronary disease are the main causes of mortality in Brazil.[1] In 2019, it was responsible for more than 170,000 deaths in Brazil. Given its severity, the Cardiology made a great effort to constantly improve the tools for the correct diagnosis to avoid the release of patients with Acute Coronary Syndrome (ACS) and its clinical and legal consequences. They are considered pillars for the diagnosis and a good anamnesis with the characterization of the type of pain, electrocardiographic changes, and biomarkers (mainly troponin).

Biomarkers play an important role in recognizing ACS, and diagnostic algorithms have adapted as they evolve. At first, they were nonspecific markers (e.g., lactic dehydrogenase, oxacetic transaminase, total creatine phosphokinase – CK). Then they evolved to a slightly more specific marker (creatine phosphokinase MB portion) with its difficult criteria: e.g., total CK/MB). Finally, we have an extremely specific marker of myocardial injuries, such as troponin. The evolution of biomarkers has allowed the simplification of chest pain protocols and the reduction of inappropriate discharge of patients with ACS.[2] Due to troponin's high sensitivity and specificity, in the fourth consensus on the universal definition of myocardial infarction, it was concluded that to establish the clinical diagnosis, an elevation above the 99th percentile of this biomarker was associated with clinical evidence of myocardial infarction ischemia.[3] Given the low cutoff for troponin, there are doubts in this consensus regarding the clinical relevance.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Tapas-Filho et al.[4] compare the 99th percentile cutoff level versus the troponin manufacturer's label cutoff. They observed that the troponin values above the 99th percentile used by the 4th Universal Definition of Infarction were useful in prognosis; they could predict the composite outcome of death and reinfarction within 30 days. An additional observation is that minimally elevated troponin levels made it possible to stratify patients better and identify those most likely to benefit from early invasive strategy and coronary revascularization procedures.

Keywords

Myocardial Infarction; Biomarkers; Troponin; Mortality; Epidemiology; Myocardial Ischemia; Myocardial Revascularization; Acute Coronary Syndrome; Prognosis

Mailing Address: Ricardo Wang •
Rua José Patrocínio Pontes, 1355. Postal Code 30210-090, Belo Horizonte, MG – Brazil
E-mail: rwang@terra.com.br

DOI: https://doi.org/10.36660/abc.20220353

Despite supporting the recommendations, some issues are to be analyzed regarding the published work. First, it is a single-center registry with a limited sample (494 patients), among which patients with troponin between 0.034 and 0.12ng/dL were only 39. Second, we observed that the mortality of the groups is low (2.4% to 3.9%) in the registry, which can be explained by the low-risk population (GRACE SCORE: 102 (trop > 0.034-0.12ng/dL) x 120 (trop >0.12 ng/dL)). Another possible explanation for the low mortality mentioned by the authors is the high rate of invasive strategy and early coronary revascularization. Higher troponin levels had a higher incidence of reinfarction (16.2% versus 4.8%) and occurred mainly in the first 15 days. In the study, the causes of this increase were not clear. We can speculate: incomplete revascularization? Procedure-related infarction (type IV or V AMI)? These are issues to be carefully considered.

In addition to the limitation of the study sample size, another point of attention is the follow-up period. Compared with the SWEDEHEART registry (with more than 48,000 patients included) and the analysis of this subgroup (9,800 patients), followed for ten years, an increase in cardiovascular events was observed in this population in the order of 15.4%.[5] This fact reinforces the importance of small increases in troponin as a long-term prognostic marker.

If, on the one hand, lowering the cutoff point of biomarkers is a predictor of events, on the other hand, there is concern about reducing the specificity of the test, with an increase in the number of false positives,[6] which could lead to unnecessary procedures, and an increase, for example, coronary angiographies without coronary lesions (so-called "white catheters"), which can stigmatize the patient and expose them to complications related to care. In the Tapas-Filho[4] registry, we observed that in patients with lower troponin levels, 92% underwent coronary angiography, and the revascularization rate was > 75% (similar to the higher troponin group). We emphasize that, in general, 25% of patients could not have undergone invasive tests.

From our point of view, the time is now to look for markers that prevent patients from being unnecessarily submitted to the invasive strategy. To have the dimension of the numbers, if we consider approximately 110,000 revascularizations performed by the Unified Health System (SUS) in 2019,[1] we would be talking about approximately 35,000 patients undergoing coronary angiography unnecessarily per year! We have advanced a lot with these new "super" markers, we have improved our diagnosis and ability to predict events, but it is time to know the best way to use them in clinical practice and reduce unnecessary procedures.

References

1. Oliveira GMM, Brant LCC, Polanczyk CA, Malta AC, Biolo A, Nascimento BR, et al. Estatística cardiovascular – Brasil 2021. Arq Bras Cardiol. 2022;118:115-373. doi: 10.36660/abc.20211012.
2. Soeiro AM, Biselli B, Leal TCAT, Bossa AS, Serrano Jr CV, Jallad S, et al. Desempenho diagnóstico da angiotomografia computadorizada e da avaliação seriada de troponina cardíaca sensível em pacientes com dor torácica e risco intermediário para eventos cardiovasculares. Arq Bras Cardiol. 2022 Feb 07; S0066-782X2022005001216. Doi: 10.36660/abc.20210006.
3. 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. doi:10.1093/eurheartj/ey462.
4. Tapias-Filho AH, Oliveira G, França JÍD, Ramos RF. Troponina I por Percentil 99 da Definição Universal de Infarto do Miocárdio versus Ponto de Corte de Melhor Acurácia em Síndromes Coronárias Agudas. Arq Bras Cardiol. 2022; 118(6):1006-1015.
5. Eggers KM, Jernberg T, Lindahl B. Cardiac troponin elevation in patients without a specific diagnosis. J Am Coll Cardiol. 2019 Jan 8;73(1):1-9. doi: 10.1016/j.jacc.2018.09.082.
6. Januzzi J L, McCarthy C P. Trivializing an elevated troponin. J Am Coll Cardiol.2019;73(1):10-2. doi: 10.1016/j.jacc.2018.10.042

Achievement of LDL-Cholesterol Goals after Acute Myocardial Infarction: Real-World Data from the City of Curitiba Public Health System

André Bernardi,[1,2] Marcia Olandoski,[1] Lucas Olandoski Erbano,[1] Luiz Cesar Guarita-Souza,[1] Cristina Pellegrino Baena,[1] José Rocha Faria-Neto[1]

Faculdade de Medicina, Pontifícia Universidade Católica do Paraná,[1] Curitiba, PR – Brazil

Hospital Universitário Evangélico Mackenzie,[2] Curitiba, PR – Brazil

Abstract

Background: **Reduction of LDL-cholesterol (LDL-c) levels is the cornerstone in risk reduction, but many high-risk patients are not achieving the recommended lipid goals, even in high-income countries.**

Objective: **To evaluate whether patients seen in the city of Curitiba public health system are reaching LDL-c goals after an acute myocardial infarction (AMI).**

Methods: **This retrospective cohort explored the data of patients admitted with AMI between 2008 and 2015 in public hospitals from the city of Curitiba. In order to evaluate the attainment of the LDL-c target, we have used the last value registered in the database for each patient up to 2016. For those who had at least one LDL-c registered in the year before AMI, percentage of reduction was calculated. The level of significance adopted for statistical analysis was $p<0.05$.**

Results: **Of 7,066 patients admitted for AMI, 1,451 were followed up in an out-patient setting and had at least one evaluation of LDL-c. Mean age was 60.8±11.4 years and 35.8%, 35.2%, 21.5%, and 7.4% of patients had LDL-c levels ≥100, 70–99, 50–69 and <50 mg/dL, respectively. Of these, 377 patients also had at least one LDL-c evaluation before the AMI. Mean LDL-c concentrations were 128.0 and 92.2 mg/dL before and after AMI, with a mean reduction of 24.3% (35.7 mg/dL). LDL-c levels were reduced by more than 50% in only 18.3% of the cases.**

Conclusion: **In the city of Curitiba public health system patients, after myocardial infarction, are not achieving adequate LDL-c levels after AMI.**

Keywords: **Cardiovascular Diseases; Myocardial Infarction; Dyslipidemias; Secondary Prevention; Diabetes Mellitus; Choleterol LDL; Epidemiology; Prevention and Control; Risk Factors.**

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in Brazil and worldwide. Globally, it is estimated that there were 18 million deaths from CVDs in 2017, 85% of which were attributed to ischemic heart and cerebrovascular diseases.[1] According to the Cardiovascular Statistics – Brazil, approximately 388,268 people died from CVDs in this country.[2] Although the mortality rate for ischemic heart disease (IHD) remained stable in the 2000s,[3] current data have shown that age-standardized mortality rate from IHD has been decreasing in Brazil.[2]

High plasma low-density lipoprotein cholesterol (LDL-c) levels are closely correlated with increased cardiovascular risk, regardless of the age group.[4] Moreover, reduction in LDL-c is associated with reduced cardiovascular risk: a 39 mg/dL decrease is associated with an approximate 20% reduction in the risk of major cardiovascular events,[5] an effect that is similar between sexes.[6] In patients at high risk for cardiovascular events, especially those with established coronary disease, massive LDL-c reductions with higher doses of statins have shown better results than those for lower doses.[7,8] Similarly, additional reductions in LDL-c using additional therapies combined with statins in highest-risk patients at the optimized maximum doses are also associated with further reduction in new events.[9,10]

Although an optimal minimum LDL-c level at which there is no risk for CVDs has not been identified, the current consensuses and guidelines seek to establish lipid goals to guide individualized medical care.[11-13] These goals may be expressed as absolute LDL-c target values or as minimum percentages of LDL-c reduction. However, many high-risk patients are not achieving the recommended lipid goals,[14] even under lipid-lowering therapy.[15] This is a multifactorial problem requiring quantification in specific local contexts to ensure the local feasibility and effectiveness of the proposed solutions.[16] In Brazil, although health is considered a duty of the State, access to potent statins is limited in the Unified Health System (SUS), the Brazilian public health system that assists more than 70% of the population.[17]

Mailing Address: André Bernardi •
Rua Eduardo Sprada, 630. Postal Code 81.220-000, Curitiba, PR - Brazil
E-mail: bernardiandre@hotmail.com
Manuscript received April 13, 2021, revised manuscript August 18, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210328

Until now, a few real-world studies have been conducted in Brazil, showing that patients at cardiovascular risk are achieving the recommended lipid goals.[18,19] The objective of this study was to determine the percentage of patients in the public health system from the city of Curitiba, Brazil, who achieved the LDL-c goals after admission for acute myocardial infarction (AMI), including both the attainment of the target LDL-c level and the percentage of LDL-c reduction compared to the levels before AMI.

Method

This retrospective cohort study was conducted using the Municipal Health Secretariat of Curitiba (SMS) database containing all information on patients admitted to the city's public health system from the date of admission to the date of discharge. This study was approved by the SMS Research Ethics Committee (REC) and by the academic institution involved.

The patient cohort selected from the database included those of both sexes aged 18 and over, who were admitted to a local public hospital with primary diagnosis of AMI (code ICD-I21) between January 2008 and December 2015. The laboratory test results were obtained from a second database and patient IDs were thoroughly checked to avoid duplication and inconsistency. Duplicate cases and cases with inconsistencies were excluded. Patients without at least one LDL-c value recorded in the year following AMI were also excluded. A search was performed in the laboratory database to find those patients (among the included patients, i.e., those with at least one test after the AMI) who also had at least one LDL-c test in the year before the AMI to calculate the percentage reduction.

LDL-c evaluation

The last LDL-c value, based on the Friedewald formula, recorded in the database following AMI, i.e., the most distant from the date of the AMI, was obtained, except for patients with triglycerides over 400 mg/dL. The percentages of patients who achieved mean LDL-c levels <50, 50–69, 70–99, or ≥100 mg/dL were determined.

To determine the percentage reduction achieved, the database was searched for patients with at least one LDL-c test in the year before the AMI. In cases of patients with more than one test, the LDL-c value closest to the acute event was used. The LDL-c value closest to the AMI in the year before the event was compared to the last value obtained after the AMI. The percentages of patients who achieved LDL-c reductions of 50–100% or <50% or with <50% or 50–100% increases were also determined.

Statistical analysis

A descriptive statistical analysis of the data was carried out. The results were expressed as means and standard deviations (quantitative variables) or as frequencies and percentages (categorical variables). Paired Student's t-test was used to compare LDL-c before and after AMI. Data normality was analyzed by Kolmogorov-Smirnov test. Statistical significance was accepted for $p < 0.05$. Data were analyzed using IBM SPSS Statistics v.20.0. Armonk, NY: IBM Corp.

Results

Of 7,066 total patients admitted for AMI between January 2008 and December 2015, 61 were excluded due to at least one of the exclusion criteria (duplication or inconsistency in dates of admission). Of the 7,005 remaining cases, 5,554 were excluded for lack of LDL-c results after the AMI. Therefore, the level of LDL-c after the AMI event was evaluated in 1,451 cases (Figure 1). Of these, 377 patients also had at least one test in the year before the AMI, which allowed calculation of the percentage variation.

The mean age of the 1,451 patients was 60.8±11.4. Table 1 shows the mean and the standard deviation (SD) of LDL-c among the 1,451 cases after the AMI event. The mean time

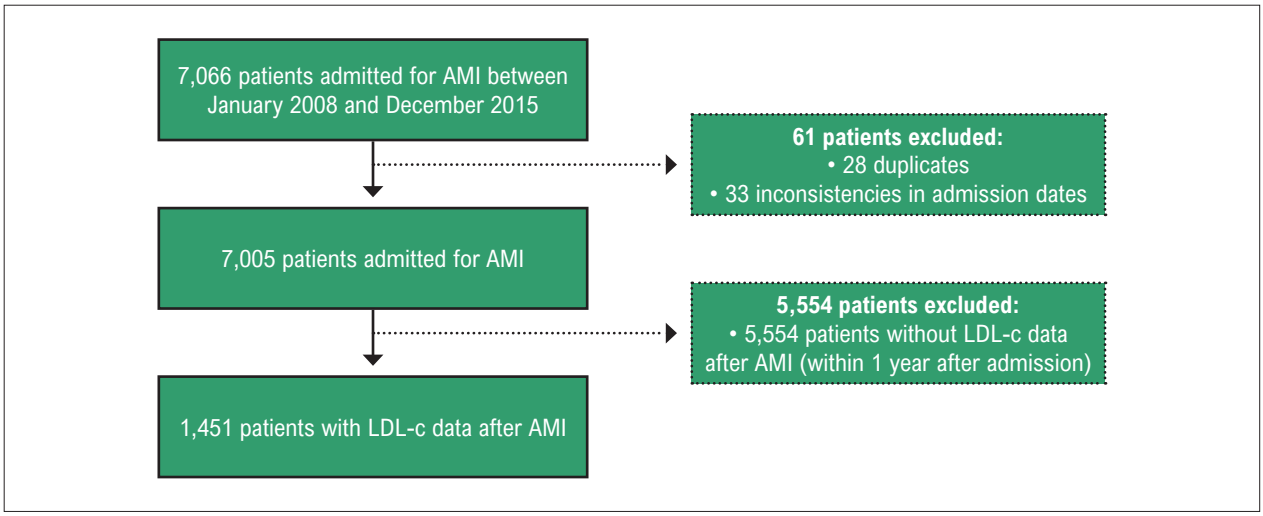


Figure 1 – *Flowchart of study sample characteristics. AMI: Acute myocardial infarction; LDL-c: Low-density lipoprotein cholesterol.*

Table 1 – Mean and standard deviation of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol and triglycerides among the 1,451 cases after acute myocardial infarction

	Mean	SD
LDL-c (mg/dL)	93.3	34.2
HDL-c (mg/dL)	42.9	11.6
Total cholesterol (mg/dL)	168.1	39.8

LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; SD: standard deviation.

to the last LDL-c test performed after the AMI was 32.7 months. Figure 2 shows the patients' percentages of LDL-c levels. Thus, only 28.9% of the patients had LDL-c levels <70 mg/dL after AMI.

LDL-c values after AMI, among the 377 patients with LDL-c data in the year before the AMI and at least one LDL-c test after the event, were as follows: in the same range as before (40.3%), in a lower range than before (53.3%), and in a higher range than before (6.4%) (Table 2). The mean time between the LDL-c tests before and closest to the AMI and the event itself was 4.8 months. The mean LDL-c concentrations (Figure 3) were 128.0 and 92.2 mg/dL before and after AMI, respectively (Table 3). Figure 4 shows that 19.3% of patients had a more than 50% reduction in LDL-c levels after AMI. Additionally, approximately 82% of the patients achieved some degree of LDL-c reduction (Figure 4).

Discussion

Despite the effectiveness of lipid reduction on the reduction of cardiovascular events, many high-risk patients are not achieving the recommended lipid goal. This novel study conducted with data on AMI patients admitted to the public health system of Curitiba found that approximately 82% of the patients achieved some degree of LDL-c reduction, with only approximately 30% attaining mean levels <70 mg/dL and approximately 20% having a reduction >50% compared to the levels before AMI.

The results of this study are similar to those conducted in very different socioeconomic contexts. Recent data from 27 European countries showed that, among 8,261 coronary patients included in the EUROASPIRE V study, 80% were using statins and 71% had LDL-c concentrations ≥70 mg/dL.[15] In an older US study also evaluating patients after acute coronary syndrome (ACS) through assessment of lipid control in the first year after the event, only 31% of patients achieved the target LDL-c level <70 mg/dL.[20] The data obtained in this study are alarming because these are post-ACS patients, a population at very high risk for new cardiovascular events in the short- to medium-term. The GRACE Registry showed that approximately 10% of patients discharged after an ACS will suffer a non-fatal AMI or a cardiovascular-related death within six months.[21] A more recent subanalysis of patients with prior AMI included in the FOURIER study demonstrated that a more recent AMI presents a higher risk for a new cardiovascular event than a more distant AMI (more than two years) and these patients are precisely the ones who benefit from a more aggressive lipid reduction.[22]

The proposed goals for LDL-c levels were extrapolated from the results of studies with fixed doses of statins because the first study aiming at a specific LDL-c target of 25–50 mg/dL was only recently conducted.[23] Therefore, in 2013, the American Heart Association and the American College of Cardiology stopped recommending a specific LDL-c goal and proposed the treatment of high-risk patients with high doses of potent statins capable of reducing LDL-c by >50% based on the results of randomized intervention studies conducted in these populations.[24] A clinical study comparing strategies to reduce cardiovascular risk (level attained or percentage of reduction) to determine which is the most effective has not yet been performed, but an analysis of data on 13,937 patients from the three distinct studies on secondary prevention with statins suggests that a >50% reduction would reduce the risk incrementally, even in patients with LDL-c levels <70 mg/dL.[25]

In the present sample, more patients achieved LDL-c levels <70 mg/dL than those achieving a >50% reduction. This may be explained by the fact that the percentage of reduction is directly associated with the use of high-dose potent statins. Access to these medications within the Brazilian public health system is restricted and the unavailability of these medications in this system is a recognized barrier to their use.[26] Lower use of medications necessary for secondary prevention in lower-income countries has been reported. For instance, the PURE study reported 66.5% and 3.3% statin use for secondary prevention in high-and low-income countries, respectively.[27]

By the time this study was conducted, the 5th Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis[28] recommended LDL-c goals under 70 mg/dL for patients with high cardiovascular risk. Moreover, the recommendation to lower LDL-c by at least 50% appears only in the 2017 Brazilian guideline.[11] Current evidence indicates that the clinical benefit does not depend on the type of statin used but rather on the extent of LDL-c reduction. Most importantly, it is necessary to assess the patient's cardiovascular risk and initiate treatment aiming at adequate risk reduction. For very high-risk individuals, an LDL-c goal of <55 mg/dL and a reduction of ≥50% from baseline LDL-c should be achieved.[13]

The American Association of Clinical Endocrinologists and the American College of Endocrinology proposed an LDL-c goal of <55 mg/dL for a new category of risk

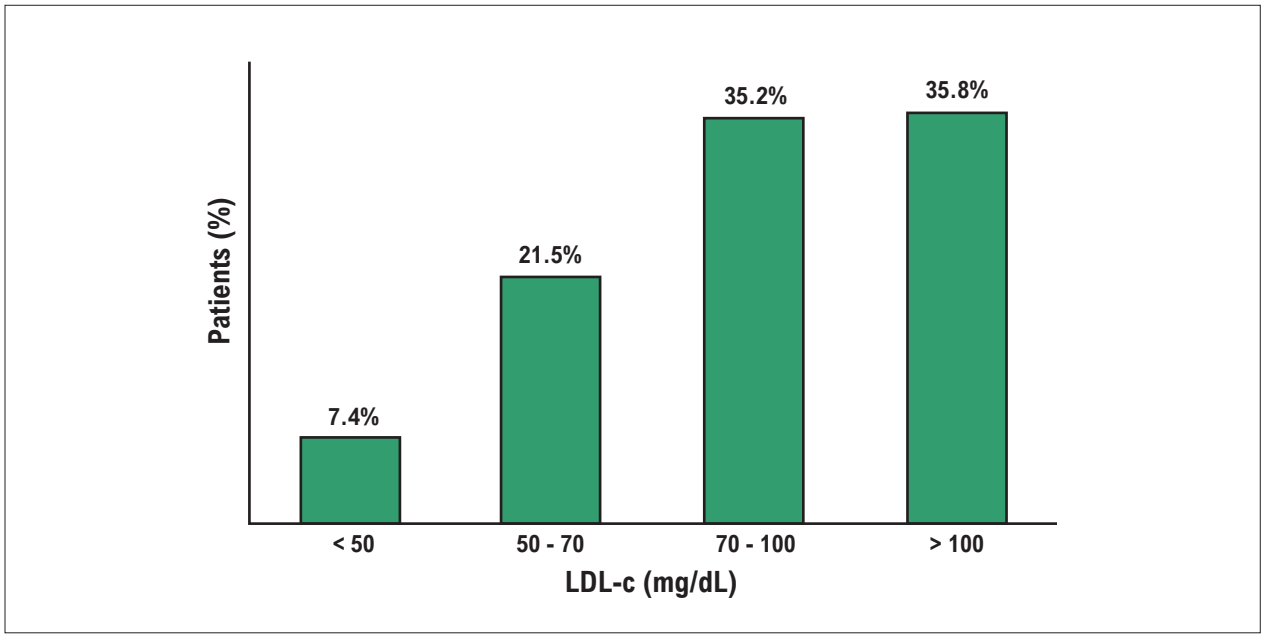


Figure 2 – *Distribution of low-density lipoprotein cholesterol (LDL-c) levels (n=1,451). LDL-c: Low-density lipoprotein cholesterol.*

Table 2 – Distribution of low-density lipoprotein cholesterol levels before and after acute myocardial infarction

LDL-c after AMI (mg/dL)	LDL-c before AMI (mg/dL)				Total
	<50	50–69	70–99	≥100	
<50	1	6	8	11	26
	0.3%	1.6%	2.1%	2.9%	
50–69	2	6	29	56	93
	0.5%	1.6%	7.7%	14.6%	
70–99	2	4	31	93	130
	0.5%	1.3%	8.2%	24.4%	
≥100	0	0	13	115	128
	0.0%	0.0%	3.7%	30.2%	
Total	6	17	82	272	377

LDL-c: Low-density lipoprotein cholesterol; AMI: acute myocardial infarction.

termed "extreme risk".[29] This category refers to patients with progressive atherosclerotic cardiovascular disease (ASCVD), including unstable angina persisting after an LDL-c of <70 mg/dL has been achieved, or clinically stable ASCVD with diabetes, stage 3 or 4 chronic kidney disease and/or heterozygous familial hypercholesterolemia, or patients with a history of premature ASCVD (<55 years of age for men or <65 years of age for women). In this study, only 7.4% of patients achieved levels lower than 50 mg/dL after AMI.

Whereas the American guidelines recommend lowering LDL-C levels by at least 50% of the baseline in coronary patients,[30] the European guidelines propose a target LDL-c of <55 mg/dL and at least a 50% reduction in LDL-c in patients with documented coronary artery disease (CAD).[13] The American and European guidelines recommend treatment with a combination of lipid-lowering drugs to achieve these goals. However, the American guideline agrees that the focus is LDL-c reduction, mainly based on a >50% reduction from the baseline value rather than on the attainment of specific LDL-c target levels. However, it is important to highlight that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe are reasonable in patients with AMI considered to be at very high risk and with LDL-c ≥ 70 mg/dL on maximally tolerated statins.

The results of the IMPROVE-IT study showed that significantly more patients with CAD treated with a combination of statin and ezetimibe achieved the LDL-c goals compared to statins alone.[31]

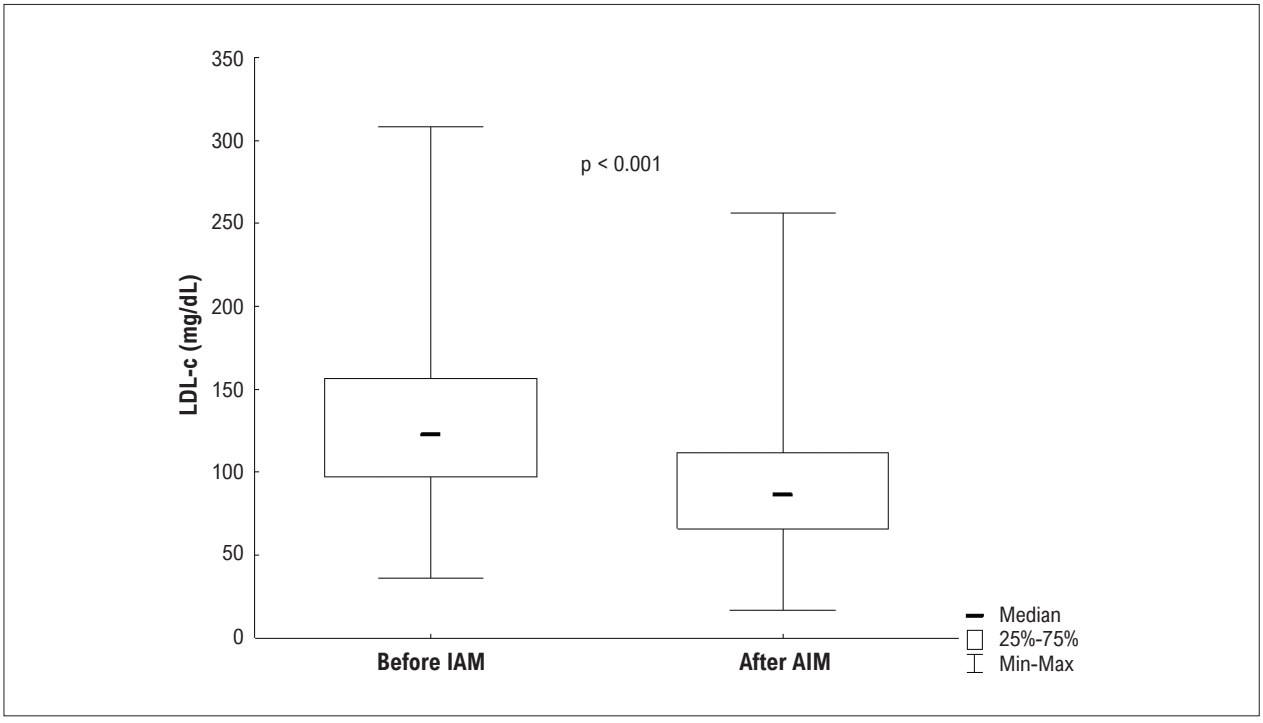


Figure 3 – *Box-plot for low-density lipoprotein before and after acute myocardial infarction. Student's t-test, p<0.05. AMI: acute myocardial infarction; LDL-c: Low-density lipoprotein cholesterol.*

Table 3 – Mean and decrease in low-density lipoprotein cholesterol before and after acute myocardial infarction among the 377 cases

Variable	Mean	SD	p*
Before AMI (mg/dL)	128.0	42.7	<0.001
After AMI (mg/dL)	92.2	36.9	
Decrease (absolute) (mg/dL)	35.7	40.1	
Decrease (relative) (%)	24.3%	28.4%	

**Paired Student's t test, p<0.05. AMI: acute myocardial infarction; SD: standard deviation.*

Study limitations

This analysis has several potential limitations. Only a minority of patients admitted for AMI in the public health system of Curitiba underwent a cholesterol test in the year after the AMI. Many patients that were treated for the event in Curitiba were likely not actually from the city. Therefore, the loss to outpatient follow-up was significant because these patients returned to their hometowns for medical follow-up and secondary prevention care or even discontinued follow-up care. No LDL-c data from patients who did not receive outpatient follow-up in the public health system of Curitiba were obtained. Nevertheless, the analysis cohort was representative of a real-world population of Curitiba with myocardial infarction that survived hospitalization. Lastly, the greatest limitation of this study was the absence of sociodemographic and medication details, either regarding the use (or not) of statins or the doses administered before and after AMI.

Conclusion

After AMI, a minority of cardiovascular high-risk patients achieved the recommended LDL-c goals in this cohort of patients admitted to the city of Curitiba public health system. The similarity between the results of this study and those from studies conducted in countries with very different socioeconomic conditions suggests that other factors, probably related to physicians and patients themselves, may be associated with this scenario.

Author Contributions

Conception and design of the research: Bernardi A, Erbano LO, Guarita-Souza LC, Baena CP, Faria-Neto JR; Acquisition of data: Bernardi A, Olandoski M, Erbano LO; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Bernardi A, Olandoski M, Guarita-Souza LC, Baena CP, Faria-Neto JR; Statistical

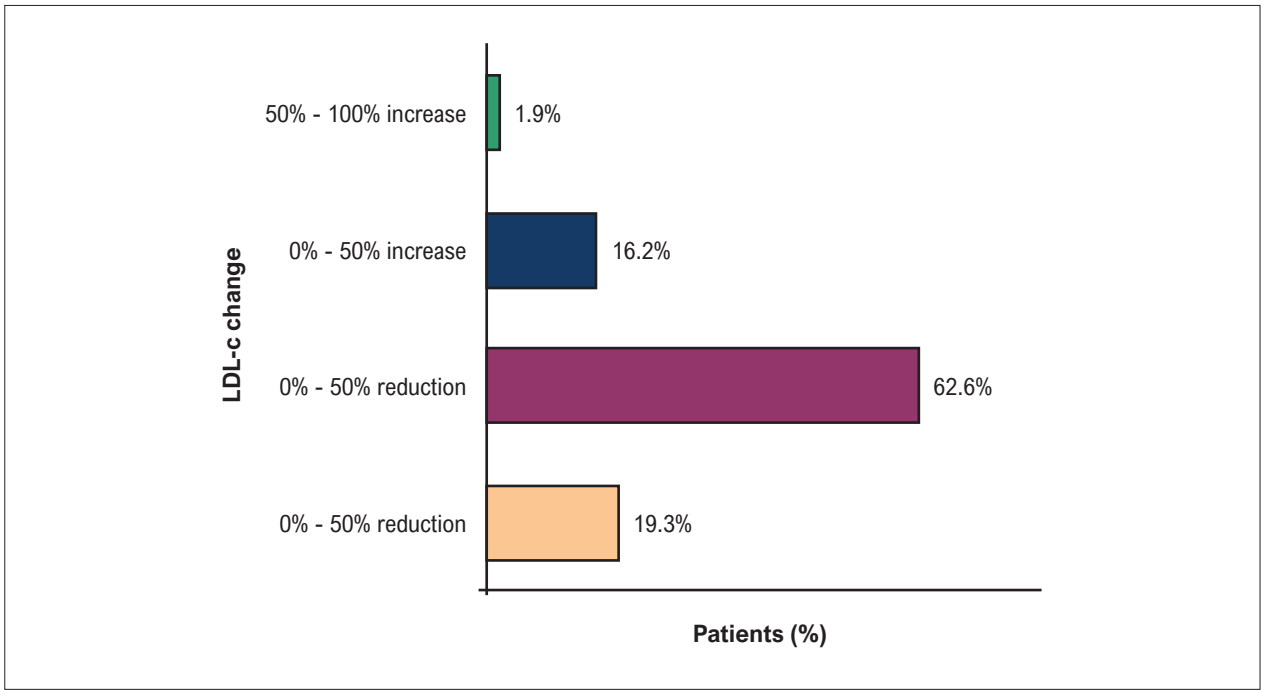


Figure 4 – *Distribution of patients according to the change in low-density lipoprotein cholesterol before and after acute myocardial infarction. LDL-c: Low-density lipoprotein cholesterol.*

analysis: Olandoski M, Erbano LO, Faria-Neto JR; Writing of the manuscript: Bernardi A, Faria-Neto JR.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by André Bernardi, from Universidade Católica do Paraná.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Secretaria Municipal de Saúde de Curitiba under the protocol number 1.647.450. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. 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: doi: 10.1016/S0140-6736(18)32203-7.
2. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. Arq Bras Cardiol. 2020 Sep;115(3):308-439. doi: 10.36660/abc.20200812.
3. Baena CP, Chowdhury R, Schio NA, Sabbag AE Jr, Guarita-Souza LS, Olandoski M, et al. Ischaemic heart disease deaths in Brazil: current trends, regional disparities and future projections. Heart 2013;99:1359-64. DOI: 10.1136/heartjnl-2013-303617
4. Clarke R, Sherliker P, Emberron J, Halsey I,Emberson J, Halsey J, et al. Prospective Studies C, Lewington S, Whitlock G, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370(9602):1829-39. doi: 10.1016/S0140-6736(07)61778-4.
5. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. 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(9753):1670-81. doi: 10.1016/S0140-6736(10)61350-5.
6. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;385:1397-405.
7. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al.et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med.2005;352(14):1425-35. doi: 10.1056/NEJMoa050461.
8. 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. New England Journal of Medicine 2004;350:(14)1495-504.
9. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(15):2387-97. doi: 10.1056/NEJMoa040583.

10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22. doi: 10.1056/NEJMoa1615664

11. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune A Neto, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017 Jul;109(2 Supl 1):1-76. doi: 10.5935/abc.20170121.

12. Lloyd-Jones DM, Morris PB, Ballantyne CM,Birtcher KK, Daly DD Jr, De Palma AS, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways . J Am Coll Cardiol.2017;70(14):1785-822.

13. Mach F, Baigent C, Catapano AL, Koskinas KC. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019;41(1):111-88. doi: 10.1093/eurheartj/ehz455.

14. Waters DD, Brotons C, Chiang CW, Ferrieres J, Foody J, Wouter J, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. Circulation 2009;120(1):28-34. 10.1161/CIRCULATIONAHA.108.838466

15. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019;26(8):824-35. doi: 10.1177/2047487318825350.

16. Murphy A, Faria-Neto JR, Al-Rasadi K, Blom D, Catapano A, Cuevas A, et al World Heart Federation Cholesterol Roadmap. Glob Heart. 2017;12(3):179-97 e5. doi: 10.1016/j.gheart.2017.03.002.

17. Massuda A, Hone T, Leles FAG, de Castro MC, Atun R. The Brazilian health system at crossroads: progress, crisis and resilience. BMJ Glob Health 2018;3(4):e000829. doi: 10.1136/bmjgh-2018-000829.

18. Waters DD, Brotons C, Chiang CW, Ferrières J, Foody J, Jukema JW, Santos RD,et al. Lipid Treatment Assessment Project 2 Investigators. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. Circulation. 2009 Jul 7;120(1):28-34. doi: 10.1161/CIRCULATIONAHA.108.838466.

19. Lotufo PA, Santos RD, Figueiredo RM, Pereira AC, Mill JG, Alvim SM, Fonseca MJ, Almeida MC, Molina MC, Chor D, Schmidt MI, Ribeiro AL, Duncan BB, Bensenor IM. Prevalence, awareness, treatment, and control of high low-density lipoprotein cholesterol in Brazil: Baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Clin Lipidol. 2016 May-Jun;10(3):568-76. doi: 10.1016/j.jacl.2015.12.029.

20. Melloni C, Shah BR, Ou FS, Roe MT, Smith SC Jr, Pollack CV Jr, et al. Lipid-lowering intensification and low-density lipoprotein cholesterol achievement from hospital admission to 1-year follow-up after an acute coronary syndrome event: results from the Medications Applied aNd SusTAINed Over Time (MAINTAIN) registry. Am Heart J 2010;160:1121-9, 9 e1. doi: 10.1016/j.ahj.2010.09.008.

21. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Vander Werf 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. doi: 10.1136/bmj.38985.646481.55.

22. Sabatine MS, De Ferrari GM, Giugliano RP,Huber K, Lewis BS, Ferreira J, et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: An Analysis from FOURIER. Circulation 2018;138(8):756-66. doi: 10.1161/CIRCULATIONAHA.118.034309.

23. Schwartz GG, Bessac L, Berdan LG,Bhatt DL, Bittner V, Diaz R, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J 2014;168(5):682-9. doi: 10.1016/j.ahj.2014.07.028.

24. Stone NJ, Robinson JG, Lichtenstein AH, Bairdy Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B):2889-934. doi: 10.1016/j.jacc.2013.11.002.

25. Bangalore S, Fayyad R, Kastelein JJ, Laskey R, Amarenco P, De Micco DA, et al. 2013 Cholesterol Guidelines Revisited: Percent LDL Cholesterol Reduction or Attained LDL Cholesterol Level or Both for Prognosis? Am J Med 2016;129(4):384-91. DOI: 10.1016/j.amjmed.2015.10.024

26. Banerjee A, Khandelwal S, Nambiar L, Saxena M, Peck V, Moniruzza M,et al. Health system barriers and facilitators to medication adherence for the secondary prevention of cardiovascular disease: a systematic review. Open Heart 2016;3(2):e000438. doi: 10.1136/openhrt-2016-000438.

27. Yusuf S, Islam S, Chow CK, Rangarajavan S, Dagemais G, Diaz R, et al. et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. The Lancet 2011;378(9798):1231-43. doi: 10.1016/S0140-6736(11)61215-4.

28. Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. et al. V Diretriz Brasileira de Dislipidemia e Prevenção da Aterosclerose. Arq Bras Cardiol. 2013 101(4 Supl1):1-22. DOI: 10.5935/abc.2013S010

29. Jellinger PS. American Association of Clinical Endocrinologists/American College of Endocrinology Management of Dyslipidemia and Prevention of Cardiovascular Disease Clinical Practice Guidelines. Diabetes Spectr 2018;31(3):234-45. doi: 10.2337/ds18-0009.

30. Grundy SM, Stone NJ, Bailey AL, Bam C, Birtcher KK, Blumenthall RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625

31. Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy AS, White JÁ, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation 2015;132(13):1224-33. doi: 10.1161/CIRCULATIONAHA.115.018381.

Achievement of LDL-cholesterol Targets: Why do We Fail, and How Can We Improve?

Fernando Cesena[1]

Cenocor,[1] *Guarulhos, SP – Brazil*

Short Editorial related to the article: Achievement of LDL-Cholesterol Goals after Acute Myocardial Infarction: Real-World Data from the City of Curitiba Public Health System.

Atherosclerotic cardiovascular disease (ASCVD) remains the first cause of death in the world, and Brazil.[1, 2] Individuals with previous ASCVD are at the highest risk of subsequent events, and guidelines recommend aggressive lowering of low-density lipoprotein cholesterol (LDL-c) levels to prevent bad outcomes.[3, 4]

However, several reports from around the world indicate a gap between guideline recommendations and clinical practice, and a large proportion of the population, especially in secondary prevention, lives with LDL-c levels above those considered reasonable to prevent events.[5-8] Indeed, lack of adherence to guideline-recommended therapies was independently associated with major cardiovascular events in a Brazilian population after acute coronary syndrome.[9]

In this context, Bernardi et al. report on LDL-c levels after myocardial infarction in the city of Curitiba-PR, Brazil. The authors retrospectively analyzed patients admitted for myocardial infarction in public hospitals between 2008 and 2015. Among 1451 patients evaluated 33 months on average after the event, only 29% and 7% had an LDL-c level <70 mg/dL and <50 mg/dL, respectively, while LDL-c was ≥100 mg/dL in 36% of the sample.[10]

This valuable information sheds light on an old debate: why is it so hard to achieve LDL-c targets, and how can we improve? The answer is nothing less than complex and should involve multiple parts.

Physicians may not know the guidelines, may not agree with them or may fear too low LDL-c levels. However, the best evidence from randomized clinical trials supports not only the efficacy but also the safety of aggressive LDL-c lowering in high-risk patients.[4] Some physicians are affected by clinical inertia. Others may feel that there is no substantial difference between keeping LDL-c <50, 70, or 100 mg/dL. It is worth remembering that preventive strategies' impact on absolute risk reduction increases with time, decreasing the number needed to treat (NNT) to prevent one event in the long-term perspective of ASCVD.

Keywords

Cardiovascular Diseases; Hypercholesterolemia; Anticholesteremic Agents; Practice Guideline; Quality of Health Care

Mailing Address: Fernando Cesena •
Cenocor. Rua Dr Ramos de Azevedo, 159, sala 1510. Postal Code 07012-020. Guarulhos, SP – Brazil
E-mail: cesenaf@gmail.com

DOI: https://doi.org/10.36660/abc.20220288

Conversely, patients may underestimate the risk and be unaware of LDL-c targets,[11] may overestimate the efficacy of non-pharmacological strategies and downplay the need for drug treatment, may not afford the medications, or be just non-adherent to them due to several reasons, including the development of muscle symptoms or exaggerated fear of adverse effects. However, it is widely accepted that the nocebo effect is highly prevalent, and a real statin intolerance is far less common than many can think.[4]

If the final goal is to implement evidence-based therapies successfully, continuing medical education and public campaigns are essential but not enough. Deeper, broader, and more impactful measures should be discussed. We need to take this issue more seriously.

Actions to valorize and rescue the scientific method as the core driver of medical decisions would be welcome, serving as a counterpoint to alternative practices and pseudoscience that have gained the sympathy of so many people, including medical doctors. Medical schools and health professionals have a fundamental role in this process.

It is imperative to correctly identify the barriers to guideline implementation, which may vary according to the region, setting (public versus private practice, primary versus specialized care), or socioeconomic conditions. The identified factors should be targets for quality improvement programs. In Brazil, there are good examples to follow, such as the Best Practice in Cardiology program adapted from the American Heart Association's Get With The Guidelines Program,[12] and quality improvement interventions tested in cluster randomized trials.[13, 14]

At the institutional level, establishing performance metrics and goals, independent audits, accreditation programs, and value-based payment models are proposals that can be debated to improve healthcare quality. At the physician level, periodic assessment of competence to practice Medicine should be considered.

Modern technologies need to be leveraged in the quest for improving healthcare quality. It is increasingly easier to identify at-risk patients who do not achieve LDL-c targets or do not have plasma lipids measured. Automatic alerts via mobile phones or e-mails encouraging such individuals to seek medical care may find a place in this context. Moreover, telemedicine allows integration between primary care and expert centers and may be useful for managing more complex cases.

At last, all the efforts mentioned above are worthless if the access to adequate pharmacological treatment remains restricted. In Brazil, most individuals depend on the public health system and have access only to the lowest-potent statins.[15] There is an urgent need to facilitate the availability of atorvastatin,

rosuvastatin, and ezetimibe, at least for those who need them to attain LDL-c targets.

In conclusion, guideline development is useless if the recommendations are not applied to the population. Implementing the best scientific evidence regarding LDL-c lowering in clinical practice is challenging. Medical and patient education are the pillars to succeed, but more comprehensive attitudes are needed. Different sectors of society, including health managers, policymakers, medical societies, and professional regulators, should take this responsibility.

References

1. Oliveira GMM, Brant LCC, Polanczyk CA, Malta DC, Biolo A, Nascimento BR, et al. Cardiovascular Statistics - Brazil 2021. Arq Bras Cardiol. 2022;118(1):115-373. doi: 10.36660/abc.20211012.
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
3. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune AN, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl 1):1-76. doi: 10.5935/abc.20170121.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e143. doi: 10.1161/CIR.0000000000000625.
5. Danchin N, Almahmeed W, Al-Rasadi K, Azuri J, Berrah A, Cuneo CA, et al. Achievement of low-density lipoprotein cholesterol goals in 18 countries outside Western Europe: The International ChoLesterol management Practice Study (ICLPS). Eur J Prev Cardiol. 2018;25(10):1087-94. doi: 10.1177/2047487318777079.
6. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. Eur J Prev Cardiol. 2021;28(11):1279-89. doi: 10.1093/eurjpc/zwaa047.
7. Cannon CP, de Lemos JA, Rosenson RS, Ballantyne CM, Liu Y, Gao Q, et al. Use of Lipid-Lowering Therapies Over 2 Years in GOULD, a Registry of Patients With Atherosclerotic Cardiovascular Disease in the US. JAMA Cardiol. 2021;6(9):1-9. doi: 10.1001/jamacardio.2021.1810.
8. Silva PGMB, Berwanger O, Precoma DB, Cavalcante MA, Vilela-Martin JF, Figueiredo EL, et al. Evaluation of 1-Year Follow-up of Patients Included in the Registry of Clinical Practice in Patients at High Cardiovascular Risk (REACT). Arq Bras Cardiol. 2021;116(1):108-16.
9. Silva P, Berwanger O, dos Santos ES, Sousa ACS, Cavalcante MA, de Andrade PB, et al. One year follow-up Assessment of Patients Included in the Brazilian Registry of Acute Coronary Syndromes (ACCEPT). Arq Bras Cardiol. 2020;114(6):995-1003. doi: 10.36660/abc.20190885.
10. Bernardi A, Olandoski M, Erbano LO, Guarita-Souza LC, Baena CP, Faria-Neto JR. Alcance das Metas de Colesterol LDL após Infarto Agudo do Miocárdio: Dados Reais do Sistema Público de Saúde da Cidade de Curitiba. Arq Bras Cardiol. 2022; 118(6):1018-1025.
11. Santos RD, Pereira C, Cesena F, Laurinavicius AG, Tabone V, Bittencourt MS. Cardiovascular Risk Misperception and Low Awareness of Familial Hypercholesterolemia in Individuals with Severe Hypercholesterolemia. Arq Bras Cardiol. 2021;116(4):706-12. doi: 10.36660/abc.20190516.
12. Taniguchi FP, Bernardez-Pereira S, Silva SA, Ribeiro ALP, Morgan L, Curtis AB, et al. Implementation of a Best Practice in Cardiology (BPC) Program Adapted from Get With The Guidelines® in Brazilian Public Hospitals: Study Design and Rationale. Arq Bras Cardiol. 2020;115(1):92-9. doi: 10.36660/abc.20190393. Epub 2020
13. Machline-Carrion MJ, Soares RM, Damiani LP, Campos VB, Sampaio B, Fonseca FH, et al. Effect of a Multifaceted Quality Improvement Intervention on the Prescription of Evidence-Based Treatment in Patients at High Cardiovascular Risk in Brazil: The BRIDGE Cardiovascular Prevention Cluster Randomized Clinical Trial. JAMA Cardiol. 2019;4(5):408-17. doi: 10.1001/jamacardio.2019.0649.
14. Berwanger O, Guimarães HP, Laranjeira LN, Cavalcanti AB, Kodama AA, Zazula AD, et al. Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. JAMA. 2012;307(19):2041-9. doi: 10.1001/jamacardio.2019.0649.
15. Schmidt A, Moreira HT, Volpe GJ, Foschini VB, Lascala TF, Romano MMD, et al. Statins Prescriptions and Lipid Levels in a Tertiary Public Hospital. Arq Bras Cardiol. 2021;116(4):736-41. doi: 10.36660/abc.20190513.

Burden of Cardiovascular Diseases Attributable to Risk Factors in Portuguese-Speaking Countries: Data from the "Global Burden of Disease 2019" Study

Bruno Ramos Nascimento,[1] Luisa Campos Caldeira Brant,[1] André Dias Nassar Naback,[1] Guilherme Augusto Veloso,[2] Carisi Anne Polanczyk,[3,4,5] Antonio Luiz Pinho Ribeiro,[1] Deborah Carvalho Malta,[6] Albano Vicente Lopes Ferreira,[7] Gláucia Maria Moraes de Oliveira[8]

Faculdade de Medicina e Hospital das Clínicas, Universidade Federal de Minas Gerais,[1] Belo Horizonte, MG – Brazil
Programa de Pós-Graduação em Estatística, Departamento de Estatística, Universidade Federal de Minas Gerais,[2] Belo Horizonte, MG – Brazil
Instituto Nacional de Avaliação de Tecnologias em Saúde, IATS/CNPq,[3] Porto Alegre, RS – Brazil
Faculdade de Medicina - Universidade Federal do Rio Grande do Sul,[4] Porto Alegre, RS – Brazil
Hospital Moinhos de Vento,[5] Porto Alegre, RS – Brazil
Escola de Enfermagem, Universidade Federal de Minas Gerais,[6] Belo Horizonte, MG – Brazil
Faculdade de Medicina, Universidade Katyavala Bwila,[7] Benguela – Angola
Universidade Federal do Rio de Janeiro,[8] Rio de Janeiro, RJ – Brazil

Abstract

Background: **The impact of risk factors (RF) on morbidity and mortality from cardiovascular disease (CVD) for most Portuguese-speaking countries (PSC) is little known.**

Objectives: **We aimed to analyze the morbidity and mortality from CVD attributable to RF and its variation, from 1990 to 2019, in PSC, based on estimates from the Global Burden of Disease (GBD) 2019 study.**

Methods: **We evaluated changes in cardiovascular RF, mortality rates and age-standardized disability-adjusted life years (DALYs) between 1990 and 2019. The correlation between percentage changes in mortality rates and the sociodemographic index (SDI) of each PSC was evaluated by the Spearman method. A p-value <0.05 was considered statistically significant.**

Results: **Elevated systolic blood pressure (SBP) was the main RF for mortality and DALYs for CVD for all PSC. Mortality from CVD showed a downward trend in 2019, more accentuated in Portugal (-66.6%, 95%CI -71.0 - -61.2) and in Brazil (-49.8%, 95%CI -52.5 - -47.1). There was a trend towards an inverse correlation between SDI and the percent change in mortality, which was significant for dietary risks (r=-0.70, p=0.036), high LDL cholesterol (r=-0.77, p=0.015) and high SBP (r=-0.74, p=0.023).**

Conclusions: **In addition to SBP, dietary and metabolic RF justified a greater variation in the burden of CVD correlated with SDI in the PSC, suggesting the need to adopt health policies adapted to the reality of each country, aiming to reduce their impact on population.**

Keywords: **Cardiovascular Disease; Risk Factors; Global Burden of Disease; Epidemiology; Community of Portuguese-Speaking Countries.**

Introduction

Cardiovascular diseases (CVDs) are the leading causes of death worldwide, although they are not yet the main cause in many low- and middle-income countries, where the epidemiological transition occurred later.[1] However, with the control of infectious and maternal and child diseases, in addition to the increase in life expectancy and urbanization, the importance of CVDs tends to grow even in these countries, requiring adaptation of health systems. Many of these countries already show an increase in the proportion of CVDs in the total number of all-cause deaths.[2,3]

In addition, CVDs have had a significant impact on morbidity, as an important cause of disability and, consequently, loss of healthy life-years.[2,4] In order to establish CVD control and prevention strategies, it is essential to determine the main cardiovascular risk factors (RF) and their prevalence. Hypertension and dietary factors continue to be the main RF for CVDs in the world.[4,5] However, in recent years, other factors have played a greater role in the development of CVDs, such as high body mass index (BMI), high fasting plasma glucose and LDL-cholesterol, alcohol use, and renal disease.[4]

Mailing Address: Bruno Ramos Nascimento •
Faculdade de Medicina da Universidade Federal de Minas Gerais - Hospital das Clínicas da Universidade Federal de Minas Gerais - Rua Muzambinho 710/802. Postal Code 30210-530, Serra, Belo Horizonte, MG - Brazil
E-mail: ramosnas@gmail.com
Manuscript received August 17, 2021, revised manuscript October 19, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210680

Portuguese-speaking countries (PSC) have been culturally influenced by Portugal in different levels, with the type of colonization and political-economic models being important determinants of heterogeneity among them.[6] Despite several sociocultural similarities, they are countries with different socioeconomic backgrounds, which has a direct impact on the pattern and temporal trends of the disease burden. Data presented in a study[3] of trends in morbidity and mortality from CVDs showed differences in the relative importance of CVD burden in these countries. However, the most relevant RF attributable to CVD (hypertension and dietary factors) are shared among most PSC.[4] A detailed analysis of these data may provide information exchange between the countries, regarding successful actions to fight CVD, especially related to the control of the main RF and reduction of their impact on cardiovascular morbidity and mortality.

The "*Global Burden of Disease Study*" (GBD) is an important observational epidemiological study that uses morbidity and mortality metrics related to the main diseases and risk factors at global, national, and regional levels. One of the GBD's objectives is to understand, through the assessment of trends, the changes in the profile of diseases that affect populations in the 21st century, and serve as a tool for decision-making in the development of health policies.[4,7] The aim of this study was to analyze the trends of cardiovascular RF and the burden of CVDs attributable to these RF from 1990 to 2019 in PSC, based on the estimates of the GBD 2019 study by the Institute of Health Metrics and Evaluation (IHME).[8]

Methods

Portuguese-speaking countries

PSC are those officially members of the Community of Portuguese Language Countries: Angola, Brazil, Cape Verde, Guinea-Bissau, Mozambique, Portugal and São Tomé and Príncipe, East Timor and Equatorial Guinea.[6] Equatorial Guinea, originally a Portuguese colony, has three official languages (Spanish, French and Portuguese), and is the most recent member of the Community, since 2014. Considering the Portuguese influence – with different magnitudes – on sociocultural characteristics, habits, health behaviors, and on the organization of health systems, contrasting with the heterogeneity in socioeconomic development, we considered relevant the study of cardiovascular RF in the group of PSC.

Attributable burden estimates and exposure to RF

GBD uses a hierarchical list of RF that are analyzed at four levels. Level 1 stratifies the RF into three groups: metabolic, behavioral and environmental RF. Level 1 FR are detailed at level 2, resulting in 20 FR. Levels 3 and 4 go further into the detail and, at total, the GBD study analyzed 87 RF in 2019.[4] In the current study, we analyzed 12 RF, as shown in Table 1. The choice for this group of RF was due to its more robust and well established epidemiological association in the literature, with the burden of disease and mortality from CVD, objects of this study.

Particularly for the estimates of Brazil, more than 200 data sources were included, from national surveys, such as the National Health Survey (*Pesquisa Nacional de Saúde*: PNS), the surveillance of risk and protection factors for chronic diseases by telephone survey (*Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico*: VIGITEL), the National Household Survey Sample (*Pesquisa Nacional por Amostra de Domicílios*), to the National School-based Health Survey and other cohort studies.[9-16] Different data sources were used according to the particularities of each PSC.[2,4]

To estimate the burden of disease attributable to RF, the GBD follows the comparative risk assessment (CRA) framework. In brief, CRA is processed through five steps: 1) estimation of the exposure level from available sources, such as household surveys, administrative data, censuses, vital records, and environmental measures. After identifying the data, different definitions are standardized, in addition to adjustments by gender and standardized age groups – a step called *Crosswalking*. Then, spatial-temporal smoothing analyses are performed to estimate data over time, age group and area and, finally, the 95% confidence interval for the estimates (95%CI) are calculated; 2) identification of risk-outcome pairs, according to available evidence; 3) calculation of relative risk (RR), identified in cohort studies, and synthesized by meta-analysis and meta-regression methods. The RRs used by the GBD are universal, the same for morbidity and mortality, and applied to men and women and to all countries and geographic regions; 4) estimation of the *Theoretical Minimum Risk Exposure Level* (TMREL), defined as the minimum exposure level to each FR that would result in the lowest possible probability of a clinical event be attributable to it. The TMREL is used to calculate the population attributable factor (PAF) for different causes of death, diseases or disabilities; 5) calculation of the population attributable fraction, defined as the proportion of the number of cases that can be independently attributed to a given exposure.[4,15]

According to the GBD 2019 study, the estimated TMREL for the RF evaluated in the present study are:1) Systolic blood pressure (SBP): 110 to 115 mmHg; 2) Fasting blood glucose: 85 to 99 mg/dL; 3) LDL cholesterol: between 27 and 50 mg/dL; 4) BMI: 20 to 25 kg/m^2 for adults; 5) renal function: albumin-to-creatinine ratio <30 mg/g or glomerular filtration rate >60 mL/min per 1.73 m^2 ; 6) ambient air pollution: 2.4 to 5.9 μg/m3; 7) tobacco: no exposure, including secondhand smoke; 8) dietary habits, including salt intake of 1 - 5 g and 200 to 400 g of fruits and vegetables daily, among others; 9) physical activity: 8,000 METs per day; 10) alcohol use: no consumption; 11) ideal temperature: 25.6ºC. In this study, the 12th group of other environmental risk factors was also considered, which do not include air pollution, ambient temperature and exposure to tobacco smoke.[4]

To estimate exposure to risk factors, the GBD uses the summary measure of risk exposure (summary exposure value, or SEV), which represents the risk-weighted prevalence. The scale for the SEV ranges from 0 to 100%, with 0% reflecting no exposure to risk and 100% indicating maximum exposure. A decline in SEV indicates reduced exposure and an increase in SEV means the opposite. The SEV is estimated for each age, sex, location and year. The detailed methodology for estimating the SEV has been previously published.[4,15,16]

Table 1 – Age-standardized mortality rates

Country	Risk Factor	Female			Male			Both		
		1990	2019	Percent Change %	1990	2019	Percent Change %	1990	2019	Percent Change %
Angola	All risk factors	287.8 (201.2 ; 369.9)	245.7 (200.3 ; 300.0)	-14.6 (-37.4 ; 21.5)	338.1 (257.8 ; 411.9)	274.3 (231.3 ; 327.8)	-18.9 (-37.2 ; 11.9)	314.4 (255.6 ; 375.7)	260.2 (219.5 ; 310.4)	-17.2 (-34.3 ; 6.1)
	Air pollution	94.2 (58.6 ; 133.9)	51.3 (36.5 ; 69.0)	-45.5 (-63.0 ; -16.2)	122.0 (91.7 ; 156.3)	66.0 (49.5 ; 85.3)	-45.9 (-60.8 ; -22.3)	108.4 (82.6 ; 140.8)	58.1 (43.1 ; 75.7)	-46.4 (-61.2 ; -27.3)
	Alcohol use	-0.1 (-4.3 ; 4.2)	8.7 (2.4 ; 16.4)	-11607.2 (-5407.9 ; 5127.9)	4.5 (-2.8 ; 13.0)	21.3 (12.4 ; 31.2)	367.8 (-3677.7 ; 4350.4)	2.2 (-2.5 ; 6.9)	14.1 (8.4 ; 21.3)	555.0 (-4697.5 ; 4693.6)
	Dietary risks	94.2 (59.0 ; 141.1)	74.6 (50.1 ; 112.6)	-20.8 (-44.1 ; 16.8)	126.7 (91.0 ; 174.1)	92.8 (67.3 ; 131.2)	-26.7 (-45.7 ; 3.1)	110.8 (81.0 ; 154.2)	83.2 (58.6 ; 120.5)	-24.9 (-43.4 ; -0.5)
	High body mass index	19.2 (4.1 ; 46.4)	40.1 (19.8 ; 64.9)	108.5 (17.6 ; 551.7)	19.2 (3.7 ; 48.5)	38.0 (17.7 ; 62.7)	97.8 (12.6 ; 533.9)	19.4 (4.0 ; 47.3)	39.5 (19.6 ; 63.8)	103.6 (20.2 ; 517.9)
	High fasting plasma glucose	33.2 (17.6 ; 59.3)	42.4 (23.6 ; 70.1)	28.0 (-22.5 ; 116.4)	67.8 (41.9 ; 102.0)	79.6 (51.9 ; 115.9)	17.3 (-18.7 ; 85.7)	49.6 (32.2 ; 75.4)	58.4 (37.8 ; 87.3)	17.8 (-14.6 ; 71.0)
	High LDL cholesterol	40.9 (24.9 ; 63.3)	40.8 (25.0 ; 60.4)	-0.2 (-32.5 ; 46.7)	51.8 (35.4 ; 73.3)	46.8 (31.4 ; 66.4)	-9.7 (-34.4 ; 28.5)	46.8 (32.1 ; 66.3)	44.0 (28.6 ; 62.8)	-6.0 (-31.5 ; 26.1)
	High systolic blood pressure	216.1 (153.1 ; 284.2)	188.7 (148.2 ; 236.2)	-12.7 (-37.4 ; 27.4)	230.7 (171.4 ; 291.4)	188.9 (154.6 ; 230.9)	-18.1 (-38.1 ; 15.3)	225.3 (178.2 ; 279.6)	191.0 (156.9 ; 233.6)	-15.2 (-33.8 ; 10.8)
	Kidney dysfunction	13.4 (8.2 ; 20.4)	15.0 (10.3 ; 20.8)	11.4 (-20.0 ; 64.3)	16.6 (11.2 ; 22.9)	16.7 (12.1 ; 22.3)	0.3 (-25.0 ; 39.7)	15.1 (10.4 ; 20.9)	15.9 (11.3 ; 21.6)	5.1 (-20.1 ; 37.9)
	Low physical activity	8.0 (3.1 ; 16.6)	9.0 (3.8 ; 18.0)	12.8 (-20.7 ; 67.8)	5.2 (1.4 ; 13.0)	5.7 (1.8 ; 14.1)	10.4 (-20.5 ; 64.7)	6.8 (2.6 ; 15.1)	7.8 (3.0 ; 16.4)	14.3 (-16.9 ; 56.3)
	Non-optimal temperature	11.1 (5.3 ; 17.9)	8.8 (5.1 ; 13.4)	-20.9 (-45.7 ; 31.0)	12.8 (6.8 ; 20.5)	9.5 (5.7 ; 14.9)	-25.6 (-45.0 ; 10.4)	12.0 (6.2 ; 18.6)	9.2 (5.5 ; 14.1)	-23.6 (-42.7 ; 11.3)
	Other environmental risks	12.3 (4.7 ; 23.2)	11.6 (5.4 ; 19.7)	-6.2 (-32.9 ; 45.1)	20.2 (10.9 ; 31.6)	17.2 (10.1 ; 25.6)	-14.8 (-35.6 ; 19.2)	16.2 (8.1 ; 26.6)	14.0 (7.6 ; 21.8)	-13.4 (-31.9 ; 13.9)
	Smoking	13.1 (8.6 ; 18.3)	10.9 (7.9 ; 14.6)	-16.4 (-44.1 ; 28.2)	58.3 (43.6 ; 73.5)	43.8 (34.9 ; 55.4)	-24.9 (-45.5 ; 6.2)	35.4 (27.6 ; 43.9)	25.6 (20.2 ; 32.5)	-27.9 (-46.2 ; -1.5)
Brazil	All risk factors	259.5 (237.7 ; 274.8)	118.2 (103.9 ; 128.2)	-54.4 (-57.0 ; -52.2)	352.0 (331.8 ; 368.2)	175.8 (161.3 ; 187.3)	-50.0 (-53.2 ; -47.4)	303.1 (282.6 ; 317.6)	144.3 (130.8 ; 153.5)	-52.4 (-54.5 ; -50.6)
	Air pollution	46.3 (34.4 ; 60.2)	10.8 (7.8 ; 13.9)	-76.7 (-83.5 ; -67.8)	65.0 (46.7 ; 84.7)	16.6 (11.9 ; 21.8)	-74.5 (-82.1 ; -64.2)	55.1 (40.4 ; 71.9)	13.4 (9.8 ; 17.6)	-75.6 (-82.9 ; -66.0)
	Alcohol use	-0.1 (-1.7 ; 1.6)	0.2 (-0.6 ; 1.2)	-315.7 (-576.3 ; 511.4)	11.5 (5.8 ; 18.0)	6.5 (3.2 ; 9.9)	-43.7 (-60.0 ; -19.6)	5.3 (2.4 ; 8.5)	3.0 (1.4 ; 4.8)	-43.5 (-62.5 ; -11.6)
	Dietary risks	95.1 (74.8 ; 121.0)	38.4 (29.3 ; 50.7)	-59.6 (-63.8 ; -55.9)	144.9 (115.3 ; 181.6)	65.7 (50.4 ; 84.1)	-54.7 (-59.0 ; -50.5)	118.4 (94.6 ; 148.9)	50.7 (39.2 ; 65.7)	-57.2 (-60.9 ; -53.9)
	High body mass index	54.7 (32.2 ; 81.1)	36.2 (25.4 ; 48.4)	-33.9 (-43.7 ; -16.7)	62.1 (32.4 ; 98.6)	47.9 (30.4 ; 66.8)	-22.8 (-35.9 ; 6.2)	58.5 (32.7 ; 89.7)	41.8 (28.1 ; 56.8)	-28.5 (-38.8 ; -8.6)
	High fasting plasma glucose	58.1 (38.4 ; 88.3)	27.2 (18.0 ; 41.6)	-53.2 (-59.3 ; -46.1)	85.4 (58.1 ; 128.3)	47.1 (32.1 ; 68.6)	-44.9 (-50.4 ; -37.8)	70.4 (47.4 ; 106.1)	35.9 (24.5 ; 53.0)	-49.0 (-53.4 ; -43.9)
	High LDL cholesterol	72.9 (54.2 ; 97.8)	33.8 (25.0 ; 45.1)	-53.7 (-56.9 ; -50.4)	105.7 (82.4 ; 133.6)	54.2 (42.3 ; 68.4)	-48.8 (-52.1 ; -44.9)	88.6 (67.8 ; 114.8)	43.1 (33.4 ; 55.9)	-51.3 (-53.8 ; -48.6)
	High systolic blood pressure	161.6 (140.1 ; 182.2)	76.8 (64.8 ; 87.4)	-52.5 (-56.0 ; -49.0)	212.6 (187.4 ; 236.0)	113.0 (98.4 ; 126.1)	-46.8 (-50.3 ; -43.3)	186.1 (163.8 ; 206.7)	93.4 (80.2 ; 104.2)	-49.8 (-52.5 ; -47.1)
	Kidney dysfunction	21.9 (16.9 ; 27.2)	11.0 (8.6 ; 13.7)	-49.7 (-53.4 ; -46.4)	29.3 (23.1 ; 35.8)	16.8 (13.2 ; 20.5)	-42.9 (-47.0 ; -38.5)	25.5 (19.9 ; 31.3)	13.6 (10.8 ; 16.7)	-46.5 (-49.6 ; -43.4)
	Low physical activity	25.1 (13.1 ; 38.0)	12.3 (7.4 ; 17.9)	-50.9 (-56.7 ; -39.7)	27.0 (11.4 ; 45.7)	15.4 (7.9 ; 24.5)	-42.9 (-50.3 ; -24.9)	26.1 (12.6 ; 41.4)	13.7 (7.6 ; 20.8)	-47.6 (-53.6 ; -35.0)
	Non-optimal temperature	8.7 (2.0 ; 13.7)	3.1 (0.9 ; 4.8)	-64.0 (-78.6 ; -27.2)	11.0 (1.4 ; 17.5)	4.4 (0.9 ; 6.7)	-60.3 (-83.9 ; -5.5)	9.8 (1.8 ; 15.4)	3.7 (0.8 ; 5.6)	-62.3 (-78.6 ; -19.0)
	Other environmental risks	8.7 (3.3 ; 14.5)	3.9 (1.5 ; 6.7)	-55.7 (-59.4 ; -51.1)	17.5 (9.7 ; 25.5)	7.8 (4.1 ; 11.9)	-55.3 (-60.2 ; -51.4)	12.7 (6.2 ; 19.5)	5.6 (2.6 ; 8.9)	-56.1 (-60.0 ; -52.8)
	Smoking	68.4 (60.9 ; 76.3)	19.9 (17.9 ; 22.1)	-70.8 (-74.3 ; -67.1)	115.8 (108.7 ; 122.4)	36.9 (33.8 ; 39.7)	-68.1 (-70.7 ; -65.5)	90.6 (84.6 ; 96.5)	27.6 (25.5 ; 29.7)	-69.5 (-72.0 ; -67.1)

Cabo Verde	All risk factors	163.7 (142.5 ; 184.5)	184.7 (152.9 ; 212.8)	12.8 (-5.0 ; 33.2)	233.8 (204.9 ; 257.4)	274.6 (245.8 ; 303.6)	17.4 (3.5 ; 34.8)	192.1 (171.0 ; 209.8)	222.6 (193.8 ; 247.8)	15.9 (1.6 ; 32.0)
	Air pollution	51.0 (41.4 ; 62.5)	44.5 (34.8 ; 55.0)	-12.7 (-32.8 ; 13.7)	79.1 (66.8 ; 94.3)	75.6 (60.3 ; 90.9)	-4.4 (-23.6 ; 16.4)	62.5 (52.7 ; 74.6)	57.8 (46.6 ; 69.3)	-7.5 (-27.0 ; 15.3)
	Alcohol use	1.5 (-1.0 ; 4.5)	1.9 (-1.2 ; 5.5)	22.7 (-692.9 ; 1213.6)	6.2 (1.4 ; 11.2)	11.9 (5.4 ; 19.6)	93.5 (-1.3 ; 463.0)	3.5 (0.7 ; 6.5)	6.1 (2.1 ; 10.8)	75.1 (-33.1 ; 490.7)
	Dietary risks	62.9 (48.6 ; 82.7)	64.1 (46.1 ; 89.3)	1.8 (-16.2 ; 22.4)	105.5 (82.9 ; 133.2)	101.1 (76.7 ; 134.8)	-4.2 (-18.4 ; 13.1)	80.1 (63.1 ; 101.9)	79.7 (59.4 ; 108.0)	-0.5 (-15.6 ; 15.9)
	High body mass index	24.3 (11.8 ; 39.0)	41.4 (26.5 ; 60.0)	70.3 (24.0 ; 174.8)	20.8 (7.1 ; 38.9)	53.3 (32.3 ; 79.4)	156.0 (80.8 ; 427.3)	22.8 (9.8 ; 38.8)	47.1 (29.7 ; 68.4)	107.1 (55.0 ; 249.1)
	High fasting plasma glucose	26.7 (15.4 ; 45.0)	59.1 (34.8 ; 92.6)	121.1 (57.8 ; 219.5)	41.5 (24.8 ; 69.3)	85.3 (54.4 ; 125.9)	105.5 (47.8 ; 189.0)	32.6 (19.4 ; 53.9)	69.5 (43.1 ; 106.5)	113.3 (61.1 ; 187.2)
	High LDL cholesterol	34.9 (23.2 ; 48.0)	43.4 (28.2 ; 61.3)	24.3 (2.9 ; 49.5)	56.5 (39.2 ; 76.3)	61.0 (41.8 ; 82.9)	8.0 (-7.1 ; 28.2)	43.5 (30.0 ; 59.2)	51.1 (34.7 ; 69.9)	17.4 (1.0 ; 35.2)
	High systolic blood pressure	111.5 (90.3 ; 134.6)	127.6 (98.1 ; 155.9)	14.4 (-10.7 ; 44.5)	149.7 (123.5 ; 177.1)	186.9 (156.5 ; 219.0)	24.9 (5.9 ; 48.5)	127.0 (106.9 ; 148.8)	153.2 (125.6 ; 179.6)	20.7 (2.9 ; 41.8)
	Kidney dysfunction	11.2 (7.7 ; 15.1)	17.7 (12.3 ; 23.4)	58.4 (29.2 ; 96.6)	16.4 (10.9 ; 22.3)	24.4 (17.4 ; 31.7)	49.0 (26.4 ; 79.6)	13.3 (9.0 ; 17.9)	20.5 (14.7 ; 26.8)	54.6 (31.5 ; 85.0)
	Low physical activity	4.7 (1.7 ; 10.2)	6.7 (2.6 ; 14.1)	43.6 (16.1 ; 85.9)	5.5 (1.5 ; 14.5)	7.0 (2.1 ; 17.0)	26.3 (-1.4 ; 74.0)	5.0 (1.7 ; 11.8)	6.9 (2.5 ; 15.9)	37.5 (13.5 ; 77.5)
	Non-optimal temperature	7.5 (-0.0 ; 15.6)	7.7 (2.0 ; 16.1)	2.3 (-33.1 ; 63.5)	11.0 (0.6 ; 22.5)	11.0 (2.5 ; 23.3)	0.0 (-39.7 ; 68.0)	8.9 (0.2 ; 18.3)	9.1 (2.2 ; 19.1)	1.9 (-31.6 ; 66.1)
	Other environmental risks	4.5 (1.1 ; 8.3)	4.8 (1.3 ; 8.7)	6.3 (-13.9 ; 42.5)	7.5 (2.6 ; 12.9)	8.0 (2.8 ; 14.0)	7.0 (-10.4 ; 27.1)	5.7 (1.7 ; 10.1)	6.1 (2.0 ; 10.9)	6.7 (-8.7 ; 27.0)
	Smoking	10.6 (8.3 ; 13.1)	7.8 (6.1 ; 9.7)	-25.9 (-44.1 ; -2.7)	37.4 (32.5 ; 42.7)	28.9 (24.6 ; 33.5)	-22.9 (-35.7 ; -7.0)	21.8 (19.1 ; 24.5)	16.9 (14.5 ; 19.8)	-22.2 (-34.8 ; -6.2)
Equatorial Guinea	All risk factors	312.2 (195.9 ; 439.0)	231.1 (163.4 ; 304.0)	-26.0 (-55.7 ; 25.7)	401.8 (299.2 ; 494.7)	211.0 (155.6 ; 269.7)	-47.5 (-61.9 ; -21.2)	354.2 (266.7 ; 450.9)	224.4 (171.1 ; 285.6)	-36.6 (-56.7 ; -10.7)
	Air pollution	110.1 (61.0 ; 175.4)	47.7 (28.7 ; 70.1)	-56.7 (-77.8 ; -18.4)	155.9 (112.9 ; 206.2)	49.0 (30.6 ; 70.4)	-68.6 (-81.7 ; -48.4)	130.9 (92.0 ; 181.6)	48.4 (30.5 ; 69.4)	-63.0 (-79.1 ; -41.8)
	Alcohol use	0.9 (-4.5 ; 7.1)	6.4 (-0.2 ; 15.1)	607.8 (-3342.7 ; 3175.8)	7.6 (-3.2 ; 19.9)	13.7 (5.2 ; 23.5)	80.7 (-1716.7 ; 1479.2)	3.8 (-3.0 ; 11.4)	9.3 (2.6 ; 17.0)	148.5 (-2409.6 ; 2496.0)
	Dietary risks	97.6 (54.9 ; 161.4)	65.3 (38.5 ; 104.8)	-33.1 (-59.7 ; 15.0)	146.3 (100.8 ; 204.3)	65.3 (42.2 ; 98.3)	-55.4 (-69.0 ; -33.0)	119.6 (82.7 ; 171.8)	65.7 (41.8 ; 101.7)	-45.0 (-62.8 ; -20.8)
	High body mass index	27.2 (7.2 ; 59.7)	68.2 (40.0 ; 104.7)	150.9 (20.1 ; 665.3)	24.2 (4.8 ; 59.4)	55.5 (31.8 ; 86.2)	128.9 (9.4 ; 813.1)	26.1 (6.3 ; 58.3)	63.5 (38.5 ; 97.1)	143.0 (18.3 ; 670.7)
	High fasting plasma glucose	33.9 (17.0 ; 60.7)	44.1 (25.0 ; 74.9)	30.0 (-29.6 ; 140.1)	74.7 (44.3 ; 116.1)	63.3 (39.1 ; 97.4)	-15.2 (-44.9 ; 36.4)	51.0 (32.5 ; 77.6)	51.8 (31.1 ; 80.7)	1.5 (-35.4 ; 50.4)
	High LDL cholesterol	45.1 (23.6 ; 74.6)	39.9 (21.4 ; 61.7)	-11.6 (-48.6 ; 55.4)	63.2 (42.2 ; 89.2)	36.1 (22.2 ; 54.1)	-42.9 (-60.6 ; -11.8)	53.8 (34.5 ; 78.9)	38.7 (22.3 ; 59.0)	-28.0 (-54.0 ; 5.2)
	High systolic blood pressure	232.7 (145.3 ; 329.7)	179.8 (124.1 ; 241.0)	-22.7 (-55.2 ; 33.7)	273.3 (195.5 ; 347.1)	149.3 (105.4 ; 194.7)	-45.4 (-61.3 ; -17.6)	253.5 (187.1 ; 327.0)	168.9 (124.5 ; 218.2)	-33.4 (-54.9 ; -3.9)
	Kidney dysfunction	14.7 (8.0 ; 23.8)	16.2 (10.0 ; 24.0)	10.2 (-35.3 ; 95.5)	20.0 (13.5 ; 27.8)	14.0 (9.3 ; 19.5)	-30.3 (-50.9 ; 3.2)	17.2 (11.4 ; 24.7)	15.4 (10.1 ; 21.8)	-10.3 (-40.9 ; 29.9)
	Low physical activity	8.6 (3.0 ; 19.0)	10.5 (4.4 ; 20.2)	21.1 (-27.8 ; 119.4)	6.1 (1.7 ; 15.4)	5.9 (1.9 ; 13.5)	-3.8 (-38.6 ; 63.1)	7.8 (2.8 ; 16.9)	8.8 (3.5 ; 17.4)	12.0 (-28.4 ; 76.1)
	Non-optimal temperature	7.4 (-1.1 ; 18.0)	4.0 (0.6 ; 9.8)	-45.8 (-78.1 ; 9.3)	9.4 (-0.2 ; 22.5)	3.5 (0.5 ; 8.9)	-62.6 (-95.2 ; -30.8)	8.4 (-0.8 ; 19.5)	3.9 (0.6 ; 9.6)	-54.0 (-78.8 ; -13.0)
	Other environmental risks	19.6 (9.4 ; 35.3)	12.8 (6.5 ; 21.1)	-35.1 (-61.2 ; 8.7)	35.5 (21.3 ; 51.7)	15.2 (8.9 ; 22.8)	-57.4 (-69.5 ; -38.5)	26.6 (15.7 ; 40.7)	13.7 (7.7 ; 21.3)	-48.4 (-64.0 ; -28.0)
	Smoking	10.3 (6.1 ; 16.0)	6.2 (3.9 ; 9.2)	-40.0 (-65.6 ; 7.2)	66.3 (47.2 ; 86.9)	27.3 (18.5 ; 38.1)	-58.9 (-72.9 ; -36.6)	35.0 (25.9 ; 45.4)	14.9 (10.3 ; 20.7)	-57.4 (-71.3 ; -36.8)

Guinea-Bissau	All risk factors	284.9 (210.9 ; 356.1)	300.9 (236.2 ; 378.4)	5.6 (-22.2 ; 46.2)	377.0 (298.8 ; 461.9)	341.4 (278.3 ; 408.3)	-9.5 (-30.7 ; 19.7)	329.8 (270.3 ; 392.1)	320.6 (258.7 ; 395.1)	-2.8 (-24.5 ; 26.0)
	Air pollution	116.1 (78.7 ; 161.0)	103.8 (77.5 ; 134.4)	-10.6 (-35.2 ; 27.9)	161.3 (116.7 ; 216.6)	125.4 (98.1 ; 154.8)	-22.3 (-42.2 ; 6.5)	138.2 (103.2 ; 182.1)	114.0 (88.8 ; 142.8)	-17.5 (-37.7 ; 11.4)
	Alcohol use	2.6 (-1.4 ; 7.3)	2.1 (-1.8 ; 7.3)	-17.6 (-567.9 ; 611.3)	14.2 (5.2 ; 24.2)	11.8 (3.7 ; 21.9)	-16.7 (-68.9 ; 85.5)	8.2 (2.7 ; 14.4)	6.4 (1.4 ; 12.7)	-20.9 (-81.3 ; 97.5)
	Dietary risks	107.8 (71.4 ; 153.9)	111.0 (77.2 ; 162.2)	3.0 (-25.6 ; 45.6)	165.2 (118.0 ; 222.6)	141.1 (103.9 ; 192.1)	-14.6 (-35.6 ; 15.1)	135.1 (98.5 ; 186.1)	124.6 (90.2 ; 173.8)	-7.8 (-29.8 ; 21.3)
	High body mass index	36.3 (14.0 ; 67.4)	58.1 (30.4 ; 92.6)	59.7 (7.6 ; 191.7)	27.2 (7.6 ; 59.8)	41.7 (16.3 ; 74.4)	53.5 (-0.2 ; 216.2)	32.0 (11.2 ; 62.9)	51.0 (25.4 ; 85.8)	59.3 (11.3 ; 181.6)
	High fasting plasma glucose	33.0 (19.5 ; 55.8)	68.8 (41.2 ; 109.3)	108.5 (33.7 ; 235.3)	51.1 (31.1 ; 84.5)	81.5 (48.9 ; 127.5)	59.5 (7.0 ; 145.4)	41.5 (26.5 ; 65.9)	74.0 (46.3 ; 114.7)	78.4 (25.1 ; 152.6)
	High LDL cholesterol	48.5 (30.5 ; 74.6)	58.8 (38.4 ; 84.2)	21.5 (-16.1 ; 76.4)	68.1 (45.1 ; 97.7)	69.3 (47.8 ; 94.4)	1.7 (-25.0 ; 41.2)	57.8 (39.1 ; 82.7)	63.9 (42.8 ; 88.4)	10.4 (-17.9 ; 50.7)
	High systolic blood pressure	194.4 (137.7 ; 255.5)	212.7 (159.7 ; 275.9)	9.4 (-21.2 ; 57.1)	233.4 (176.8 ; 295.8)	225.7 (174.4 ; 280.9)	-3.3 (-28.5 ; 32.7)	214.0 (168.0 ; 264.6)	220.4 (171.5 ; 277.2)	3.0 (-22.5 ; 35.5)
	Kidney dysfunction	19.2 (13.0 ; 26.7)	24.2 (17.2 ; 33.5)	26.2 (-8.1 ; 78.2)	24.4 (16.6 ; 33.8)	25.9 (18.2 ; 35.0)	6.2 (-19.7 ; 42.9)	21.7 (15.6 ; 29.0)	25.1 (18.3 ; 34.1)	15.5 (-11.5 ; 52.2)
	Low physical activity	6.3 (2.3 ; 14.0)	7.5 (2.9 ; 16.4)	20.3 (-16.3 ; 73.0)	8.1 (2.2 ; 20.4)	7.8 (2.3 ; 19.1)	-2.8 (-26.5 ; 35.7)	7.1 (2.4 ; 16.7)	7.7 (2.8 ; 17.5)	8.4 (-17.2 ; 44.5)
	Non-optimal temperature	8.4 (-23.0 ; 18.2)	9.5 (2.5 ; 17.7)	13.1 (-159.3 ; 104.1)	11.5 (-34.1 ; 23.8)	10.8 (1.1 ; 18.2)	-5.8 (-159.8 ; 47.8)	9.9 (-27.3 ; 20.4)	10.1 (1.7 ; 17.8)	2.4 (-163.6 ; 60.8)
	Other environmental risks	12.5 (5.3 ; 21.2)	14.7 (7.2 ; 23.9)	17.3 (-14.5 ; 71.4)	23.1 (12.9 ; 35.0)	22.4 (13.6 ; 32.9)	-2.8 (-27.3 ; 32.9)	17.6 (9.4 ; 26.9)	18.1 (10.0 ; 27.6)	3.0 (-21.8 ; 37.3)
	Smoking	12.2 (8.6 ; 16.4)	10.9 (7.9 ; 14.5)	-10.7 (-40.0 ; 29.7)	48.9 (36.7 ; 64.1)	32.8 (25.4 ; 40.7)	-33.0 (-52.6 ; -5.2)	29.9 (23.1 ; 38.5)	20.9 (16.2 ; 26.4)	-30.3 (-50.1 ; -4.3)
Mozambique	All risk factors	251.3 (203.0 ; 301.4)	247.6 (192.6 ; 324.9)	-1.5 (-26.5 ; 31.6)	288.1 (234.5 ; 345.8)	370.1 (311.7 ; 432.8)	28.4 (2.6 ; 61.0)	270.8 (228.0 ; 315.3)	304.8 (246.3 ; 373.7)	12.6 (-11.7 ; 41.3)
	Air pollution	96.2 (68.5 ; 136.1)	79.0 (57.2 ; 109.2)	-17.9 (-41.6 ; 17.1)	119.3 (88.9 ; 165.1)	134.1 (107.1 ; 163.5)	12.4 (-16.9 ; 49.3)	107.7 (80.7 ; 146.4)	104.2 (80.7 ; 133.0)	-3.3 (-28.7 ; 29.2)
	Alcohol use	-1.0 (-2.4 ; 0.5)	-0.8 (-3.5 ; 2.0)	-26.8 (-844.2 ; 623.6)	-0.8 (-5.3 ; 3.8)	3.4 (-6.0 ; 13.8)	-507.8 (-3041.8 ; 2468.5)	-0.9 (-3.3 ; 1.5)	1.2 (-3.5 ; 6.3)	-226.5 (-3065.6 ; 2361.7)
	Dietary risks	94.9 (56.2 ; 147.7)	85.8 (48.2 ; 140.9)	-9.6 (-35.2 ; 22.8)	123.1 (80.9 ; 180.3)	135.1 (91.4 ; 192.8)	9.8 (-18.0 ; 43.2)	108.7 (70.0 ; 161.6)	108.4 (68.2 ; 163.7)	-0.3 (-23.8 ; 28.3)
	High body mass index	17.8 (4.5 ; 40.2)	41.5 (20.3 ; 70.2)	132.9 (35.3 ; 494.2)	15.5 (3.0 ; 38.3)	49.7 (21.6 ; 84.9)	219.9 (89.5 ; 870.9)	16.9 (3.9 ; 39.9)	46.1 (21.2 ; 77.5)	172.9 (63.8 ; 609.2)
	High fasting plasma glucose	23.7 (14.2 ; 41.7)	34.7 (18.7 ; 61.9)	46.0 (-20.0 ; 145.4)	43.0 (25.6 ; 67.2)	89.3 (57.9 ; 132.1)	107.8 (45.6 ; 204.7)	32.2 (20.1 ; 50.4)	57.0 (36.5 ; 87.5)	76.9 (25.5 ; 151.2)
	High LDL cholesterol	30.0 (19.1 ; 45.8)	35.1 (20.1 ; 54.2)	16.9 (-18.9 ; 61.2)	41.1 (28.1 ; 61.4)	62.4 (43.1 ; 88.1)	52.0 (14.1 ; 104.3)	35.4 (24.3 ; 51.8)	47.4 (31.1 ; 69.0)	34.0 (2.8 ; 74.7)
	High systolic blood pressure	180.7 (139.6 ; 229.1)	185.7 (138.5 ; 247.4)	2.8 (-25.6 ; 42.5)	193.1 (149.7 ; 235.2)	264.3 (213.7 ; 319.3)	36.9 (5.2 ; 75.0)	188.8 (153.3 ; 228.7)	224.1 (177.4 ; 281.8)	18.7 (-9.1 ; 51.3)
	Kidney dysfunction	11.8 (8.5 ; 16.3)	14.7 (10.1 ; 20.8)	24.3 (-10.0 ; 69.5)	14.8 (10.8 ; 20.1)	23.6 (17.7 ; 31.1)	59.8 (23.9 ; 103.7)	13.3 (9.8 ; 17.8)	18.8 (13.8 ; 25.3)	41.4 (8.8 ; 79.9)
	Low physical activity	2.0 (0.7 ; 5.1)	2.4 (0.8 ; 6.2)	18.0 (-20.2 ; 70.2)	2.1 (0.7 ; 5.7)	3.2 (1.0 ; 8.7)	52.3 (9.0 ; 106.7)	2.1 (0.7 ; 5.4)	2.8 (1.0 ; 7.3)	33.0 (-2.5 ; 77.4)
	Non-optimal temperature	8.2 (3.9 ; 13.0)	7.6 (4.2 ; 12.1)	-7.5 (-34.6 ; 39.0)	9.4 (4.7 ; 15.2)	11.1 (6.3 ; 17.5)	18.3 (-11.8 ; 70.2)	8.8 (4.3 ; 14.1)	9.2 (5.2 ; 14.7)	4.6 (-22.7 ; 52.5)
	Other environmental risks	13.7 (6.6 ; 23.4)	14.3 (7.7 ; 23.9)	5.0 (-21.6 ; 43.2)	32.9 (22.7 ; 46.2)	36.4 (25.1 ; 49.3)	10.6 (-12.4 ; 38.7)	22.5 (14.4 ; 33.7)	23.4 (14.8 ; 34.6)	4.0 (-18.1 ; 30.6)
	Smoking	11.4 (8.3 ; 15.5)	10.6 (7.3 ; 14.8)	-7.7 (-40.2 ; 38.0)	43.8 (33.7 ; 55.6)	50.6 (39.6 ; 63.5)	15.4 (-13.7 ; 55.1)	26.7 (21.3 ; 32.6)	28.2 (21.9 ; 35.4)	5.4 (-21.1 ; 41.0)

Portugal	All risk factors	255.9 (229.2 ; 276.1)	83.8 (71.0 ; 93.8)	-67.3 (-70.3 ; -64.6)	358.4 (336.7 ; 378.3)	124.2 (112.3 ; 133.7)	-65.3 (-67.6 ; -63.2)	299.9 (275.5 ; 319.2)	102.0 (89.8 ; 111.5)	-66.0 (-68.3 ; -63.9)
	Air pollution	21.3 (7.7 ; 38.2)	3.1 (1.8 ; 4.6)	-85.3 (-92.6 ; -64.5)	30.6 (10.1 ; 55.6)	5.2 (3.0 ; 7.6)	-82.9 (-91.5 ; -56.4)	25.4 (8.8 ; 46.0)	4.1 (2.4 ; 5.9)	-83.9 (-91.9 ; -60.0)
	Alcohol use	7.4 (1.9 ; 13.3)	1.7 (0.4 ; 3.3)	-76.7 (-90.7 ; -55.8)	42.1 (26.6 ; 57.0)	12.1 (7.4 ; 16.9)	-71.3 (-77.0 ; -65.3)	20.7 (14.0 ; 27.6)	5.9 (3.8 ; 8.2)	-71.4 (-77.9 ; -64.1)
	Dietary risks	81.0 (66.4 ; 97.7)	26.4 (20.8 ; 33.1)	-67.5 (-70.7 ; -63.7)	123.9 (102.0 ; 150.3)	45.5 (36.5 ; 56.7)	-63.3 (-66.5 ; -59.8)	99.7 (82.6 ; 120.2)	34.9 (28.2 ; 43.5)	-65.0 (-67.7 ; -61.7)
	High body mass index	38.0 (20.3 ; 58.4)	15.8 (9.3 ; 23.6)	-58.5 (-65.5 ; -45.3)	47.7 (21.5 ; 78.0)	22.1 (11.5 ; 34.2)	-53.6 (-60.3 ; -38.4)	42.8 (21.6 ; 67.6)	18.9 (10.6 ; 28.7)	-55.9 (-61.9 ; -42.4)
	High fasting plasma glucose	57.2 (34.6 ; 99.7)	26.7 (16.3 ; 43.3)	-53.3 (-68.0 ; -34.2)	72.3 (47.1 ; 118.4)	40.5 (27.1 ; 60.9)	-44.0 (-59.2 ; -25.7)	64.0 (40.9 ; 103.3)	32.7 (21.3 ; 51.3)	-48.9 (-61.3 ; -33.1)
	High LDL cholesterol	76.8 (48.5 ; 118.7)	23.8 (14.8 ; 36.1)	-69.0 (-72.4 ; -65.3)	112.6 (79.6 ; 160.9)	38.1 (27.7 ; 51.6)	-66.2 (-69.6 ; -62.6)	92.5 (62.4 ; 137.0)	30.3 (20.8 ; 43.1)	-67.2 (-70.3 ; -63.8)
	High systolic blood pressure	152.8 (116.8 ; 187.4)	48.7 (37.7 ; 59.6)	-68.2 (-74.7 ; -60.0)	212.5 (177.4 ; 248.0)	73.0 (61.9 ; 85.3)	-65.7 (-70.3 ; -60.7)	179.0 (147.4 ; 210.6)	59.8 (49.6 ; 70.1)	-66.6 (-71.0 ; -61.2)
	Kidney dysfunction	23.7 (16.9 ; 30.3)	8.2 (5.7 ; 10.6)	-65.6 (-69.3 ; -61.9)	28.9 (22.0 ; 35.8)	10.2 (7.7 ; 12.8)	-64.6 (-67.6 ; -61.4)	26.1 (19.3 ; 32.8)	9.1 (6.7 ; 11.6)	-65.0 (-68.1 ; -61.8)
	Low physical activity	20.0 (8.2 ; 36.7)	6.8 (2.9 ; 11.9)	-66.2 (-72.1 ; -57.6)	20.0 (6.2 ; 41.6)	7.2 (2.4 ; 13.7)	-64.2 (-71.1 ; -52.8)	20.4 (7.8 ; 38.8)	7.1 (2.8 ; 12.7)	-65.4 (-70.9 ; -57.5)
	Non-optimal temperature	29.1 (23.8 ; 34.7)	8.9 (7.1 ; 10.8)	-69.4 (-72.1 ; -67.3)	38.5 (31.6 ; 45.9)	12.3 (10.0 ; 14.8)	-68.1 (-70.1 ; -66.1)	33.1 (27.2 ; 39.5)	10.4 (8.4 ; 12.5)	-68.5 (-70.6 ; -66.6)
	Other environmental risks	10.4 (5.0 ; 16.0)	3.4 (1.6 ; 5.4)	-67.5 (-72.3 ; -62.0)	23.6 (15.4 ; 32.3)	7.4 (4.6 ; 10.5)	-68.5 (-72.4 ; -65.1)	15.7 (9.3 ; 22.3)	5.0 (2.9 ; 7.4)	-68.0 (-71.7 ; -64.3)
	Smoking	26.6 (23.2 ; 30.4)	6.0 (5.2 ; 6.8)	-77.6 (-80.8 ; -74.1)	87.2 (81.5 ; 93.1)	24.0 (22.2 ; 25.9)	-72.5 (-74.8 ; -70.2)	52.2 (48.6 ; 55.6)	14.0 (12.9 ; 15.1)	-73.2 (-75.4 ; -70.8)
Sao Tome and Principe	All risk factors	240.9 (206.0 ; 272.8)	272.0 (212.5 ; 326.4)	12.9 (-8.6 ; 39.1)	224.4 (186.5 ; 263.0)	260.1 (217.3 ; 295.7)	15.9 (-5.5 ; 41.8)	230.6 (197.7 ; 262.7)	267.1 (219.4 ; 304.8)	15.8 (-3.4 ; 38.6)
	Air pollution	87.9 (72.5 ; 107.3)	73.5 (54.9 ; 93.9)	-16.4 (-36.4 ; 10.2)	80.8 (64.8 ; 100.3)	72.4 (55.4 ; 88.2)	-10.4 (-31.9 ; 16.1)	84.0 (69.4 ; 101.7)	73.1 (56.3 ; 89.5)	-12.9 (-32.1 ; 11.2)
	Alcohol use	1.3 (-2.5 ; 5.7)	3.9 (-1.4 ; 10.3)	214.7 (-2697.6 ; 2301.0)	6.6 (1.5 ; 12.5)	11.9 (4.9 ; 20.1)	79.8 (-16.3 ; 525.4)	3.7 (0.0 ; 8.0)	7.7 (2.7 ; 13.8)	106.1 (-92.6 ; 987.4)
	Dietary risks	82.0 (61.8 ; 114.3)	91.7 (62.9 ; 132.3)	11.8 (-11.2 ; 36.8)	88.5 (66.0 ; 119.8)	98.3 (71.9 ; 133.7)	11.0 (-9.5 ; 37.2)	83.4 (63.4 ; 114.3)	94.9 (68.3 ; 130.9)	13.8 (-6.5 ; 37.5)
	High body mass index	40.8 (21.0 ; 65.1)	64.8 (40.1 ; 96.1)	59.1 (14.3 ; 142.9)	21.5 (7.3 ; 42.0)	50.7 (29.9 ; 79.0)	135.6 (58.2 ; 376.5)	31.6 (14.9 ; 52.7)	58.2 (36.2 ; 86.4)	84.2 (35.0 ; 190.2)
	High fasting plasma glucose	42.7 (25.3 ; 71.2)	73.4 (43.0 ; 115.0)	71.8 (21.1 ; 152.3)	47.7 (25.7 ; 82.7)	78.2 (47.0 ; 119.5)	64.0 (18.5 ; 146.4)	43.8 (25.8 ; 72.4)	75.6 (46.5 ; 116.9)	72.8 (31.4 ; 133.4)
	High LDL cholesterol	44.1 (29.9 ; 61.5)	59.2 (37.4 ; 83.0)	34.5 (6.5 ; 67.7)	43.7 (27.9 ; 63.6)	58.9 (39.4 ; 80.6)	34.9 (7.2 ; 68.4)	43.3 (28.8 ; 61.0)	59.3 (39.6 ; 81.4)	36.9 (12.1 ; 66.6)
	High systolic blood pressure	166.4 (132.1 ; 200.7)	193.5 (142.8 ; 241.7)	16.3 (-11.9 ; 50.3)	143.7 (111.1 ; 179.0)	176.4 (139.9 ; 210.6)	22.8 (-2.3 ; 56.2)	154.9 (125.9 ; 183.4)	186.1 (144.7 ; 223.2)	20.1 (-3.6 ; 48.6)
	Kidney dysfunction	20.0 (15.0 ; 25.0)	30.4 (22.3 ; 39.7)	52.2 (23.1 ; 90.2)	15.5 (10.9 ; 20.9)	23.7 (17.1 ; 30.6)	53.0 (24.6 ; 90.1)	17.8 (13.0 ; 22.7)	27.3 (20.3 ; 35.1)	53.8 (28.1 ; 87.3)
	Low physical activity	6.4 (2.6 ; 13.3)	9.0 (3.7 ; 18.3)	41.3 (8.6 ; 82.0)	5.5 (1.6 ; 13.1)	7.1 (2.1 ; 16.8)	29.1 (0.6 ; 67.7)	5.9 (2.2 ; 13.2)	8.2 (3.0 ; 17.3)	37.7 (12.3 ; 70.2)
	Non-optimal temperature	0.9 (-3.0 ; 4.6)	1.3 (-0.7 ; 4.8)	40.9 (-303.6 ; 394.2)	0.9 (-2.7 ; 4.4)	1.2 (-0.8 ; 4.7)	43.8 (-316.7 ; 362.9)	0.9 (-2.8 ; 4.4)	1.2 (-0.7 ; 4.7)	44.4 (-370.9 ; 366.8)
	Other environmental risks	7.7 (2.4 ; 13.3)	8.8 (3.1 ; 15.2)	14.6 (-8.7 ; 52.3)	9.7 (4.7 ; 15.9)	11.3 (5.8 ; 17.6)	16.7 (-6.3 ; 46.6)	8.4 (3.4 ; 14.0)	10.0 (4.4 ; 15.9)	18.3 (-1.9 ; 47.9)
	Smoking	6.1 (4.7 ; 7.8)	7.0 (5.1 ; 9.1)	14.8 (-17.7 ; 62.0)	17.7 (13.7 ; 22.3)	23.4 (18.1 ; 28.6)	32.3 (-0.5 ; 79.4)	11.5 (9.1 ; 14.0)	14.9 (11.6 ; 18.2)	29.4 (0.1 ; 72.0)

Timor-Leste	All risk factors	255.1 (202.6 ; 310.9)	298.2 (246.9 ; 347.9)	16.9 (-9.0 ; 49.2)	237.9 (182.3 ; 321.3)	346.6 (263.2 ; 447.6)	45.7 (9.6 ; 82.9)	247.0 (202.6 ; 304.4)	322.3 (260.4 ; 389.9)	30.5 (2.5 ; 60.2)
	Air pollution	98.5 (73.5 ; 129.6)	89.6 (71.5 ; 108.6)	-9.0 (-33.0 ; 22.3)	88.4 (63.6 ; 123.7)	102.6 (71.9 ; 141.3)	16.1 (-16.8 ; 51.6)	93.6 (71.2 ; 121.9)	96.1 (73.8 ; 120.9)	2.6 (-23.0 ; 31.3)
	Alcohol use	-0.2 (-0.7 ; 0.3)	0.3 (-0.9 ; 1.9)	-233.5 (-2319.5 ; 2717.1)	0.9 (-2.5 ; 5.0)	10.2 (0.6 ; 21.6)	1094.3 (-8391.8 ; 11248.0)	0.4 (-1.4 ; 2.5)	5.2 (0.1 ; 11.6)	1361.0 (-5698.7 ; 5258.1)
	Dietary risks	110.6 (75.5 ; 154.4)	121.1 (85.6 ; 164.7)	9.5 (-16.5 ; 42.3)	115.9 (78.9 ; 164.4)	158.6 (107.4 ; 222.2)	36.9 (2.2 ; 75.5)	113.3 (80.3 ; 155.5)	139.7 (98.5 ; 190.0)	23.3 (-5.1 ; 52.1)
	High body mass index	13.1 (3.0 ; 30.6)	20.5 (6.7 ; 42.0)	56.4 (4.4 ; 199.8)	8.7 (1.4 ; 23.7)	22.8 (7.1 ; 47.2)	163.1 (61.7 ; 605.6)	10.9 (2.3 ; 26.8)	21.7 (7.1 ; 44.2)	99.5 (36.3 ; 308.3)
	High fasting plasma glucose	30.1 (18.5 ; 49.0)	89.0 (57.0 ; 136.3)	196.0 (101.9 ; 326.6)	34.4 (18.9 ; 59.9)	103.4 (63.7 ; 163.1)	200.7 (99.0 ; 358.7)	32.0 (19.6 ; 52.7)	96.0 (61.3 ; 148.9)	199.7 (117.9 ; 316.8)
	High LDL cholesterol	48.3 (32.7 ; 68.4)	61.7 (39.9 ; 87.0)	27.9 (-2.7 ; 65.4)	42.3 (27.0 ; 63.8)	65.3 (39.4 ; 97.4)	54.4 (12.5 ; 98.9)	45.6 (30.5 ; 64.0)	63.6 (41.2 ; 89.3)	39.6 (7.3 ; 75.0)
	High systolic blood pressure	168.4 (127.6 ; 214.7)	190.1 (148.9 ; 236.4)	12.9 (-15.1 ; 51.4)	149.2 (109.9 ; 204.3)	230.8 (169.5 ; 308.2)	54.7 (14.2 ; 101.2)	159.4 (125.0 ; 204.5)	210.4 (163.4 ; 263.8)	32.0 (1.0 ; 67.3)
	Kidney dysfunction	23.4 (16.6 ; 31.2)	35.2 (25.8 ; 46.0)	50.7 (15.7 ; 95.4)	19.5 (12.7 ; 28.7)	35.5 (23.4 ; 50.7)	82.2 (36.7 ; 134.1)	21.5 (15.5 ; 29.4)	35.4 (25.2 ; 47.6)	64.5 (28.1 ; 103.7)
	Low physical activity	5.7 (2.0 ; 13.0)	7.6 (2.6 ; 16.6)	32.5 (-3.5 ; 78.3)	6.2 (1.8 ; 13.9)	9.7 (3.0 ; 22.2)	56.8 (16.5 ; 103.8)	6.0 (2.1 ; 13.3)	8.6 (2.8 ; 19.5)	44.9 (13.0 ; 81.2)
	Non-optimal temperature	4.2 (0.7 ; 7.9)	4.3 (1.4 ; 8.2)	2.5 (-47.5 ; 103.8)	3.9 (0.7 ; 7.5)	4.9 (1.6 ; 9.7)	26.9 (-34.7 ; 154.0)	4.0 (0.7 ; 7.6)	4.6 (1.5 ; 9.0)	14.0 (-40.0 ; 126.9)
	Other environmental risks	8.5 (2.6 ; 15.7)	10.9 (4.3 ; 18.8)	27.9 (-1.2 ; 83.5)	12.7 (6.4 ; 20.9)	19.2 (10.6 ; 30.2)	50.8 (11.8 ; 98.9)	10.6 (4.6 ; 17.9)	15.0 (7.7 ; 23.4)	41.9 (9.3 ; 83.4)
	Smoking	25.3 (18.6 ; 33.4)	23.5 (17.9 ; 30.3)	-7.0 (-32.4 ; 27.8)	69.6 (51.3 ; 95.4)	93.3 (66.3 ; 126.1)	33.9 (-5.2 ; 76.5)	47.6 (36.7 ; 62.5)	58.2 (42.8 ; 76.5)	22.5 (-10.5 ; 59.1)

LDL: low-density lipoprotein cholesterol.

Definitions of cardiovascular diseases

Standard definitions of the CVDs were used.[2] Ischemic heart disease include acute myocardial infarction,[17] stable angina (defined by the Rose Angina Questionnaire), chronic ischemic heart disease and heart failure secondary to myocardial ischemia. For stroke, acute and persistent clinical signs of brain dysfunction that lasted >24 hours or caused death were considered (World Health Organization). Lower extremity peripheral artery disease was defined as an ankle-brachial index <0.9, and for aortic aneurysm, the presence of thoracic and abdominal aneurysms was considered. Atrial fibrillation and *flutter* were diagnosed by electrocardiogram. For hypertensive heart disease, symptomatic heart failure was considered due to the direct and indirect long-term effects attributable to hypertension. Cardiomyopathy was defined as symptomatic heart failure due to primary myocardial disease or exposure to toxins, whereas acute myocarditis was defined as an acute, time-limited condition due to inflammation. For endocarditis and rheumatic heart disease, clinical diagnosis was used, and estimates for rheumatic heart disease included cases identified by clinical history, physical examination, or standardized echocardiographic criteria for definite disease (including subclinical disease). For non-rheumatic valve diseases, calcific aortic valve disease, mitral degenerative valve disease and others were considered.[2,8]

Statistical analysis

The statistical models reported in the GBD 2019 study were used (Supplement 1: Supplementary Methods).[2,4,7] Data sources for models are available online at the Global Health Data Exchange website (*http://ghdx.healthdata.org/*).[8]

Metrics

In the present study, the metrics used to estimate the burden of disease attributable to RF were mortality and years of life lost due to disability – disability-adjusted life years (DALYs) – from 1990 to 2019.

For Brazil, GBD mortality estimates have some particularities. Mortality was estimated using data from the mortality information system (*Sistema de Informação Sobre Mortalidade*: SIM) coded according to the International Classification of Diseases.[18] To adjust for quality issues in the reporting of causes of death, corrections were made for underreporting of deaths and for causes considered of little use for public health, called *garbage codes*, or unspecific causes. *Garbage code* redistribution algorithms were developed by the GBD study considering evidence from various sources, such as medical literature, expert opinion, and statistical techniques.[7]

To calculate DALYs, the years of life lost due to premature death (years of life lost, YLLs) are added, with reference to the maximum observed life expectancy, to the years lived with disability (YLD). YLDs represent the non-fatal disease burden and are determined by the prevalence of the condition multiplied by the *disability weight* caused by the condition. The prevalence of the conditions was estimated using representative population data, including cohort studies, registries, population surveys, and administrative data, applying statistical methods that adjust for differences in study

definitions and methods. *Disability weights* reflect the severity of different conditions and were developed through previously validated surveys with the general population.[8]

In comparisons over time and between PSC, age-standardized rates were considered utilizing the direct method, using the global age composition of the GBD 2019. For the other analyses, non-standardized rates were presented. For each of the analyzed RFs, the attributable burden for total CVDs and for each disease separately, when applicable, was estimated. The ranking of RF was constructed to assess the changes that occurred between 1990 and 2019, according to sex, as well as the risk factor *ranking* for each of the PSC in 2019. The 95% UI was calculated and cited for each estimate, as previously described in the GBD methodology.[2]

Sociodemographic index

The sociodemographic index (SDI) is used by the GBD as an estimate of the socioeconomic level of each country to assess its association with CVD risk factor and burden metrics, as a function of the global epidemiological transition.[4,7] SDI was calculated for each country or territory from 1990 to 2019 and represents the weighted geometric mean of *per capita* income, education level and total fertility rate, allowing for the comparison of the performance of each country with others of similar socioeconomic level.

Additionally, the SPSS software version 23.0 for Mac OSX (*SPSS Inc., Chicago, Illinois*) was used to perform correlations (*Spearman's* method) between the percent change in age-standardized mortality rates and SEV between 1990 and 2019 and the SDI of each PSC in 2019. A p-value <0.05 was considered statistically significant.

Results

The geographic and sociodemographic characteristics of each of the PSC can be accessed in Table S1.

The percent contribution of CVD attributable to RF to mortality in 2019 in the different PSC was heterogeneous, ranging from 32.1%, 31.7%, 30.7% and 28.2% in Portugal, East Timor, Cape Verde and Brazil, respectively, to rates as low as 12% to 13.9% in the other countries (Figure S1). The percentage attributable to RF was high (>75%) in all PSC, being lowest in Portugal (78.8%) and Brazil (82.6%). Table S2 shows the age-standardized SEV rates for each cardiovascular RF, with 95% UI, by sex, for 1990 and 2019 and the percent change in the period. A significant increase in SEV related to alcohol consumption and high BMI was observed in all countries. For high SBP, a significant reduction was observed in Portugal and a trend towards stability in Brazil and East Timor, contrasting with a trend to increase in other countries, especially Equatorial Guinea (Table S2).

Figure 1 shows the *ranking* of age-standardized CVD mortality rates attributable to RF in the PSC, by sex, in 1990 and 2019. It was observed that high SBP remained as the main risk factor for CVD in all countries during this period. There was an increase in the importance of high fasting blood glucose – except in Brazil – and this factor ranked between the 3rd and 4th positions in 2019 in all PSC. On the other hand, smoking fell in the ranking of attributable mortality in all countries except Sao Tome and Principe (where it remained in the 8th the position). There was a greater reduction in Brazil (3rd to 6th) and Equatorial Guinea (6th to 8th). High LDL cholesterol had a stable or decreasing trend in all countries, except in Portugal and Brazil. The Figure S2 depicts a similar pattern for DALYs rates attributable to cardiovascular RF.

The Figure S3 shows the crude and age-standardized CVD mortality and DALYs rates attributed to the selected FR between 1990 and 2019. There was an increase in the absolute number of CVD deaths and DALYs attributable to all FR except for some trends observed in Portugal, with a decline for dietary factors, high LDL cholesterol and high SBP, and a stable trend for high BMI and high fasting plasma glucose. On the other hand, when analyzing age-standardized mortality rate and DALYs, there is a contrast between Brazil and Portugal – which showed a decline for all RFs – and the other PSC, that showed a trend towards stability or increase. The exception was smoking, which declined in all PSC, except for Mozambique, São Tomé and Príncipe and East Timor (Figure S3, Tables 1 and 2, Supplementary Tables 3 and 4).

Figure 2 shows the percentage of CVD deaths attributable to each cardiovascular risk factor, by country, in 1990 and 2019. High SBP remained with the highest percentage, with even an increase observed in all PSC except Portugal. Still, it was noted an overall increase in the contribution of dietary risks between 1990 and 2019 (3rd to 2nd) as well as in alcohol consumption, high fasting plasma glucose and high BMI. Conversely, there was a percent reduction of high LDL cholesterol and, especially, smoking, although the latter still has a more significant contribution in Portugal, Brazil and East Timor.

In the analysis of CVD mortality rates attributable to selected RF by PSC (Figure 3), it was observed that high SBP ranked first in all PSC in 1990 and 2019. In 1990, CVD mortality rates per 100,000 inhabitants attributed to PAS were highest in Equatorial Guinea (253.5), Angola (225.3) and Guinea Bissau (214.0), while in 2019, these rates were highest in Mozambique (224.1), Guinea Bissau (220.4) and East Timor (210.4), with the most significant reductions observed in Portugal (-66.6%, 95% UI -71.0 - 61.2%) and Brazil (-49.8%, 95% UI -52.5 - -47.1%). Dietary risks, high fasting plasma glucose, high LDL-cholesterol and air pollution were among the top five RF in most PSC in 1990 and 2019, except for the markedly lower rates attributable to air pollution in Brazil and Portugal both in 1990 and in 2019, also with a more significant reduction in these countries in the period. The increase in mortality rates attributable to alcohol consumption in nearly all PSC, except for Brazil and Portugal, and the reduction in smoking (also notably in Brazil [-69.5%] and Portugal [-73.2%]) were also remarkable, despite the still relatively higher rates in these two countries and in East Timor in 2019 (Figure 3, Table 1). Table 2 shows similar patterns for DALYs attributable to RF in the PSC.

Assessing CVD mortality rate and DALYs attributable to the combined cardiovascular RF, Figure 4 shows a trend towards stability between 1990 – 2019 in most PSC for crude rates, with a decreasing trend in Portugal and Equatorial Guinea, and an increase in East Timor. For age-standardized rates, Portugal

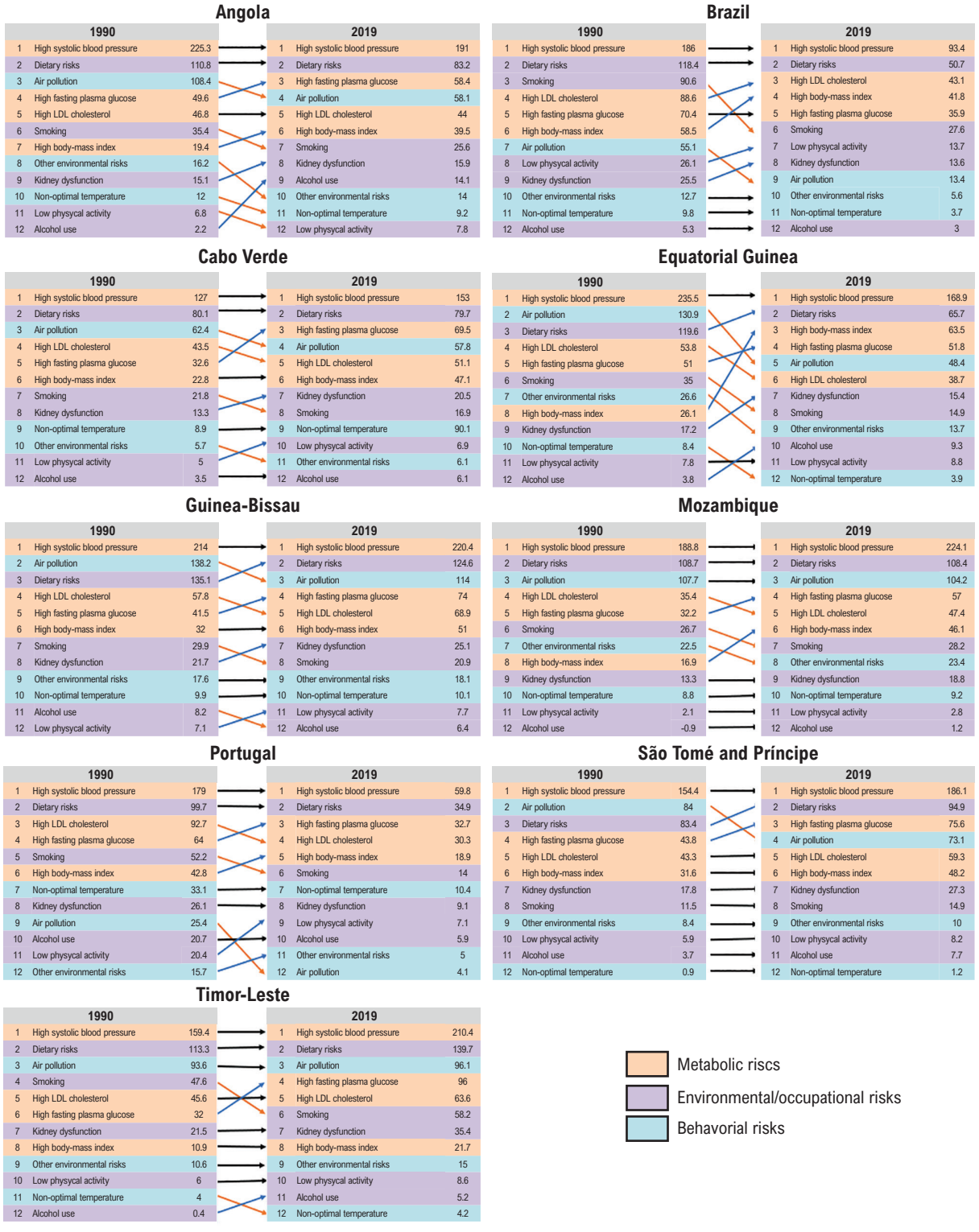


Figure 1 – *Ranking of cardiovascular disease age-standardized mortality rates (/100,000 inhabitants) attributable to risk factors in Portuguese-speaking countries in 1990 and 2019.*

Table 2 – Age-standardized disability-adjusted life years (DALYs) per 100,000 inhabitants

Countries	Risk Factors	Female			Male			Both		
		1990	2019	Percent Change %	1990	2019	Percent Change %	1990	2019	Percent Change %
Angola	All risk factors	5999.5 (4395.2 ; 7665.4)	4685.7 (3830.6 ; 5842.6)	-21.9 (-42.3 ; 9.6)	7806.8 (6071.9 ; 9648.6)	5927.2 (4931.1 ; 7175.3)	-24.1 (-42.7 ; 4.1)	6929.8 (5616.7 ; 8339.7)	5274.4 (4415.4 ; 6432.1)	-23.9 (-40.1 ; -0.7)
	Air pollution	2127.2 (1414.2 ; 2901.9)	1115.8 (806.5 ; 1503.7)	-47.5 (-63.4 ; -22.7)	3009.4 (2271.4 ; 3794.0)	1590.1 (1196.9 ; 2069.5)	-47.2 (-62.6 ; -24.9)	2577.7 (1987.6 ; 3287.7)	1336.5 (992.5 ; 1759.4)	-48.2 (-62.4 ; -28.8)
	Alcohol use	15.3 (-77.1 ; 114.3)	198.8 (70.0 ; 347.4)	1202.9 (-11035.7 ; 5853.2)	134.6 (-44.1 ; 339.4)	503.4 (303.1 ; 728.6)	273.9 (-2894.5 ; 3150.6)	74.5 (-35.3 ; 193.4)	335.1 (209.2 ; 493.8)	349.7 (-3664.4 ; 3172.1)
	Dietary risks	2014.8 (1306.8 ; 2966.1)	1425.8 (965.2 ; 2141.5)	-29.2 (-49.7 ; 2.1)	3077.2 (2228.5 ; 4197.0)	2070.4 (1501.1 ; 2877.1)	-32.7 (-50.8 ; -4.7)	2556.4 (1894.9 ; 3468.2)	1726.4 (1214.6 ; 2489.6)	-32.5 (-49.2 ; -8.7)
	High body mass index	509.4 (110.9 ; 1175.3)	1039.4 (534.9 ; 1624.8)	104.0 (12.2 ; 528.9)	551.6 (108.5 ; 1342.1)	1064.7 (505.3 ; 1729.3)	93.0 (8.1 ; 500.2)	532.7 (113.3 ; 1263.7)	1055.2 (545.3 ; 1649.2)	98.1 (13.9 ; 486.0)
	High fasting plasma glucose	616.7 (366.8 ; 994.2)	732.7 (425.4 ; 1157.0)	18.8 (-23.8 ; 92.8)	1328.9 (862.0 ; 2000.9)	1562.0 (1032.1 ; 2231.3)	17.5 (-21.1 ; 83.9)	963.5 (652.6 ; 1428.2)	1101.7 (739.8 ; 1595.8)	14.3 (-18.0 ; 66.0)
	High LDL cholesterol	863.5 (551.8 ; 1271.1)	791.9 (523.5 ; 1110.4)	-8.3 (-37.2 ; 33.9)	1329.1 (921.5 ; 1815.8)	1108.4 (789.7 ; 1522.1)	-16.6 (-41.3 ; 20.7)	1105.2 (792.6 ; 1493.0)	943.7 (663.9 ; 1292.7)	-14.6 (-37.7 ; 17.8)
	High systolic blood pressure	4547.3 (3319.4 ; 5912.5)	3629.9 (2857.3 ; 4543.0)	-20.2 (-41.9 ; 14.2)	5449.8 (4097.4 ; 6949.2)	4190.3 (3338.0 ; 5147.4)	-23.1 (-43.4 ; 8.2)	5025.9 (3962.3 ; 6245.9)	3912.6 (3189.4 ; 4828.3)	-22.2 (-40.0 ; 2.6)
	Kidney dysfunction	290.8 (188.4 ; 422.6)	284.8 (203.9 ; 389.4)	-2.1 (-28.8 ; 39.4)	399.0 (275.5 ; 537.0)	364.0 (270.1 ; 491.8)	-8.8 (-32.1 ; 27.1)	346.4 (248.9 ; 471.7)	322.6 (236.2 ; 437.1)	-6.9 (-28.4 ; 22.6)
	Low physical activity	131.1 (49.5 ; 276.6)	136.6 (55.2 ; 283.5)	4.2 (-26.1 ; 48.7)	99.7 (26.1 ; 252.5)	100.8 (29.7 ; 250.9)	1.1 (-26.5 ; 47.9)	117.8 (40.1 ; 266.5)	123.0 (46.0 ; 267.5)	4.4 (-23.3 ; 41.0)
	Non-optimal temperature	215.6 (108.2 ; 345.1)	153.6 (90.7 ; 237.8)	-28.7 (-50.8 ; 17.6)	281.9 (149.3 ; 452.1)	192.5 (112.2 ; 302.1)	-31.7 (-51.8 ; 2.2)	249.8 (134.5 ; 392.5)	172.2 (102.1 ; 268.5)	-31.1 (-49.4 ; 2.4)
	Other environmental risks	267.9 (100.7 ; 489.2)	209.8 (90.4 ; 363.2)	-21.7 (-42.7 ; 17.1)	485.8 (257.2 ; 760.0)	354.1 (196.6 ; 537.9)	-27.1 (-46.1 ; 1.6)	377.5 (184.9 ; 618.3)	275.0 (141.5 ; 437.0)	-27.1 (-43.4 ; -3.3)
	Smoking	346.2 (233.2 ; 481.0)	272.9 (195.7 ; 369.1)	-21.2 (-47.4 ; 20.3)	1602.4 (1208.8 ; 2044.9)	1163.6 (921.0 ; 1489.6)	-27.4 (-47.9 ; 4.4)	977.9 (757.7 ; 1229.1)	678.9 (539.0 ; 876.8)	-30.6 (-49.5 ; -2.7)
Brazil	All risk factors	5140.9 (4871.7 ; 5380.8)	2380.3 (2200.5 ; 2544.9)	-53.7 (-55.9 ; -51.4)	7756.5 (7453.1 ; 8034.5)	3888.3 (3646.9 ; 4112.3)	-49.9 (-52.8 ; -47.3)	6385.9 (6112.9 ; 6619.3)	3075.2 (2881.5 ; 3230.7)	-51.8 (-53.9 ; -50.0)
	Air pollution	1074.6 (805.7 ; 1372.7)	261.8 (189.5 ; 335.6)	-75.6 (-82.6 ; -66.5)	1617.5 (1168.8 ; 2094.1)	421.0 (304.6 ; 550.7)	-74.0 (-81.6 ; -63.1)	1333.9 (972.1 ; 1717.8)	335.8 (245.2 ; 436.8)	-74.8 (-82.3 ; -65.2)
	Alcohol use	24.8 (-16.1 ; 70.3)	14.8 (-6.7 ; 38.8)	-40.2 (-202.7 ; 184.0)	369.0 (227.5 ; 534.8)	183.5 (103.5 ; 267.1)	-50.3 (-62.5 ; -35.6)	189.0 (114.0 ; 272.5)	92.6 (53.3 ; 134.8)	-51.0 (-64.3 ; -34.6)
	Dietary risks	1976.8 (1603.5 ; 2462.7)	830.8 (654.2 ; 1067.4)	-58.0 (-62.0 ; -54.2)	3373.7 (2700.5 ; 4120.9)	1546.0 (1214.4 ; 1948.9)	-54.2 (-58.3 ; -50.0)	2641.3 (2140.9 ; 3252.7)	1160.8 (913.6 ; 1466.2)	-56.1 (-59.5 ; -52.8)
	High body mass index	1462.1 (907.2 ; 2094.3)	924.3 (682.4 ; 1181.6)	-36.8 (-45.0 ; -22.2)	1768.1 (955.9 ; 2704.4)	1315.5 (882.4 ; 1774.0)	-25.6 (-37.9 ; 2.2)	1611.6 (936.5 ; 2376.0)	1108.9 (778.3 ; 1460.7)	-31.2 (-40.5 ; -12.4)
	High fasting plasma glucose	1007.6 (715.9 ; 1432.7)	483.6 (345.7 ; 673.9)	-52.0 (-58.5 ; -44.5)	1593.2 (1141.6 ; 2253.9)	906.1 (635.8 ; 1274.9)	-43.1 (-49.4 ; -35.1)	1279.7 (922.2 ; 1800.5)	673.5 (485.1 ; 947.7)	-47.4 (-52.2 ; -41.9)
	High LDL cholesterol	1425.8 (1165.2 ; 1745.1)	692.2 (567.0 ; 842.5)	-51.5 (-54.8 ; -47.9)	2496.0 (2090.2 ; 2980.2)	1310.6 (1097.4 ; 1543.0)	-47.5 (-50.9 ; -43.8)	1940.1 (1614.4 ; 2322.9)	981.3 (817.1 ; 1162.4)	-49.4 (-52.0 ; -46.8)
	High systolic blood pressure	3264.0 (2911.5 ; 3596.7)	1551.6 (1365.7 ; 1731.8)	-52.5 (-55.6 ; -49.0)	4825.1 (4330.2 ; 5295.9)	2560.7 (2294.0 ; 2810.7)	-46.9 (-50.3 ; -43.5)	4011.3 (3600.8 ; 4407.4)	2019.3 (1806.5 ; 2216.0)	-49.7 (-52.0 ; -47.1)
	Kidney dysfunction	405.4 (330.0 ; 485.6)	204.4 (166.3 ; 247.4)	-49.6 (-53.4 ; -46.4)	625.9 (507.2 ; 754.1)	351.7 (284.7 ; 423.0)	-43.8 (-47.6 ; -39.9)	510.8 (414.8 ; 611.6)	272.1 (221.5 ; 325.5)	-46.7 (-49.5 ; -43.9)
	Low physical activity	387.4 (187.6 ; 624.2)	197.2 (110.7 ; 303.3)	-49.1 (-54.9 ; -38.3)	483.4 (191.0 ; 878.6)	275.7 (127.9 ; 478.4)	-43.0 (-49.8 ; -27.6)	434.5 (193.2 ; 747.3)	233.1 (118.2 ; 375.7)	-46.4 (-52.1 ; -34.5)
	Non-optimal temperature	160.5 (44.4 ; 251.2)	55.1 (15.0 ; 84.8)	-65.7 (-81.5 ; -34.3)	233.7 (53.3 ; 364.4)	87.6 (15.8 ; 135.2)	-62.5 (-86.1 ; -17.9)	195.7 (47.7 ; 304.9)	70.1 (13.4 ; 108.1)	-64.2 (-84.6 ; -30.1)
	Other environmental risks	180.0 (62.9 ; 301.9)	68.7 (23.0 ; 123.4)	-61.9 (-66.9 ; -58.2)	387.6 (201.3 ; 572.2)	150.1 (70.8 ; 237.3)	-61.3 (-67.0 ; -57.0)	277.4 (127.9 ; 428.4)	105.1 (44.6 ; 175.8)	-62.1 (-67.2 ; -58.3)
	Smoking	1720.6 (1562.0 ; 1894.4)	524.3 (473.0 ; 579.1)	-69.5 (-72.8 ; -66.1)	3008.3 (2835.8 ; 3176.8)	972.3 (899.1 ; 1048.2)	-67.7 (-70.1 ; -65.1)	2332.2 (2200.7 ; 2463.5)	731.3 (681.2 ; 782.2)	-68.6 (-70.9 ; -66.4)

Cabo Verde	All risk factors	3232.1 (2881.9 ; 3588.7)	3229.7 (2736.6 ; 3742.1)	-0.1 (-16.2 ; 19.6)	4980.5 (4462.4 ; 5466.7)	5375.2 (4739.6 ; 6059.0)	7.9 (-6.4 ; 24.7)	3949.1 (3575.7 ; 4282.9)	4178.4 (3663.4 ; 4722.8)	5.8 (-8.7 ; 22.2)
	Air pollution	1085.5 (916.9 ; 1284.9)	873.8 (686.1 ; 1074.6)	-19.5 (-37.3 ; 3.1)	1872.6 (1601.9 ; 2162.1)	1641.8 (1300.4 ; 2001.5)	-12.3 (-30.3 ; 7.9)	1409.1 (1221.4 ; 1628.4)	1218.3 (971.7 ; 1472.0)	-13.5 (-31.5 ; 6.8)
	Alcohol use	56.4 (1.2 ; 123.5)	53.8 (-5.9 ; 122.8)	-4.5 (-146.8 ; 342.6)	209.7 (95.7 ; 329.3)	296.6 (160.6 ; 461.8)	41.5 (-14.5 ; 145.4)	120.1 (54.2 ; 195.2)	161.2 (78.9 ; 260.9)	34.2 (-30.0 ; 158.2)
	Dietary risks	1200.0 (929.4 ; 1610.7)	1100.3 (800.4 ; 1528.9)	-8.3 (-25.5 ; 10.9)	2226.2 (1763.9 ; 2828.4)	1984.2 (1477.5 ; 2687.2)	-10.9 (-26.2 ; 6.6)	1620.7 (1283.0 ; 2085.9)	1494.1 (1100.1 ; 2041.3)	-7.8 (-23.1 ; 8.9)
	High body-mass index	667.6 (350.3 ; 1006.8)	996.0 (686.6 ; 1370.1)	49.2 (10.9 ; 132.8)	634.4 (231.2 ; 1133.9)	1415.4 (895.0 ; 2019.2)	123.1 (55.0 ; 364.7)	651.1 (305.9 ; 1050.2)	1197.0 (801.8 ; 1682.0)	83.8 (35.4 ; 201.0)
	High fasting plasma glucose	424.0 (272.3 ; 638.9)	891.1 (569.5 ; 1292.8)	110.2 (53.8 ; 192.3)	709.3 (474.4 ; 1049.6)	1390.1 (950.8 ; 1954.4)	96.0 (47.5 ; 165.4)	540.6 (356.6 ; 799.3)	1100.1 (744.7 ; 1552.5)	103.5 (58.5 ; 165.0)
	High LDL cholesterol	641.5 (478.6 ; 832.2)	754.7 (542.3 ; 998.2)	17.6 (-4.5 ; 41.4)	1211.2 (921.3 ; 1525.0)	1227.4 (907.3 ; 1582.9)	1.3 (-15.5 ; 20.9)	872.9 (669.5 ; 1097.6)	971.8 (717.6 ; 1245.1)	11.3 (-4.9 ; 31.5)
	High systolic blood pressure	2304.0 (1921.5 ; 2702.3)	2322.6 (1862.6 ; 2791.3)	0.8 (-20.1 ; 25.0)	3430.1 (2927.3 ; 3948.6)	3862.3 (3257.9 ; 4532.1)	12.6 (-5.7 ; 34.3)	2764.5 (2413.2 ; 3140.2)	3014.4 (2510.3 ; 3542.8)	9.0 (-7.2 ; 28.5)
	Kidney dysfunction	204.5 (150.6 ; 268.1)	286.8 (208.8 ; 371.1)	40.2 (15.4 ; 72.9)	322.2 (228.8 ; 420.9)	445.8 (330.5 ; 564.7)	38.4 (16.5 ; 63.7)	252.7 (185.4 ; 328.1)	356.8 (267.5 ; 455.0)	41.2 (21.0 ; 67.0)
	Low physical activity	66.9 (25.1 ; 147.8)	90.3 (35.4 ; 195.0)	35.0 (9.3 ; 70.9)	85.2 (23.4 ; 234.3)	107.9 (30.4 ; 270.0)	26.6 (1.0 ; 64.6)	74.3 (23.7 ; 184.2)	98.6 (34.5 ; 227.6)	32.6 (10.5 ; 63.0)
	Non-optimal temperature	130.6 (-1.5 ; 271.7)	119.7 (31.3 ; 249.1)	-8.4 (-44.8 ; 44.2)	209.7 (14.1 ; 434.8)	197.0 (43.0 ; 415.5)	-6.1 (-40.8 ; 38.0)	163.1 (11.3 ; 338.4)	153.8 (37.2 ; 320.2)	-5.7 (-37.9 ; 45.2)
	Other environmental risks	89.7 (16.5 ; 174.7)	75.0 (15.3 ; 145.3)	-16.4 (-33.1 ; 9.6)	162.8 (49.3 ; 289.0)	142.2 (40.7 ; 261.4)	-12.6 (-30.3 ; 3.3)	119.8 (29.9 ; 216.5)	103.6 (26.8 ; 192.6)	-13.5 (-29.3 ; 0.0)
	Smoking	255.0 (200.8 ; 309.6)	177.5 (140.3 ; 219.7)	-30.4 (-47.4 ; -8.8)	1025.1 (887.5 ; 1168.5)	730.9 (610.8 ; 861.7)	-28.7 (-41.4 ; -13.2)	573.3 (506.5 ; 645.6)	427.3 (360.6 ; 500.8)	-25.5 (-38.1 ; -8.9)
Equatorial Guinea	All risk factors	6569.8 (4287.1 ; 9089.7)	4163.8 (2926.5 ; 5799.9)	-36.6 (-60.5 ; 4.9)	9527.0 (7147.6 ; 11927.0)	4260.3 (3067.7 ; 5613.6)	-55.3 (-68.4 ; -33.0)	7918.4 (5983.2 ; 9983.4)	4227.0 (3165.8 ; 5693.3)	-46.6 (-62.5 ; -23.9)
	Air pollution	2482.8 (1481.8 ; 3765.3)	982.2 (596.0 ; 1473.7)	-60.4 (-79.0 ; -27.6)	3909.8 (2833.2 ; 5128.4)	1101.5 (689.6 ; 1597.4)	-71.8 (-83.0 ; -54.0)	3128.9 (2266.2 ; 4171.6)	1036.8 (645.1 ; 1528.6)	-66.9 (-80.4 ; -48.9)
	Alcohol use	40.9 (-78.3 ; 193.9)	141.0 (13.8 ; 305.7)	244.4 (-3080.2 ; 2575.4)	216.4 (-57.0 ; 539.2)	307.6 (129.9 ; 516.4)	42.1 (-1112.9 ; 1274.7)	118.2 (-46.4 ; 314.2)	210.5 (79.5 ; 381.6)	78.1 (-1552.1 ; 1339.9)
	Dietary risks	2125.4 (1242.0 ; 3354.3)	1184.7 (689.2 ; 1888.4)	-44.3 (-67.0 ; -7.2)	3671.8 (2554.0 ; 5092.8)	1360.5 (874.5 ; 2048.1)	-62.9 (-74.7 ; -43.6)	2823.4 (1987.6 ; 3980.8)	1266.3 (821.3 ; 1949.9)	-55.2 (-69.8 ; -34.4)
	High body-mass index	732.6 (198.2 ; 1561.9)	1507.2 (908.0 ; 2310.4)	105.7 (-0.1 ; 524.7)	705.4 (137.8 ; 1707.1)	1398.5 (815.0 ; 2158.8)	98.3 (-8.0 ; 714.5)	723.5 (187.0 ; 1594.7)	1471.1 (904.3 ; 2214.8)	103.3 (-1.7 ; 549.0)
	High fasting plasma glucose	658.2 (357.3 ; 1088.6)	744.7 (434.3 ; 1193.3)	13.1 (-36.4 ; 99.5)	1553.6 (973.5 ; 2331.5)	1175.5 (754.0 ; 1744.0)	-24.3 (-50.4 ; 20.2)	1046.1 (698.0 ; 1551.0)	921.0 (596.3 ; 1372.7)	-12.0 (-42.2 ; 31.2)
	High LDL cholesterol	972.1 (552.2 ; 1559.5)	722.0 (428.7 ; 1124.7)	-25.7 (-57.0 ; 26.1)	1683.6 (1153.8 ; 2312.9)	782.6 (492.7 ; 1176.6)	-53.5 (-68.8 ; -26.2)	1298.4 (875.7 ; 1817.4)	754.8 (478.0 ; 1133.3)	-41.9 (-61.9 ; -13.4)
	High systolic blood pressure	4934.3 (3200.0 ; 6958.9)	3270.3 (2258.5 ; 4577.1)	-33.7 (-59.8 ; 11.2)	6611.8 (4760.9 ; 8476.4)	3093.9 (2140.7 ; 4141.8)	-53.2 (-67.7 ; -29.1)	5714.8 (4252.3 ; 7288.3)	3218.6 (2341.0 ; 4384.1)	-43.7 (-61.2 ; -18.4)
	Kidney dysfunction	321.0 (187.7 ; 508.2)	286.4 (183.8 ; 427.6)	-10.8 (-46.3 ; 51.5)	493.2 (334.7 ; 677.9)	281.3 (190.3 ; 403.4)	-43.0 (-59.7 ; -15.8)	399.3 (278.4 ; 561.6)	286.1 (190.9 ; 411.9)	-28.4 (-51.0 ; 2.9)
	Low physical activity	143.2 (49.4 ; 319.9)	152.2 (62.1 ; 308.1)	6.2 (-36.3 ; 82.9)	122.1 (32.9 ; 318.6)	97.6 (28.6 ; 233.5)	-20.1 (-50.0 ; 33.6)	136.9 (46.4 ; 310.4)	131.4 (50.6 ; 274.1)	-4.0 (-37.4 ; 50.0)
	Non-optimal temperature	145.8 (-15.2 ; 347.3)	65.4 (9.8 ; 163.8)	-55.1 (-82.2 ; -10.3)	215.1 (-4.8 ; 506.9)	65.3 (8.9 ; 169.8)	-69.7 (-95.6 ; -42.1)	177.5 (-11.7 ; 418.0)	65.9 (9.9 ; 164.6)	-62.9 (-85.6 ; -30.0)
	Other environmental risks	435.3 (213.2 ; 748.2)	212.3 (102.9 ; 355.0)	-51.2 (-70.5 ; -21.8)	879.4 (538.8 ; 1293.4)	280.7 (154.4 ; 437.1)	-68.1 (-78.2 ; -53.3)	633.6 (374.6 ; 952.0)	240.9 (126.7 ; 382.1)	-62.0 (-73.4 ; -46.5)
	Smoking	263.5 (160.7 ; 408.5)	138.5 (84.6 ; 219.1)	-47.4 (-70.5 ; -5.7)	1885.9 (1341.1 ; 2486.9)	702.2 (473.2 ; 1003.9)	-62.8 (-75.6 ; -41.8)	990.3 (726.1 ; 1299.4)	377.1 (258.1 ; 542.7)	-61.9 (-74.9 ; -42.9)

Guinea-Bissau	All risk factors	6,230.3 (4699.3 ; 7828.9)	6284.9 (4934.5 ; 7962.6)	0.9 (-26.3 ; 39.6)	8677.3 (6803.9 ; 10844.6)	7626.5 (6117.8 ; 9356.4)	-12.1 (-34.9 ; 19.9)	7415.5 (5951.3 ; 9059.8)	6919.5 (5515.9 ; 8586.3)	-6.7 (-29.8 ; 23.5)
	Air pollution	2680.9 (1920.2 ; 3605.5)	2375.9 (1785.9 ; 3066.2)	-11.4 (-36.9 ; 24.9)	3918.3 (2878.4 ; 5226.8)	3047.4 (2349.2 ; 3813.7)	-22.2 (-43.8 ; 9.1)	3279.7 (2470.8 ; 4272.8)	2692.3 (2078.8 ; 3414.8)	-17.9 (-39.5 ; 11.6)
	Alcohol use	90.2 (-11.3 ; 210.3)	76.1 (-23.7 ; 209.3)	-15.6 (-242.3 ; 303.3)	431.4 (195.9 ; 707.7)	350.1 (140.1 ; 607.3)	-18.8 (-62.9 ; 60.8)	254.1 (109.4 ; 424.2)	202.5 (68.1 ; 373.0)	-20.3 (-69.4 ; 68.7)
	Dietary risks	2447.2 (1684.4 ; 3503.7)	2406.1 (1665.2 ; 3521.1)	-1.7 (-30.0 ; 38.5)	3923.7 (2770.2 ; 5444.2)	3266.2 (2369.6 ; 4473.7)	-16.8 (-40.0 ; 15.6)	3155.9 (2275.0 ; 4403.3)	2804.6 (1995.1 ; 3895.0)	-11.1 (-34.2 ; 20.6)
	High body mass index	1065.0 (416.6 ; 1923.0)	1665.5 (942.3 ; 2572.9)	56.4 (2.1 ; 186.9)	824.4 (233.4 ; 1772.1)	1257.4 (510.7 ; 2209.9)	52.5 (-1.7 ; 212.7)	950.3 (330.9 ; 1810.6)	1480.4 (763.7 ; 2401.0)	55.8 (6.2 ; 186.6)
	High fasting plasma glucose	609.5 (387.3 ; 951.1)	1235.5 (745.1 ; 1946.8)	102.7 (31.1 ; 221.6)	969.6 (628.3 ; 1475.4)	1460.9 (933.3 ; 2188.9)	50.7 (0.5 ; 132.0)	782.3 (518.7 ; 1164.3)	1332.4 (863.9 ; 2007.8)	70.3 (18.8 ; 144.0)
	High LDL cholesterol	1079.7 (717.8 ; 1574.2)	1276.2 (872.9 ; 1764.5)	18.2 (-20.2 ; 72.0)	1665.4 (1122.7 ; 2384.7)	1657.0 (1154.2 ; 2188.0)	-0.5 (-30.4 ; 41.9)	1358.3 (940.5 ; 1914.3)	1456.2 (1018.8 ; 1943.0)	7.2 (-23.2 ; 51.4)
	High systolic blood pressure	4332.4 (3146.7 ; 5614.9)	4529.6 (3409.1 ; 5890.7)	4.6 (-25.3 ; 47.8)	5534.3 (4184.5 ; 7156.4)	5216.6 (3984.4 ; 6616.8)	-5.7 (-32.5 ; 31.7)	4916.5 (3848.8 ; 6174.5)	4866.1 (3790.0 ; 6146.4)	-1.0 (-26.6 ; 32.7)
	Kidney dysfunction	414.3 (293.9 ; 562.3)	490.9 (352.1 ; 667.9)	18.5 (-15.8 ; 65.4)	549.5 (381.0 ; 759.5)	558.5 (400.8 ; 742.1)	1.6 (-25.7 ; 37.9)	479.7 (349.3 ; 634.7)	523.4 (379.7 ; 701.7)	9.1 (-18.4 ; 46.1)
	Low physical activity	102.1 (35.2 ; 236.2)	118.9 (42.5 ; 276.8)	16.5 (-17.9 ; 66.6)	145.9 (39.6 ; 377.6)	137.4 (40.0 ; 350.7)	-5.8 (-31.5 ; 32.2)	123.4 (38.7 ; 302.8)	128.1 (42.0 ; 307.6)	3.9 (-20.9 ; 40.1)
	Non-optimal temperature	174.0 (-486.0 ; 390.6)	185.3 (28.6 ; 332.2)	6.5 (-163.7 ; 90.3)	253.7 (-731.3 ; 532.3)	227.8 (12.2 ; 389.2)	-10.2 (-157.2 ; 40.9)	212.6 (-593.7 ; 433.0)	205.4 (35.6 ; 361.4)	-3.4 (-168.6 ; 52.4)
	Other environmental risks	286.6 (115.1 ; 489.2)	292.8 (126.2 ; 493.2)	2.2 (-26.4 ; 49.3)	559.3 (303.4 ; 866.5)	484.1 (277.2 ; 732.4)	-13.4 (-37.2 ; 21.5)	417.5 (208.7 ; 652.4)	379.9 (197.8 ; 600.9)	-9.0 (-33.8 ; 22.7)
	Smoking	328.4 (227.6 ; 452.0)	287.5 (204.4 ; 385.8)	-12.4 (-42.4 ; 28.9)	1388.6 (1014.8 ; 1840.9)	918.1 (700.6 ; 1162.9)	-33.9 (-54.5 ; -4.6)	837.9 (637.7 ; 1089.7)	580.5 (446.5 ; 734.0)	-30.7 (-51.5 ; -3.9)
Mozambique	All risk factors	4984.7 (4089.4 ; 5939.3)	4771.3 (3678.2 ; 6235.3)	-4.3 (-29.1 ; 28.7)	6407.0 (5226.9 ; 7754.2)	8455.5 (6898.2 ; 10077.4)	32.0 (3.3 ; 67.2)	5688.1 (4798.3 ; 6665.6)	6479.1 (5166.2 ; 8024.3)	13.9 (-11.7 ; 44.9)
	Air pollution	2035.6 (1527.2 ; 2728.0)	1691.8 (1227.1 ; 2338.9)	-16.9 (-40.8 ; 16.5)	2776.1 (2089.8 ; 3714.1)	3312.6 (2608.0 ; 4064.1)	19.3 (-11.4 ; 59.6)	2397.5 (1852.1 ; 3150.0)	2440.8 (1876.1 ; 3110.1)	1.8 (-24.4 ; 36.3)
	Alcohol use	-20.9 (-52.7 ; 14.1)	-10.9 (-69.6 ; 54.9)	-47.6 (-935.3 ; 689.0)	-7.5 (-117.8 ; 110.2)	118.4 (-120.0 ; 385.4)	-1688.0 (-4458.0 ; 4236.8)	-14.2 (-73.8 ; 48.0)	49.0 (-69.1 ; 186.7)	-444.1 (-2464.3 ; 3711.1)
	Dietary risks	1965.6 (1178.6 ; 3032.0)	1714.4 (977.2 ; 2743.3)	-12.8 (-37.5 ; 20.2)	2806.2 (1846.8 ; 4085.1)	3164.3 (2127.9 ; 4520.4)	12.8 (-16.0 ; 51.4)	2373.1 (1546.7 ; 3505.3)	2383.0 (1518.4 ; 3527.0)	0.4 (-23.6 ; 32.4)
	High body mass index	470.9 (131.6 ; 997.6)	1098.0 (579.1 ; 1761.4)	133.2 (32.4 ; 484.0)	437.0 (89.7 ; 1040.9)	1477.1 (679.9 ; 2453.0)	238.0 (98.9 ; 908.9)	457.0 (115.5 ; 1038.7)	1283.8 (634.4 ; 2077.3)	180.9 (67.8 ; 605.3)
	High fasting plasma glucose	415.2 (266.7 ; 674.7)	611.2 (351.5 ; 1029.6)	47.2 (-14.4 ; 136.1)	755.9 (475.7 ; 1128.2)	1745.4 (1139.4 ; 2522.4)	130.9 (61.8 ; 241.8)	571.2 (381.3 ; 824.4)	1101.3 (720.8 ; 1622.2)	92.8 (37.9 ; 173.5)
	High LDL cholesterol	616.5 (432.7 ; 878.1)	694.6 (447.4 ; 1017.6)	12.7 (-20.9 ; 56.5)	949.1 (676.3 ; 1329.1)	1496.6 (1065.4 ; 2013.3)	57.7 (17.1 ; 116.3)	777.2 (566.7 ; 1090.9)	1062.9 (745.3 ; 1448.8)	36.7 (2.9 ; 82.7)
	High systolic blood pressure	3718.3 (2937.6 ; 4645.2)	3668.6 (2693.3 ; 4911.8)	-1.3 (-28.8 ; 37.3)	4566.7 (3562.9 ; 5600.0)	6288.4 (5000.2 ; 7703.7)	37.7 (6.4 ; 78.1)	4147.7 (3396.3 ; 5038.5)	4901.3 (3813.0 ; 6156.2)	18.2 (-9.7 ; 52.3)
	Kidney dysfunction	246.8 (184.3 ; 333.0)	290.4 (200.8 ; 408.5)	17.7 (-14.5 ; 61.2)	339.5 (250.3 ; 455.6)	547.5 (407.3 ; 713.9)	61.3 (23.7 ; 108.8)	292.0 (221.2 ; 384.1)	408.8 (302.2 ; 543.5)	40.0 (7.2 ; 78.8)
	Low physical activity	31.2 (10.9 ; 86.8)	35.6 (12.3 ; 95.7)	14.0 (-19.7 ; 59.8)	38.3 (11.9 ; 109.6)	59.7 (18.2 ; 168.5)	55.9 (13.5 ; 107.4)	34.9 (11.8 ; 96.3)	46.8 (15.5 ; 130.9)	34.0 (0.9 ; 75.9)
	Non-optimal temperature	149.8 (70.6 ; 247.3)	132.2 (71.2 ; 216.2)	-11.8 (-39.2 ; 35.3)	194.7 (95.0 ; 318.5)	237.2 (131.7 ; 383.7)	21.9 (-10.6 ; 77.9)	171.9 (84.7 ; 278.4)	180.8 (98.6 ; 290.4)	5.2 (-23.0 ; 56.2)
	Other environmental risks	261.7 (121.8 ; 446.7)	250.6 (125.9 ; 417.4)	-4.2 (-29.7 ; 32.6)	718.6 (493.5 ; 992.0)	755.6 (486.2 ; 1051.0)	5.1 (-19.0 ; 35.2)	478.1 (302.8 ; 698.4)	472.2 (285.2 ; 698.0)	-1.2 (-24.1 ; 26.3)
	Smoking	281.5 (206.0 ; 381.2)	259.9 (176.3 ; 362.1)	-7.7 (-39.2 ; 35.4)	1144.0 (886.4 ; 1461.9)	1362.9 (1056.3 ; 1739.2)	19.1 (-11.8 ; 59.9)	693.8 (552.7 ; 858.8)	761.4 (587.0 ; 968.6)	9.7 (-18.3 ; 46.7)

Portugal	All risk factors	3975.2 (3678.9 ; 4220.2)	1259.7 (1125.8 ; 1379.5)	-68.3 (-70.5 ; -66.0)	6467.6 (6199.8 ; 6737.6)	2307.9 (2164.6 ; 2458.8)	-64.3 (-66.1 ; -62.4)	5089.2 (4813.4 ; 5329.9)	1742.1 (1601.3 ; 1867.5)	-65.8 (-67.4 ; -63.9)
	Air pollution	383.5 (140.9 ; 684.6)	58.6 (34.2 ; 84.3)	-84.7 (-92.1 ; -63.2)	635.5 (214.7 ; 1135.0)	115.6 (67.1 ; 168.5)	-81.8 (-90.8 ; -53.6)	498.6 (173.3 ; 889.3)	85.1 (49.3 ; 123.3)	-82.9 (-91.3 ; -58.4)
	Alcohol use	156.7 (65.6 ; 250.4)	34.5 (11.6 ; 59.6)	-78.0 (-87.6 ; -66.2)	817.7 (545.1 ; 1084.0)	244.2 (159.3 ; 335.1)	-70.1 (-75.0 ; -65.3)	434.4 (315.3 ; 557.0)	126.3 (85.6 ; 172.2)	-70.9 (-76.6 ; -65.2)
	Dietary risks	1284.8 (1060.2 ; 1551.1)	421.2 (341.8 ; 527.1)	-67.2 (-69.9 ; -63.8)	2418.6 (1986.6 ; 2921.4)	928.3 (751.5 ; 1140.0)	-61.6 (-64.6 ; -58.1)	1799.3 (1477.3 ; 2165.0)	655.6 (535.7 ; 806.8)	-63.6 (-66.1 ; -60.4)
	High body-mass index	826.0 (466.4 ; 1206.6)	327.5 (208.2 ; 459.9)	-60.4 (-65.1 ; -51.2)	1186.0 (563.5 ; 1876.8)	554.2 (305.8 ; 830.1)	-53.3 (-59.7 ; -39.5)	997.8 (527.0 ; 1519.4)	435.5 (255.2 ; 633.1)	-56.4 (-61.4 ; -45.4)
	High fasting plasma glucose	835.3 (539.4 ; 1328.9)	370.1 (253.2 ; 541.8)	-55.7 (-69.3 ; -37.9)	1211.2 (832.5 ; 1830.0)	664.7 (475.1 ; 935.0)	-45.1 (-59.1 ; -28.6)	1005.5 (687.6 ; 1530.6)	503.2 (364.3 ; 711.2)	-50.0 (-61.6 ; -36.2)
	High LDL cholesterol	1128.6 (811.9 ; 1602.0)	346.0 (247.0 ; 476.9)	-69.3 (-72.0 ; -66.3)	2115.0 (1689.9 ; 2725.8)	750.7 (613.5 ; 924.6)	-64.5 (-67.6 ; -61.4)	1579.1 (1216.6 ; 2105.8)	534.5 (422.8 ; 687.7)	-66.1 (-68.9 ; -63.2)
	High systolic blood pressure	2545.2 (2121.7 ; 2988.7)	755.9 (614.3 ; 894.2)	-70.3 (-75.6 ; -64.2)	4088.5 (3569.3 ; 4595.6)	1437.8 (1255.6 ; 1611.7)	-64.8 (-68.7 ; -60.6)	3243.3 (2797.8 ; 3673.3)	1072.5 (938.7 ; 1209.2)	-66.9 (-70.3 ; -62.8)
	Kidney dysfunction	331.4 (255.8 ; 406.1)	107.3 (81.9 ; 134.3)	-67.6 (-70.4 ; -64.7)	472.2 (378.5 ; 570.1)	163.3 (129.3 ; 199.9)	-65.4 (-67.8 ; -62.6)	395.9 (312.8 ; 478.4)	133.4 (105.0 ; 162.6)	-66.3 (-68.6 ; -64.0)
	Low physical activity	241.0 (96.4 ; 454.2)	79.2 (34.1 ; 143.3)	-67.2 (-71.9 ; -59.5)	287.0 (86.6 ; 611.0)	105.6 (34.2 ; 210.8)	-63.2 (-70.7 ; -52.7)	265.6 (98.9 ; 524.9)	92.4 (35.7 ; 173.5)	-65.2 (-70.6 ; -58.3)
	Non-optimal temperature	402.4 (331.0 ; 480.2)	111.3 (89.0 ; 133.4)	-72.3 (-74.4 ; -70.3)	629.7 (517.6 ; 747.5)	195.3 (158.8 ; 235.2)	-69.0 (-70.9 ; -66.8)	504.2 (414.7 ; 600.5)	150.0 (121.7 ; 179.8)	-70.2 (-72.0 ; -68.3)
	Other environmental risks	163.0 (77.1 ; 253.2)	44.3 (18.6 ; 72.6)	-72.8 (-77.5 ; -69.2)	439.9 (284.8 ; 596.2)	119.0 (67.6 ; 171.9)	-72.9 (-77.6 ; -69.6)	282.9 (169.0 ; 398.2)	76.9 (39.9 ; 115.5)	-72.8 (-77.1 ; -69.7)
	Smoking	644.0 (564.1 ; 726.7)	167.6 (147.9 ; 189.1)	-74.0 (-77.6 ; -70.0)	2087.3 (1971.8 ; 2207.3)	638.6 (591.6 ; 685.4)	-69.4 (-71.8 ; -67.0)	1285.1 (1205.3 ; 1361.9)	384.2 (355.8 ; 414.3)	-70.1 (-72.5 ; -67.6)
Sao Tome and Principe	All risk factors	4903.8 (4146.2 ; 5592.8)	5285.6 (4171.6 ; 6407.3)	7.8 (-14.3 ; 34.7)	4424.0 (3548.5 ; 5303.5)	5220.0 (4291.5 ; 6097.6)	18.0 (-7.1 ; 49.6)	4655.3 (3913.5 ; 5399.0)	5262.6 (4320.2 ; 6132.4)	13.0 (-8.0 ; 39.6)
	Air pollution	1927.4 (1580.0 ; 2328.9)	1612.4 (1214.5 ; 2072.8)	-16.3 (-36.9 ; 11.7)	1749.2 (1367.1 ; 2168.1)	1628.6 (1240.5 ; 2014.2)	-6.9 (-29.8 ; 23.8)	1838.3 (1482.7 ; 2214.2)	1622.8 (1253.5 ; 2017.9)	-11.7 (-32.2 ; 15.9)
	Alcohol use	54.3 (-35.1 ; 156.7)	122.0 (0.2 ; 271.2)	124.8 (-1878.3 ; 1478.3)	202.3 (87.7 ; 336.6)	317.8 (168.3 ; 499.0)	57.1 (-11.5 ; 224.3)	124.8 (38.8 ; 226.5)	216.5 (109.1 ; 349.9)	73.5 (-19.7 ; 372.5)
	Dietary risks	1651.5 (1207.6 ; 2333.8)	1742.7 (1174.3 ; 2546.6)	5.5 (-19.0 ; 34.5)	1720.3 (1250.9 ; 2386.2)	1940.4 (1375.8 ; 2690.4)	12.8 (-11.6 ; 45.3)	1671.0 (1244.1 ; 2325.2)	1840.1 (1297.4 ; 2582.2)	10.1 (-12.4 ; 39.8)
	High body mass index	1149.6 (634.4 ; 1783.9)	1748.3 (1147.1 ; 2490.6)	52.1 (8.2 ; 132.7)	610.1 (217.9 ; 1135.0)	1407.7 (866.1 ; 2120.3)	130.7 (51.9 ; 367.7)	889.6 (438.9 ; 1451.8)	1584.0 (1035.0 ; 2249.3)	78.0 (28.9 ; 180.7)
	High fasting plasma glucose	691.4 (450.7 ; 1043.4)	1163.6 (723.9 ; 1714.4)	68.3 (21.0 ; 139.6)	699.6 (424.2 ; 1103.9)	1239.2 (795.4 ; 1801.9)	77.1 (28.4 ; 151.8)	685.2 (451.9 ; 1025.6)	1198.8 (779.4 ; 1699.3)	75.0 (33.9 ; 136.3)
	High LDL cholesterol	888.6 (640.0 ; 1165.8)	1140.1 (795.8 ; 1498.6)	28.3 (-1.5 ; 65.5)	869.3 (588.7 ; 1186.0)	1198.7 (848.3 ; 1572.6)	37.9 (7.1 ; 79.1)	874.7 (622.5 ; 1152.5)	1171.4 (844.4 ; 1517.1)	33.9 (6.0 ; 69.4)
	High systolic blood pressure	3539.8 (2811.3 ; 4228.3)	3934.8 (3001.7 ; 4860.0)	11.2 (-14.1 ; 44.8)	3045.7 (2333.9 ; 3761.0)	3759.9 (2962.7 ; 4521.8)	23.5 (-4.0 ; 60.7)	3297.0 (2654.7 ; 3911.1)	3859.2 (3065.5 ; 4637.7)	17.0 (-6.3 ; 47.6)
	Kidney dysfunction	393.4 (304.1 ; 483.5)	556.2 (418.5 ; 716.7)	41.4 (12.3 ; 81.0)	290.2 (209.9 ; 388.4)	437.6 (323.3 ; 566.3)	50.8 (20.5 ; 90.3)	343.4 (259.3 ; 432.0)	500.6 (379.5 ; 629.2)	45.8 (19.3 ; 82.2)
	Low physical activity	97.0 (36.6 ; 212.3)	129.9 (51.2 ; 274.9)	33.9 (5.2 ; 72.7)	79.8 (22.8 ; 194.3)	109.0 (31.4 ; 268.5)	36.7 (4.9 ; 78.2)	88.6 (30.7 ; 202.8)	120.6 (41.9 ; 276.0)	36.1 (9.4 ; 69.8)
	Non-optimal temperature	16.3 (-55.9 ; 81.4)	21.7 (-12.1 ; 84.2)	33.3 (-278.6 ; 367.3)	15.4 (-47.6 ; 78.9)	22.3 (-13.0 ; 81.8)	45.4 (-384.5 ; 329.1)	15.8 (-53.4 ; 78.8)	22.0 (-13.1 ; 82.7)	39.9 (-334.0 ; 336.1)
	Other environmental risks	159.0 (42.7 ; 283.2)	155.8 (45.4 ; 289.4)	-2.0 (-24.1 ; 28.9)	200.0 (88.9 ; 325.3)	210.9 (96.8 ; 347.0)	5.5 (-18.7 ; 34.9)	177.1 (66.0 ; 300.8)	182.2 (70.6 ; 311.0)	2.9 (-17.5 ; 28.5)
	Smoking	154.4 (119.1 ; 196.4)	173.9 (126.4 ; 230.7)	12.6 (-19.9 ; 64.0)	470.5 (354.8 ; 599.5)	615.5 (474.0 ; 768.4)	30.8 (-1.8 ; 78.6)	306.2 (237.3 ; 377.2)	389.8 (300.0 ; 482.8)	27.3 (-3.4 ; 72.3)

Timor-Leste	All risk factors	5245.2 (4237.9 ; 6318.1)	5727.3 (4650.7 ; 6805.8)	9.2 (-16.5 ; 38.6)	5157.0 (3969.3 ; 7028.7)	7221.6 (5334.1 ; 9597.5)	40.0 (2.1 ; 77.9)	5205.8 (4272.1 ; 6425.2)	6476.7 (5147.2 ; 7999.9)	24.4 (-5.1 ; 54.9)
	Air pollution	2196.8 (1686.5 ; 2845.8)	1967.9 (1518.9 ; 2435.5)	-10.4 (-34.7 ; 19.2)	2080.5 (1505.1 ; 2932.2)	2410.1 (1650.4 ; 3329.1)	15.8 (-19.6 ; 51.9)	2140.0 (1646.1 ; 2762.8)	2190.6 (1631.0 ; 2828.2)	2.4 (-25.5 ; 33.2)
	Alcohol use	-2.7 (-13.5 ; 10.5)	11.9 (-16.3 ; 50.8)	-547.6 (-3649.5 ; 3536.9)	39.0 (-49.8 ; 142.4)	295.6 (57.7 ; 583.8)	657.3 (-5045.9 ; 6221.4)	18.9 (-28.1 ; 74.7)	154.3 (28.3 ; 318.1)	717.6 (-5256.3 ; 9199.6)
	Dietary risks	2380.6 (1638.0 ; 3255.7)	2418.4 (1677.1 ; 3291.1)	1.6 (-24.7 ; 31.4)	2645.0 (1804.2 ; 3825.0)	3452.2 (2270.2 ; 4875.1)	30.5 (-6.9 ; 71.7)	2516.4 (1794.0 ; 3435.5)	2936.2 (2011.2 ; 4031.7)	16.7 (-13.8 ; 51.1)
	High body-mass index	380.3 (96.7 ; 847.5)	590.8 (211.4 ; 1136.1)	55.4 (0.9 ; 210.6)	254.1 (43.6 ; 675.6)	668.8 (212.5 ; 1339.0)	163.2 (55.4 ; 577.8)	315.6 (71.8 ; 766.0)	630.9 (223.9 ; 1210.9)	99.9 (30.9 ; 303.3)
	High fasting plasma glucose	543.6 (359.3 ; 818.3)	1493.1 (986.7 ; 2191.2)	174.7 (94.2 ; 292.1)	597.0 (359.7 ; 941.4)	1832.7 (1179.3 ; 2821.4)	207.0 (110.8 ; 347.6)	569.1 (370.6 ; 852.3)	1659.8 (1121.0 ; 2421.9)	191.6 (113.4 ; 300.2)
	High LDL cholesterol	994.8 (710.9 ; 1343.8)	1180.1 (820.5 ; 1595.4)	18.6 (-12.4 ; 55.0)	976.6 (652.3 ; 1471.2)	1447.2 (885.4 ; 2125.4)	48.2 (1.6 ; 97.6)	988.2 (704.4 ; 1351.8)	1317.3 (894.6 ; 1800.3)	33.3 (-4.0 ; 73.7)
	High systolic blood pressure	3595.3 (2758.9 ; 4466.5)	3782.6 (2933.5 ; 4685.8)	5.2 (-24.2 ; 39.2)	3442.5 (2548.8 ; 4786.6)	5095.6 (3629.2 ; 6895.6)	48.0 (5.8 ; 92.4)	3523.1 (2794.6 ; 4533.6)	4442.1 (3386.4 ; 5642.3)	26.1 (-6.5 ; 61.4)
	Kidney dysfunction	502.7 (370.5 ; 653.6)	685.8 (504.1 ; 882.6)	36.4 (2.4 ; 75.0)	446.5 (305.9 ; 651.6)	761.5 (504.6 ; 1077.3)	70.5 (23.6 ; 121.4)	474.9 (343.5 ; 633.8)	724.4 (519.6 ; 965.7)	52.5 (15.9 ; 93.5)
	Low physical activity	83.0 (29.5 ; 195.3)	102.4 (34.9 ; 241.0)	23.4 (-7.2 ; 61.0)	93.5 (26.9 ; 217.3)	138.8 (42.0 ; 334.3)	48.5 (9.8 ; 91.8)	88.3 (28.9 ; 204.7)	120.4 (39.1 ; 285.0)	36.3 (7.3 ; 68.7)
	Non-optimal temperature	76.8 (12.6 ; 147.1)	73.8 (24.3 ; 141.0)	-3.9 (-49.4 ; 92.4)	75.7 (12.9 ; 149.9)	94.1 (30.3 ; 188.7)	24.3 (-35.6 ; 148.0)	76.4 (13.7 ; 146.5)	84.0 (27.0 ; 164.3)	10.0 (-40.5 ; 113.1)
	Other environmental risks	181.8 (50.0 ; 334.9)	199.7 (70.9 ; 355.6)	9.8 (-15.7 ; 55.3)	289.1 (141.3 ; 480.4)	384.0 (193.6 ; 622.3)	32.8 (-3.9 ; 73.2)	236.2 (97.4 ; 394.6)	291.8 (131.7 ; 468.7)	23.6 (-6.1 ; 59.4)
	Smoking	607.6 (445.7 ; 793.9)	545.8 (400.2 ; 711.8)	-10.2 (-36.7 ; 24.1)	1775.7 (1295.2 ; 2464.1)	2338.8 (1659.3 ; 3187.1)	31.7 (-9.1 ; 76.7)	1203.3 (923.6 ; 1583.0)	1445.2 (1053.0 ; 1920.8)	20.1 (-14.0 ; 59.0)

LDL: low-density lipoprotein cholesterol.

and Brazil had a strong downward trend, contrasting with the other countries, which showed a pattern of relative stability, or increase in the case of Mozambique and East Timor (PSC at the lower limits of the SDI).

Figure 5 shows the percent changes in mortality rates attributable to selected FR according to SDI in 2019 for each PSC. For all RF, an inverse correlation trend between SDI and percent change was observed, with statistical significance for dietary risks, high LDL cholesterol and high SBP. In the three PSC with the highest SDI (Portugal, Equatorial Guinea and Brazil) there was a considerable reduction in mortality rates attributable to all RF, except for high fasting glucose and high BMI, which tended, respectively, towards stability and increase only in Equatorial Guinea. For age-standardized SEV rates (Figure S4), the observed pattern was different, with a trend towards a negative correlation between the percent change in SEV rates attributable to smoking and SDI, with a significant positive correlation observed only for dietary factors.

Discussion

The PSC share sociocultural characteristics derived from the common Portuguese colonization, albeit in different degrees, often coexisting with traces of other cultures that participated in the colonization process and population composition. There are approximately 280 million Portuguese speakers in the world (approximately 216 million in Brazil); Portuguese is the fifth most spoken language in the world, and the most spoken in the southern hemisphere.[3] PSC have different socioeconomic realities and health system inequality, but similar ethnicities, which are known determining factors for CVD.[3,6,7] Our analysis of cardiovascular RF in PSC reinforces this heterogeneity, demonstrating a more significant reduction in CVD attributable to RF in countries with more structured health systems, and a close relationship between mortality trends and SDI, especially for dietary factors, high LDL cholesterol and elevated SBP.

A cross-sectional retrospective study of outpatients born in Portugal, Brazil and Africa, among others, from general practice clinics in Lambeth, South London, found that Portuguese speakers (the largest non-English language preference group) were more likely to have hypertension (OR=1.43, 95% CI 1.30 - 1.57); diabetes mellitus (OR=1.74, 95% CI=1.50 - 2.02); stroke (OR = 1.40, 95% CI = 1.08-1.81); obesity (OR=1.53, 95% CI=1.36-1.73); and smoking (OR=1.13, 95% CI = 1.02 to 1.25) compared to other ethnic groups. The authors discussed whether these differences could be explained by language barriers, or if they would derive from common genetic determinants, in addition to – above all – social and cultural factors.[19]

Our study found that CVD attributable to cardiovascular RF accounted for approximately 30% of total deaths in most PSC in 2019, although in countries with SDI less than 0.5, this percentage was less than 15%, except for Guinea Equatorial (0.69) which had the second highest SDI among all PSC. This trend is associated with a late epidemiological transition, *i.e.*, countries with the worst socioeconomic markers still tend to present increased proportions of these diseases and can, therefore, apply successful strategies previously applied to other PSC, trying to mitigate this trend.[3] The percentage attributable to RF was high (>75%) in all PSC, and high SBP was the main risk factor for

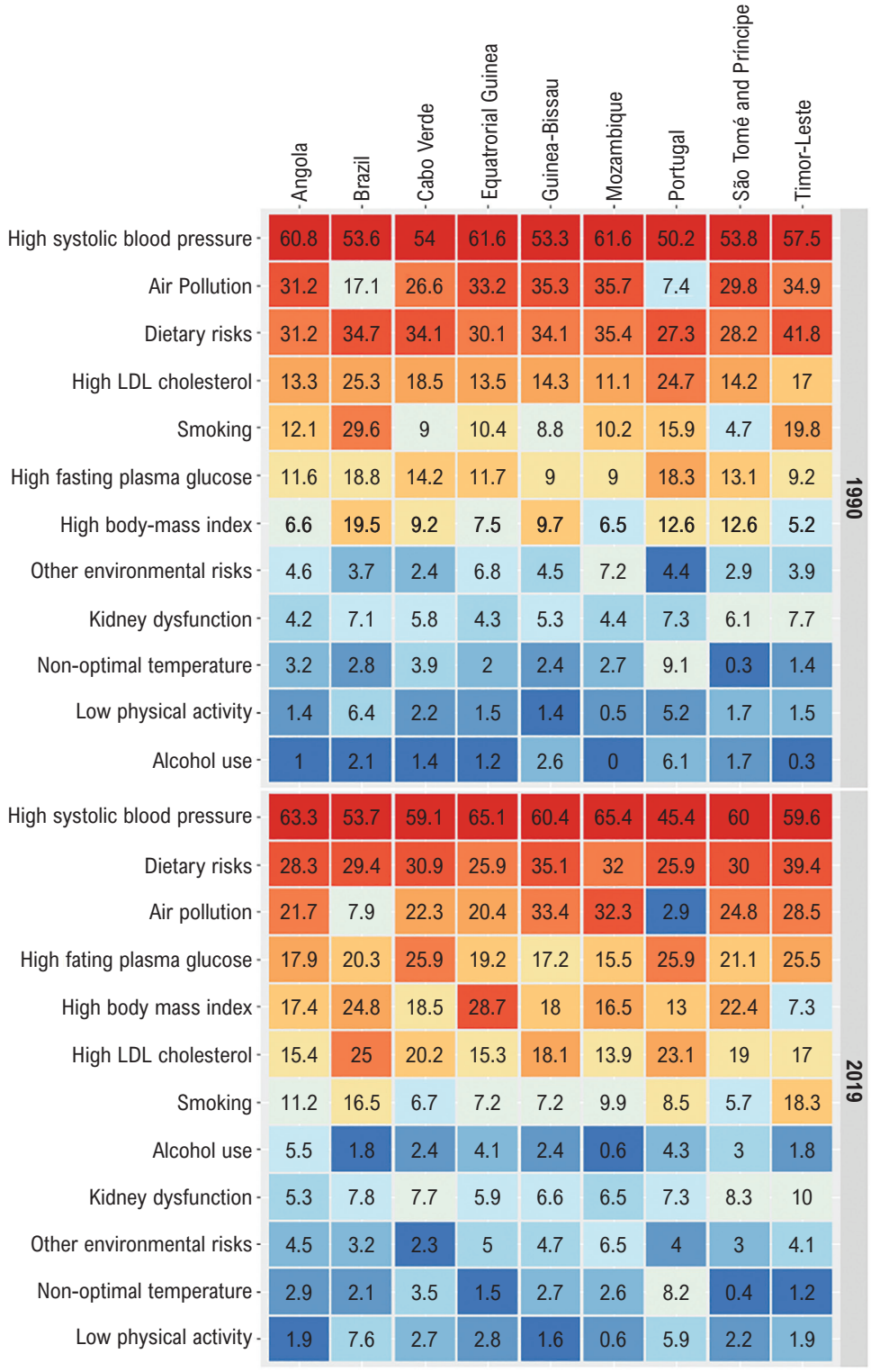


Figure 2 – *Percentage of total cardiovascular disease deaths attributable to each cardiovascular risk factor, by Portuguese-speaking country in 1990 and 2019.*

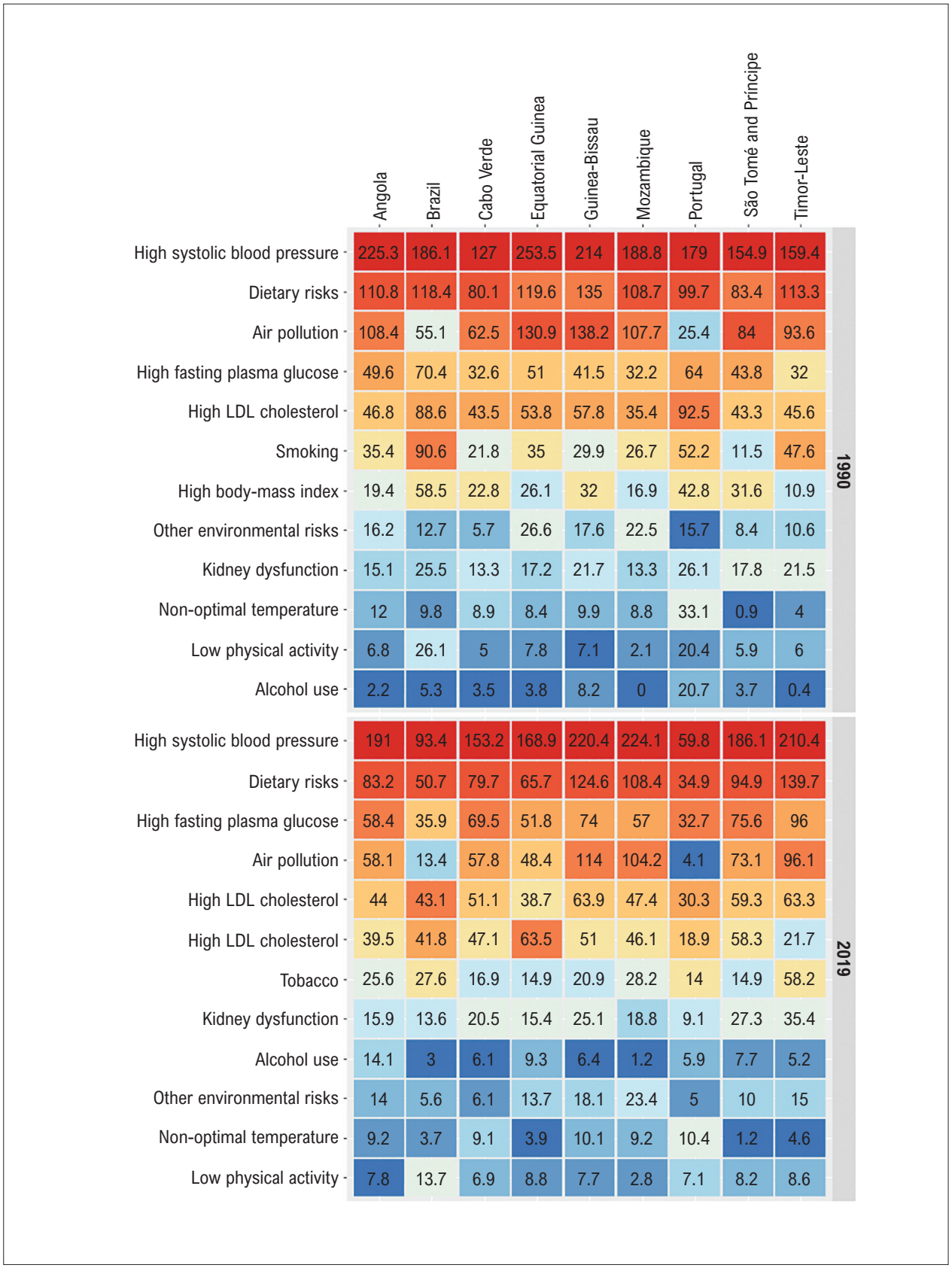


Figure 3 – *Age-standardized cardiovascular disease mortality rate (/100,000 inhabitants) attributable to cardiovascular risk factors, by Portuguese-speaking country, in 1990 and 2019.*

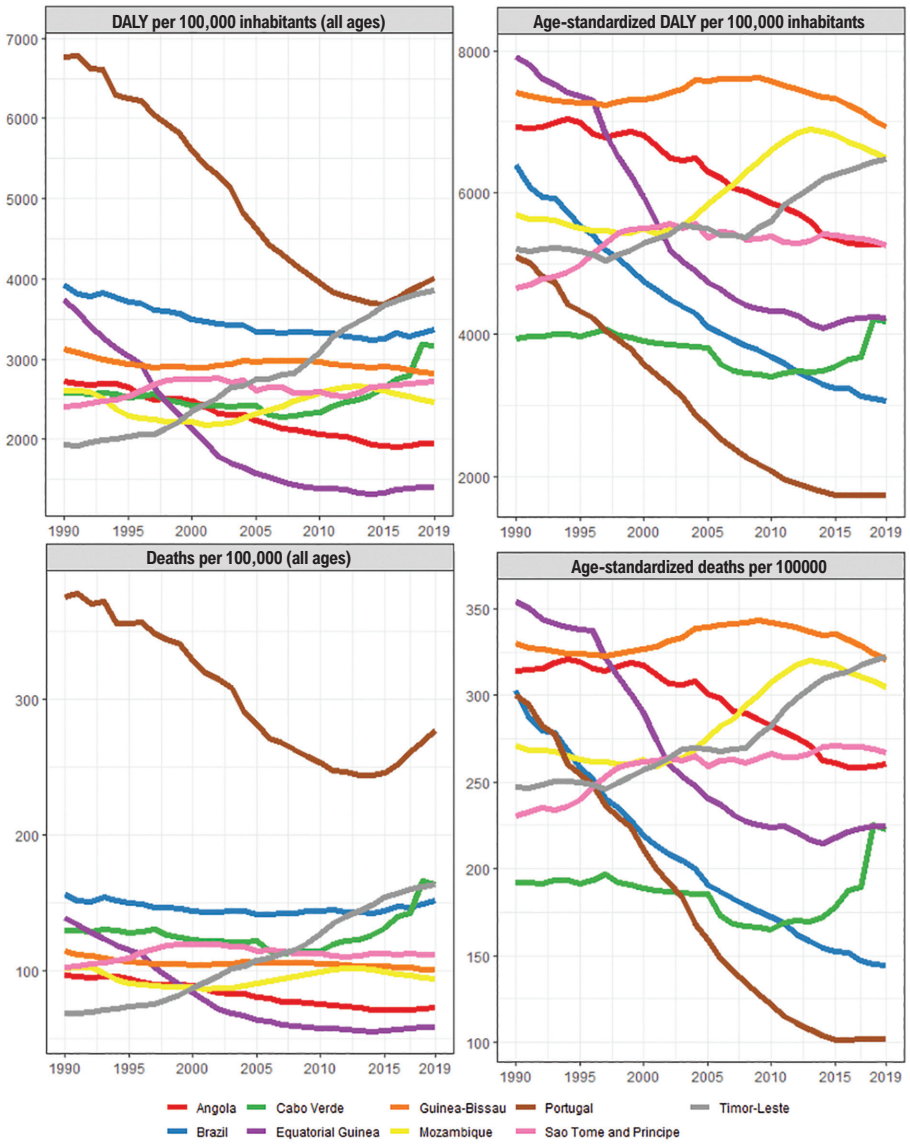


Figure 4 – *Cardiovascular disease mortality ate and disability-adjusted life years (DALYs) attributable to grouped cardiovascular risk factors in Portuguese-speaking countries, between 1990 and 2019.*

CVDs in the period analyzed. In all PSC, there was a reduction in the age-standardized CVD mortality rates attributed to RF in the period, especially in countries with higher SDI (Portugal, Equatorial Guinea and Brazil). It is noteworthy that Equatorial Guinea has the largest *per capita* gross domestic product in the African continent, however, resources are unevenly distributed, with little benefit to the general population and coexisting proportional mortality from chronic and infectious diseases.[6]

Hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking were the top five modifiable traditional cardiovascular RF observed in Africa in 2019.[4] At least one of these five RF is present in 80% to 95% of individuals who suffer a fatal or non-fatal cardiovascular event in the continent.[4,20] The same was observed for Brazil and Portugal,[3,21] except for smoking, which showed significant reductions in these countries during this period, as previously reported in another study,[4] as a result of public policies and coping campaigns.[4] On the other hand, an increase in mortality rates from CVDs attributable to alcohol consumption was observed in the PSC of Africa and in Equatorial Guinea and Guinea Bissau, probably reflecting the worldwide trend of increasing alcohol consumption with an impact on CVDs.[22]

It is noteworthy that CVD mortality rates attributable to high SBP remained first in the ranking in all PSC between 1990 and 2019. Again, more expressive reductions were observed in Portugal and Brazil,[3,21] probably associated with the

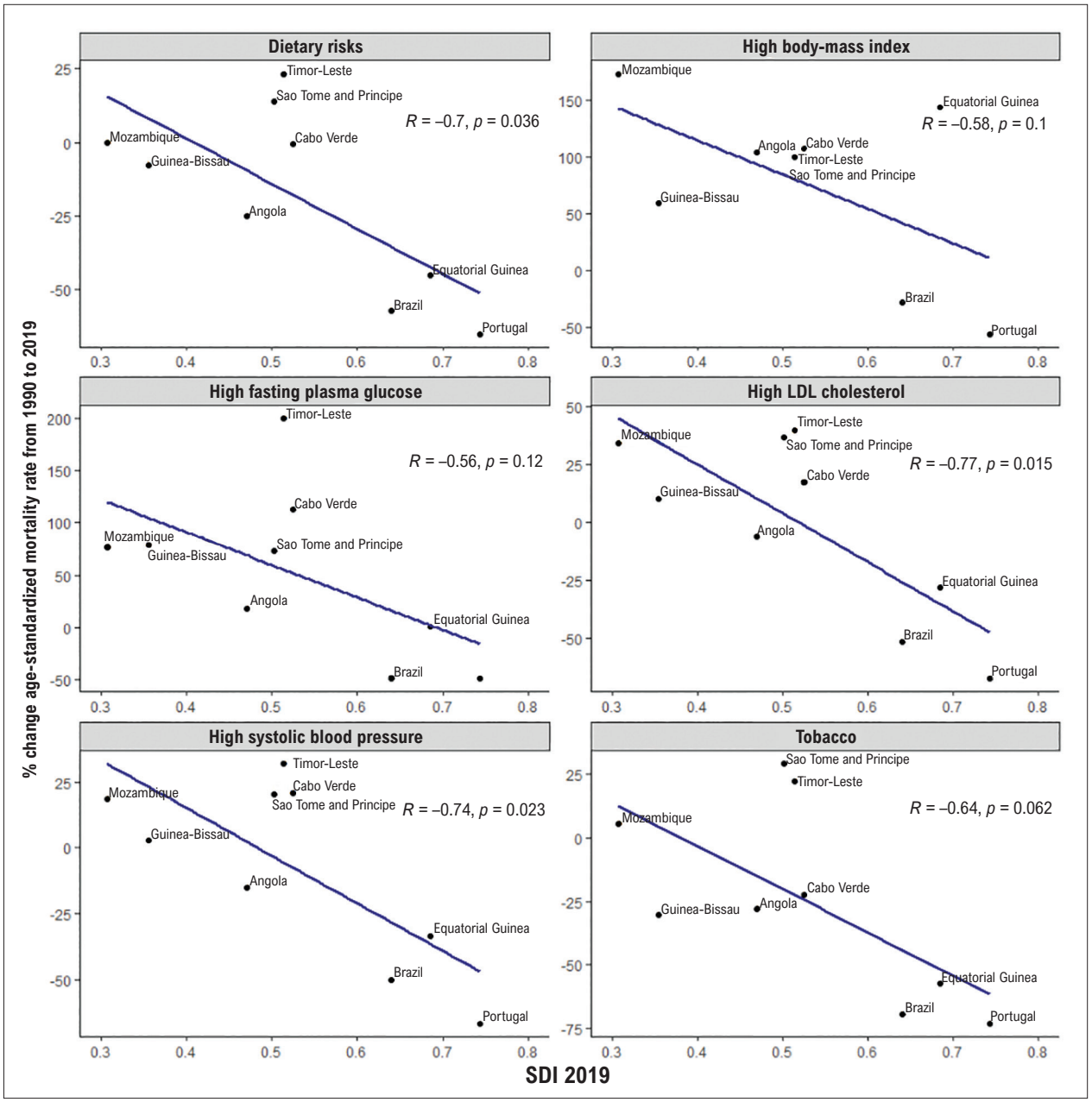


Figure 5 - *Correlation between the sociodemographic index (SDI) and the percent change in age-standardized cardiovascular disease mortality rates attributable to selected risk factors in Portuguese-speaking countries from 1990 to 2019.*

highest SDIs, but also with population policies to reduce salt intake, especially in Portugal, where there was a reduction in myocardial infarction and stroke attributable to high SBP.[21] These data show a change in the profile of countries with higher CVD mortality rates attributable to high SBP, with a decline in those with better socioeconomic indices and earlier epidemiological transition, with an inverse trend in those with lower SDIs.

The PSC showed an increase in dietary and metabolic risk factors attributable to CVD mortality. The *Prospective Urban Rural Epidemiology* (PURE) study, conducted in 21 countries, with 148,858 participants and a mean follow-up of 9.5 years, showed that higher intakes of refined grains, which accounted for 70% of caloric intake in African countries, were associated with higher SBP, and higher risk of all-cause and CVD mortality.[23] In our analysis, dietary risks associated with high fasting plasma glucose and high LDL-cholesterol were ranked among the top five RF in most PSC in 1990 and 2019, and correlated with PSC with lower SDIs. These findings were also observed in a GBD substudy that analyzed mortality and disease burden associated with CVD worldwide.[2]

A study that analyzed the burden of CVD in 194 countries around the world, between 1990 and 2019, showed a

downward trend in the DALYs, YLL and YLD, with higher rates of YLD in women compared to men,[24] with the same occurring in relation to the burden of CVDs attributable to cardiovascular RF.[4] These data highlight the heterogeneity of PSC in terms of mortality and disease burden, in which variations cannot be explained by the SDI alone, with a potential contribution of multiple factors such as gender, ethnicity and even cultural and environmental differences.

The PURE study suggested that a large proportion of premature CVD deaths could be avoided by decreasing some modifiable RF with global policies such as controlling hypertension and smoking and improving health education.[25] The impact of reducing others RF such as dietary risks and ambient air pollution may vary according to the socioeconomic level of each country, and with the development of internal regulations of economic activities (such as the emission of pollutants and rapairing of environmental damage).[26,27] Thus, strategies to address CVD mortality and burden in PSC could focus, at this time, on the most prevalent RF, with low-cost and high-impact population measures, such as reducing dietary intake of salt and calories, reducing tobacco and alcohol consumption, and blood pressure control.

Limitations and strengths of the study

Limitations related to the methodology of the GBD study have been previously detailed,[4,7] and are mainly related to the heterogeneity of primary data sources among the PSC, completeness of mortality statistics and limitations of extrapolating estimates for territories with low data quality – a condition observed for some PSC. There has been a progressive improvement in the completeness of prevalence and morbidity data; however, integrity and quality for some PSC are still limited, according to the GBD 2019.[4] As an example, there are very low rates or non-existent data on mortality in PSC in sub-Saharan Africa.[7,8] It is possible that there was also an inadequacy of the GBD study models for different countries in some groups of diseases subject to less epidemiological surveillance, especially non-notifiable cardiovascular RF. Furthermore, for some RF, there are no surveys or specific health surveillance programs in several PSC. Specifically regarding RF estimates, the GBD 2019 assumes uniform distribution of RR in all countries, for the same age and sex.[4] which may potentially increase uncertainty of the results. Primary studies, where available, report prevalence data as a measure of exposure to a risk factor, which limits comparability with risk exposure measures (SEV) of the GBD. Furthermore, the GBD methodology disregards distal RF, which can mediate the prevalence and mortality of intermediate RF, affecting their effects as social determinants of health.[28,29] Another methodological aspect is the limitation of modeling for the coexistence of simultaneous RF, which is known to result in a risk greater than the sum of individual factors (e.g., hypertension, in the presence of diabetes and smoking, potentiating ischemic heart disease).[2,30] Additionally, the adjustment method of RF for standardized definitions applied by GBD can be an additional source of bias.[4,15] Finally, despite similar colonization, the sociocultural, demographic, economic and ethnic heterogeneity of the PSC – influencing lifestyle habits, health behaviors, awareness and control of RF – may not be adequately captured by the analytical models.[6]

However, despite these limitations, GBD is a robust, comprehensive and validated methodology, from the epidemiological point of view, for estimating the burden of disease attributable to cardiovascular RF, through the production of comparable metrics between PSC – including those with scarce or no primary data. In addition, in light of the reality of local health systems, our data may help the reformulation of health policies.

Conclusions

The set of 12 cardiovascular RFs included in this analysis of GBD 2019 account for over 75% of the CVD burden in the nine PSC, with a greater impact of these diseases on mortality in Portugal, East Timor, Cape Verde and Brazil. High SBP remained as the main risk factor for cardiovascular mortality and DALYs between 1990 and 2019. There was a significant reduction in age-standardized cardiovascular mortality rates attributable to RF, especially in the PSC with better socioeconomic indices, such as Brazil, Portugal and Equatorial Guinea. Overall, there has been an increasing impact of dietary and metabolic RF, in parallel with reduced rates of tobacco smoking in most PSC. In addition, there was a marked negative correlation between the variation in cardiovascular mortality rates attributable to RF and SDI. These results show the heterogeneity among the PSC in relation to the epidemiology of the RF evaluated, suggesting the need for health policies and government actions adapted to the reality of each country, and for a collaboration between these nations to reduce the impact of CVD.

These data can help countries to identify common problems, being an important stimulus for the exchange of experiences between scientists and academic communities. The PSC must make progress in the engagement and solidarity between them,[31] especially those with more resources and technical capabilities, supporting the training of human resources and the development of partnerships.

Author Contributions

Conception and design of the research: Nascimento BR, Brant LCC, Ribeiro ALP, Oliveira GMM; Acquisition of data: Brant LCC, Polanczyk CA; Analysis and interpretation of the data: Nascimento BR, Ribeiro ALP, Malta DC, Oliveira GMM; Statistical analysis: Veloso GA; Obtaining financing: Polanczyk CA, Ribeiro ALP, Malta DC; Writing of the manuscript: Nascimento BR, Naback AND; Critical revision of the manuscript for intellectual content: Nascimento BR, Brant LCC, Naback ADN, Polanczyk CA, Ribeiro ALP, Malta DC, Ferreira AVL, Oliveira GMM.

Potential Conflict of Interest

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

Sources of Funding

Bruno R. Nascimento is partially funded by CNPq (Research Productivity Grant, 312382/2019-7), Edwards Lifesciences Foundation (*Improving the Prevention and Detection of Heart Valve Disease Across the Lifespan*, 2021) and FAPEMIG (APQ project-

000627-20). Carisi A. Polanczyk receives a research productivity grant, CNPq (313041/2017-2). Antonio LP Ribeiro is partially funded by CNPq (310679/2016-8 and 465518/2014-1) and by FAPEMIG (PPM-00428-17 and RED-00081-16). Deborah C Malta is partially funded by CNPq (Research Productivity Scholarship). The GBD Brazil project is funded by the Health Surveillance Secretariat, Ministry of Health (TED 148-2018).

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. World Health Organization. Global Action Plan for the Prevention and Control of NCDs 2013-2020. Geneva: WHO Library; 2013. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/.
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020 22;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
3. 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.
4. GBD 2019 Risk Factors Collaborators. Global Burden of 87 Risk Factors in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-49. doi: 10.1016/S0140-6736(20)30752-2.
5. Nascimento BR, Brant LCC, Yadgir S, Oliveira GMM, Roth G, Glenn SD, et al. Trends in Prevalence, Mortality, and Morbidity Associated with High Systolic Blood Pressure in Brazil from 1990 to 2017: Estimates from the "Global Burden of Disease 2017" (GBD 2017) Study. Popul Health Metr. 2020;18(Suppl 1):17. doi: 10.1186/s12963-020-00218-z.
6. Comunidade dos Países de Língua Portuguesa. Lisboa: CPLP; 2017 [cited 2022 Feb 23]. Available from: https://www.cplp.org/.
7. GBD 2019 Diseases and Injuries Collaborators. Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9.
8. GBD 2019 Diseases and Injuries Collaborators. GBD Compare - Viz Hub 2018. Washington: University of Washington; 2016 [cited 2022 Feb 23]. Available from: https://vizhub.healthdata.org/gbd-compare/.
9. Brasil. Ministério da Saúde. VIGITEL Brasil 2017: Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde; 2018.
10. Brasil. Ministério da Saúde. Indicadores e Dados Básicos de Saúde – Brasil; 2020 [Internet]. Ministério da Saúde do Brasil. 2020 [cited 2020 Jul 10]. Available from: www.saude.gov.br.
11. Malta DC, Santos NB, Perillo RD, 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. doi: 10.1590/1516-3180.2015.02090911.
12. Malta DC, Stopa SR, Iser BP, Bernal RT, Claro RM, Nardi AC, et al. Risk and Protective Factors for Chronic Diseases by Telephone Survey in Capitals of Brazil, Vigitel 2014. Rev Bras Epidemiol. 2015;18 (Suppl 2):238-55. doi: 10.1590/1980-5497201500060021.
13. Malta DC, Szwarcwald CL. Population-Based Surveys and Monitoring of Noncommunicable Diseases. Rev Saude Publica. 2017;51 (Suppl 1):2s. doi: 10.1590/S1518-8787.201705100supl1ap.
14. Telo GH, Cureau FV, Souza MS, Andrade TS, Copês F, Schaan BD. Prevalence of Diabetes in Brazil Over Time: A Systematic Review with Meta-Analysis. Diabetol Metab Syndr. 2016;8(1):65. doi: 10.1186/s13098-016-0181-1.
15. Malta DC, Felisbino-Mendes MS, Machado ÍE, Passos VMA, Abreu DMX, Ishitani LH, et al. Risk Factors Related to the Global Burden of Disease in Brazil and its Federated Units, 2015. Rev Bras Epidemiol. 2017;20 (Suppl 01):217-32. doi: 10.1590/1980-5497201700050018.
16. Malta DC, Szwarcwald CL, Silva JBD Jr. First Results of Laboratory Analysis in the National Health Survey. Rev Bras Epidemiol. 2019;22 (Suppl 02):E190001.SUPL.2. doi: 10.1590/1980-549720190001.supl.2.
17. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):618-51. doi: 10.1161/CIR.0000000000000617.
18. Malta DC, Teixeira R, Oliveira GMM, Ribeiro ALP. Cardiovascular Disease Mortality According to the Brazilian Information System on Mortality and the Global Burden of Disease Study Estimates in Brazil, 2000-2017. Arq Bras Cardiol. 2020;115(2):152-60. doi: 10.36660/abc.20190867.
19. Mackay A, Ashworth M, White P. The Role of Spoken Language in Cardiovascular Health Inequalities: A Cross-Sectional Study of People with Non-English Language Preference. BJGP Open. 2017;1(4):bjgpopen17X101241. doi: 10.3399/bjgpopen17X101241.
20. Noubiap JJ, Nansseu JR, Endomba FT, Ngouo A, Nkeck JR, Nyaga UF, et al. Active Smoking Among People with Diabetes Mellitus or Hypertension in Africa: A Systematic Review and Meta-Analysis. Sci Rep. 2019;9(1):588. doi: 10.1038/s41598-018-37858-z.
21. Abreu D, Sousa P, Matias-Dias C, Pinto FJ. Cardiovascular Disease and High Blood Pressure Trend Analyses from 2002 to 2016: After the Implementation of a Salt Reduction Strategy. BMC Public Health. 2018;18(1):722. doi: 10.1186/s12889-018-5634-z.
22. GBD 2016 Alcohol Collaborators. Alcohol Use and Burden for 195 Countries and Territories, 1990-2016: A Systematic Analysis for the Global Burden of Disease Study 2016. Lancet. 2018;392(10152):1015-35. doi: 10.1016/S0140-6736(18)31310-2.
23. Swaminathan S, Dehghan M, Raj JM, Thomas T, Rangarajan S, Jenkins D, et al. Associations of Cereal Grains Intake with Cardiovascular Disease and Mortality Across 21 countries in Prospective Urban and Rural Epidemiology Study: Prospective Cohort Study. BMJ. 2021;372:m4948. doi: 10.1136/bmj.m4948.
24. Masaebi F, Salehi M, Kazemi M, Vahabi N, Looha MA, Zayeri F. Trend Analysis of Disability Adjusted Life Years Due to Cardiovascular Diseases: Results from the Global Burden of Disease Study 2019. BMC Public Health. 2021;21(1):1268. doi: 10.1186/s12889-021-11348-w.
25. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable Risk Factors, Cardiovascular Disease, and Mortality in 155 722 Individuals from 21 High-Income, Middle-Income, and Low-Income Countries (PURE): A Prospective Cohort Study. Lancet. 2020;395(10226):795-808. doi: 10.1016/S0140-6736(19)32008-2.
26. Marć M, Tobiszewski M, Zabiegała B, Guardia M, Namieśnik J. Current Air Quality Analytics and Monitoring: A Review. Anal Chim Acta. 2015;853:116-26. doi: 10.1016/j.aca.2014.10.018.
27. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. Front Public Health. 2020;8:14. doi: 10.3389/fpubh.2020.00014.

28. Barros MBA, Lima MG, Medina LP, Szwarcwald CL, Malta DC. Social Inequalities in Health Behaviors Among Brazilian Adults: National Health Survey, 2013. Int J Equity Health. 2016;15(1):148. doi: 10.1186/s12939-016-0439-0.

29. Marmot M, Bell R. Social Determinants and Non-Communicable Diseases: Time for Integrated Action. BMJ. 2019;364:l251. doi: 10.1136/bmj.l251.

30. Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. V Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20. doi: 10.5935/abc.2013S010.

31. Desiderá Neto WA. A cooperação Internacional para o Desenvolvimento como uma Expressão Específica da Cooperação Internacional: Um levantamento Teórico. OIKOS. 2014;13(2):115-28.

*Supplemental Materials

For additional information, please click here.

Chemotherapy-induced Cardiac ^{18}F-FDG Uptake in Patients with Lymphoma: An Early Metabolic Index of Cardiotoxicity?

Mayara L. C. Dourado,[1] Luca T. Dompieri,[2] Glauber M. Leitão,[3] Felipe A. Mourato,[4] Renata G. G. Santos,[4] Paulo J. Almeida Filho,[4] Brivaldo Markman Filho,[1] Marcelo D. T. Melo,[5] Simone C. S. Brandão[1]

Departamento de Pós-Graduação em Ciências da Saúde, Universidade Federal de Pernambuco,[1] Recife, PE – Brazil
Faculdade de Medicina, Universidade Federal de Pernambuco,[2] Recife, PE – Brazil
Serviço de Oncologia, Hospital das Clínicas/Universidade Federal de Pernambuco,[3] Recife, PE – Brazil
Real Nuclear, Real Hospital Português,[4] Recife, PE – Brazil
Departamento de Medicina Interna, Universidade Federal da Paraíba,[5] João Pessoa, PB – Brazil

Abstract

Background: **It is uncertain whether myocardial fluorodeoxyglucose uptake occurs solely due to physiological features or if it represents a metabolic disarrangement under chemotherapy.**

Objective: **To investigate the chemotherapy effects on the heart of patients with lymphoma by positron emission tomography associated with computed tomography scans (PET/CT) with 2-deoxy-2[18F] fluoro-D-glucose (^{18}F-FDG PET/CT) before, during and/or after chemotherapy.**

Methods: **Seventy patients with lymphoma submitted to ^{18}F-FDG PET/CT were retrospectively analyzed. The level of significance was 5%. ^{18}F-FDG cardiac uptake was assessed by three measurements: left ventricular maximum standardized uptake value (SUVmax), heart to blood pool (aorta) ratio, and heart to liver ratio in all the exams. Body weight, fasting blood sugar, post-injection time, and the injected dose of ^{18}F-FDG between the scans were also compared.**

Results: **Mean age was 50.4 ± 20.1 years and 50% was female. The analysis was carried out in two groups: baseline vs. interim PET/CT, and baseline vs. post-therapy PET/CT. There was no significant difference in clinical variables or protocol scans variables. We observed an increase in left ventricular (LV) SUVmax from 3.5±1.9 (baseline) to 5.6±4.0 (interim), p=0.01, and from 4.0±2.2 (baseline) to 6.1±4.2 (post-therapy), p<0.001. A percentage increase ≥30% of LV SUVmax occurred in more than half of the sample. The rise of cardiac SUV was accompanied by an increase in LV SUVmax/Aorta SUVmax and LV SUVmean/Liver SUVmean ratios.**

Conclusion: **This study showed a clear increase in cardiac ^{18}F-FDG uptake in patients with lymphoma during and/or after chemotherapy. The literature corroborates with these findings and suggests that ^{18}F-FDG PET/CT is a sensitive and reliable imaging exam to detect early metabolic signs of cardiotoxicity.**

Keywords: **Cardiotoxicity; Chemotherapy; Lymphoma.**

Introduction

Chemotherapy and radiotherapy-induced cardiotoxicity (CTX) encompasses various forms of injury to the cardiovascular system, that trigger an increased production of reactive oxygen (ROS) and nitrogen species, lipid peroxidation and inflammation. This leads to cardiomyocyte apoptosis and interstitial fibrosis, increasing the risk for impaired coronary endothelial function, left ventricular (LV) dysfunction and heart failure.[1-3]

Today, CTX is monitored by periodic imaging with echocardiography for assessment of left ventricular ejection fraction (LVEF) reduction and/or decreased global longitudinal strain.[4] However, the diagnosis of CTX based on these cardiac function parameters is late, and can be an indication of a significant and irreversible myocardial injury.[5,6] Therefore, it is necessary to evaluate myocardial abnormalities at subcellular level for an early and sensitive assessment of drug-induced CTX.[7,8]

Cardiac imaging techniques of nuclear medicine have proved extremely useful to identify subclinical disease in the context of cancer therapy-induced organ damage.[9–11] Positron emission tomography associated with computed tomography scans (PET/CT) with 2-deoxy-2[18F] fluoro-

Mailing Address: Simone Cristina Soares Brandão •
Departamento de Medicina Nuclear – Hospital das Clínicas – Universidade Federal de Pernambuco – Rua Professor Moraes Rego, 1235.
Postal Code 50670-901, Recife, PE – Brazil
E-mail: sbrandaonuclearufpe@gmail.com
Manuscript received May 27, 2021, revised manuscript August 04, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210463

D-glucose (^{18}F-FDG) is widely used in oncology, especially in patients with lymphoma.[12,13] Tissue ^{18}F-FDG uptake and tissue distribution is variable and depend on several factors such as glucose level, fasting period and drugs.[14] Furthermore, recent data suggest that myocardial ^{18}F-FDG accumulation is not entirely due to glucose consumption.[15] The tracer retention was found to be dependent upon the enzymatic activity of hexose-6-phosphate-dehydrogenase (H6PD) in the endoplasmic reticulum (ER).[15] This enzyme can process many hexoses, including FDG,[16] to trigger a pentose phosphate pathway and preserve NADPH levels in response to oxidative stress conditions, such as CTX.[17]

This study aimed to identify potential early signs of metabolic cardiac injury by assessing changes in cardiac ^{18}F-FDG uptake by PET/CT in patients with lymphoma before, during and/or after chemotherapy.

Material and Methods

Patients

Seventy patients diagnosed with lymphoma and submitted to ^{18}F-FDG PET/CT in the Division of Nuclear Medicine of Real Hospital Português in Recife, Pernambuco, Brazil, between January 1, 2012 and August 28, 2017 were retrospectively analyzed in this study. The study was approved by the Research Ethics Board of the Federal University of Pernambuco Health Sciences Center, which granted a waiver of written consent due to the retrospective nature of the study.

Inclusion criteria were primary diagnosis of lymphoma, aged 10 years or older and, at least two ^{18}F-FDG PET/CT scans before, during and/or after chemotherapy. Exclusion criteria were no baseline or control tests, unavailability and/or inability to assess clinical data and imaging tests, and insulin therapy on the day of the scan.

Patients' clinical features, medical history and variables related to the ^{18}F-FDG PET/CT protocol recorded in their medical records were collected, such as, weight, injected dose of ^{18}F-FDG, fasting blood sugar (FBS) and time after injection. For imaging exams, ^{18}F-FDG uptake was quantified by measuring the mean and the maximum standardized uptake value (SUVmean and SUVmax, respectively).

Four patients had only baseline and interim PET/CT scans, 40 had only baseline and post-therapy and 26 had all three. For analysis, the patients were then divided into two groups, group 1, patients with baseline and interim PET/CT scan data (n = 30); and group 2, patients with baseline and post-therapy PET/CT data (n = 66). Thus, some patients participated in both analyses.

Each group was then divided in two subgroups according to the change in the LV ^{18}F-FDG SUVmax between baseline and control tests: a percentage increase above or equal to 30% (Group ≥ 30%), and a less than 30% ^{18}F-FDG uptake change (Group <30%). The choice of a 30% cutoff was based on PERCIST[18] (PET Response Criteria in Solid Tumors), which is a set of criteria for assessment of tumor response to chemotherapy and radiotherapy, through metabolic changes verified by ^{18}F-FDG PET/CT scans.[18]

^{18}F-FDG PET/CT Protocol

For the ^{18}F-FDG PET/CT, patients were instructed to fast at least six hours prior to the test, not to discontinue any medication or exercise for 24 hours before the scan. On the day of the scan, body weight (kg) and FBS were measured and, venous puncture was used to administer ^{18}F-FDG. Blood sugar levels should be below 180 mg/dL. The ^{18}F-FDG was administered at an activity dose of 3.7 to 4.8MBq/kg and after 60 minutes, the images were obtained by the PET/CT (Biograph 16, Siemens Healthcare, USA), extending from the base of the skull to the proximal-middle third of the femur, three minutes per bed position. The acquisition parameters of the CT scan included: 5mm slices, 120kV voltage, and no intravenous contrast administration.

Imaging processing was done with iterative reconstruction (two iteractions, eight subsets with Gaussian filter) by a nuclear physician, who performed a quantitative analysis with SUVmax and SUVmean. Both SUVs were measured at the left ventricle on fused PET/CT images and determined semi-automatically with the aid of the syngo via software version 5.1 (Siemens Healthcare) through the demarcation of a volume of interest (VOI) including the entire left ventricle. SUVmax and SUVmean for blood pool were measured by reconstruction of a region of interest (ROI) in the descendent aorta just after the aortic arch. SUVmax and SUVmean for liver were measured by reconstruction of a ROI of 4.0 cm diameter in the VI segment.

Statistical analysis

Data was analyzed with Stata 12.1 statistical software. Continuous variables were expressed as mean ± standard deviation (SD); and categorical variables were summarized by frequency and percentage. Percentage comparisons between two independent groups were performed using the Pearson's chi-square test or, when it was not applicable, the Fisher's exact test. The Student's t-test was used to compare two means for both independent and paired samples. In all tests, a significance level of 5% was used to reject the null hypothesis.

Results

The mean age of the 70 patients studied was 50.4 ± 20.1 years (16-88 years) and 50% were female. Twenty patients (28.6%) had hypertension and 10 (14.3%) had diabetes. About 67% (n= 47) had non-Hodgkin's lymphoma (nHL) and the remainder (n=23) had Hodgkin's lymphoma (HL). Only three patients (4.3%) underwent mediastinal radiotherapy between the end of chemotherapy and the control ^{18}F-FDG PET/CT scan. It was possible to define the chemotherapy regimen in 33 patients (47.1%) and all regimens included known cardiotoxic drugs (Table 1).

Group 1: baseline and interim ^{18}F-FDG PET/CT

There was standardization of the ^{18}F-FDG PET/CT protocol between the baseline and interim scans. There was no difference in the injected dose of ^{18}F-FDG, FBS and time post-injection between baseline and interim exams. Mean body weight of patients also did not change significantly,

making it possible to compare the 18F-FDG uptake in the target organs (Table 2).

On the other hand, 18F-FDG LV SUVmax increased at the interim scan compared to baseline. Similarly, there was a significant increase in the LV SUVmax/aorta SUVmax and LV SUVmean/liver SUVmean ratios from baseline to interim scans (Figure 1A). The mean time interval between baseline and interim scans was 95.4 ± 32.2 days.

Of the 30 patients who underwent baseline and interim 18F-FDG PET/CT scans,16 (53.3%) presented an increase ≥30% (Group ≥ 30%) in 18F-FDG LV SUVmax. Regarding clinical variables, such as cardiovascular risk factors and drugs in use, no differences were observed.

The values of the LV SUVmax/aorta SUVmax and LV SUVmean/liver SUVmean ratios also increased significantly at the interim evaluation compared to the baseline in the group ≥30% (Figure 1B). In the group<30% (n=14), there was no statistically significant increase in these ratios from baseline to interim scans (Figure 1C).

Group 2: baseline and post-therapy 18F-FDG PET/CT

Sixty-six patients underwent baseline and post-therapy 18F-FDG PET/CT scans. No statistically significant differences were seen in FBS, 18F-FDG injected activity and time post-injection were found between the two evaluations. Patients' mean body weight was slightly higher in the post-therapy scan compared with baseline (Table 3).

Table 1 – Clinical and therapeutic characteristics of the patients (n=70)

Variable	N (%)
Female sex	35 (50.0)
Hypertension	20 (28.6)
Diabetes	10 (14.3)
Dyslipidemia	14 (20.0)
Smoking	
Non-smoker	49 (70.0)
Former smoker	20 (28.6)
Current smoker	1 (1.4)
Alcoholism	0 (0)
Coronary artery disease	5 (7.1)
Hemodialysis	1 (1.4)
Medication	
No	10 (14.3)
Non-cardioprotective medication [a]	40 (57.1)
Cardioprotective medication [a]	20 (28.6)
Cancer	
Hodgkin's Lymphoma	23 (32.9)
Non-Hodgkin's Lymphoma	47 (67.1)
Chemotherapy [b]	
RCHOP	11 (33.3)
RCHOP + alternative	6 (18.2)
ABVD	11 (33.3)
ABVD + alternative	2 (6.1)
DA-EPOCH-R	1 (3.0)
BEACOPP	1 (3.0)
RCOP	1 (3.0)
Mediastinal Radiotherapy After Baseline Pet	3 (4.3)

[a] Cardioprotective medication: angiotensin II receptor blocker, beta-blocker, angiotensin-converting enzyme inhibitor. [b] Available for 33 patients. ABVD: Adriamycin or Doxorubicin + Bleomycin + Vinblastine + Dacarbazine; BEACOPP: Bleomycin + Etoposide + Adriamycin or Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisolone; DA-EPOCH-R: Dose-Adjusted Etoposide + Prednisolone + Vincristine + Cyclophosphamide + Doxorubicin or Hydroxydaunorubicin + Rituximab, RCHOP: Rituximab + Cyclophosphamide + Doxorubicin or Hydroxydaunorubicin + Vincristine + Prednisolone, RCOP: Rituximab + Cyclophosphamide + Vincristine + Prednisolone.

Table 2 – Comparison of body weight, fasting blood sugar, injected dose of ^{18}F-fluorodeoxy glucose (^{18}FDG), and mean post-injection time of patients between baseline and interim positron emission tomography associated with computed tomography (PET/CT) scans

Variable (N=30)	Baseline	Interim	p*
	Mean ± SD	Mean ± SD	
Weight (Kg)	75.3 ± 14.3	74.7 ± 13.5	0.551
FBS (mg/dL)	92.6 ± 19.5	93.4 ± 19.9	0.816
Dose of ^{18}FDG mCi	9.1 ± 2.7	9.1 ± 2.0	0.971
Post-injection time (min)	68.8 ± 10.0	65.9 ± 9.9	0.308

**Student's t-test. FBS: Fasting Blood Sugar*

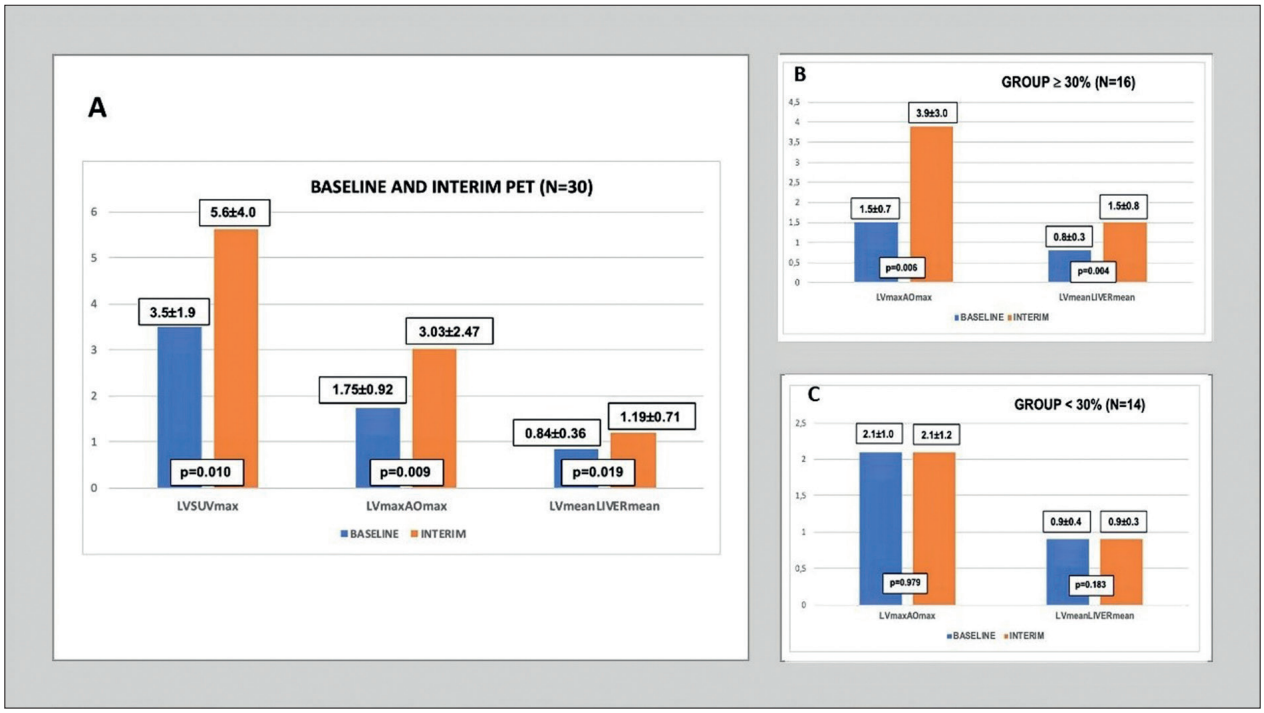


Figure 1 – *Group 01 – A) Comparison of maximum left ventricular (LV) standardized uptake value (SUVmax), LV SUVmax/aorta SUVmax and mean LV SUV (SUV mean)/liver SUVmean ratios, between baseline and interim positron emission tomography (PET). B) Comparison of LV SUVmax/aorta SUVmax and LV SUVmean/liver SUVmean ratios between baseline and interim PET in the Group with increase of LV SUVmax ≥ 30%. C) Comparison of LV SUVmax/Aorta SUVmax and LV SUVmean/Liver SUVmean ratios, between Baseline and Interim PET in the Group with increase of LV SUVmax < 30%; LVmaxAOmax: LV SUVmax/Aorta SUVmax, LVmean LIVER mean: LV SUVmean/Liver SUVmean.*

The mean value of the LV SUVmax was significantly higher in the post-therapy PET. We observed an absolute increase in the ^{18}F-FDG cardiac uptake value of 2.1 (95% CI:1.3 to 3.0), which represents a percentage increase of 66.5% (95%CI:43.3% to 89.7%) over the baseline scan.

The values of the LV SUV max/aorta SUV max and the LV SUV mean/liver SUV mean ratios also increased significantly in the post-therapy PET as compared with baseline, Figure 2A. The mean time between baseline and post-therapy exams was 231.8±125.7 days.

Of the 66 patients, 38 (57.6%) presented ≥30% increase in ^{18}F-FDG cardiac uptake (Group ≥ 30%). There were no differences between the groups regarding the clinical variables, such as cardiovascular risk factors and medications in use.

The values of the LV SUVmax/aorta SUVmax and LV SUVmean/liver SUVmean ratios increased significantly in the post-therapy evaluation compared to the baseline in the ≥30% group (Figure 2B). In the Group<30% (n=28), there was no statistically significant increase in the ratios (Figure 2C).

Figure 3 illustrates a case example of the ^{18}F-FDG LV SUV max behavior before, during and after chemotherapy.

Discussion

The present study showed that chemotherapy in patients with lymphoma caused an unbalance in cardiac metabolism, evidenced by a higher myocardial ^{18}F-FDG uptake. These

Table 3 – Comparison of body weight, fasting blood sugar, injected dose of ^{18}F-fluorodeoxy-glucose (^{18}FDG), and mean post-injection timel of patients between baseline and post-therapy positron emission tomography associated with computed tomography scans (PET/CT)

Variable (N=66)	Baseline Pet	Post-Therapy Pet	p*
	Mean ± SD	Mean ± SD	
Weight (Kg)	72.7 ± 14.8	75.2 ± 15.2	0.014
FBS (mg/dL)	91.6 ± 15.6	91.6 ± 16.7	>0.99
Dose of ^{18}FDG mCi	9.2 ± 2.3	9.5 ± 2.2	0.308
Post-injection time (min)	68.6 ± 9.1	70.4 ± 5.8	0.606

**Student's t-test. FBS: Fasting Blood Sugar*

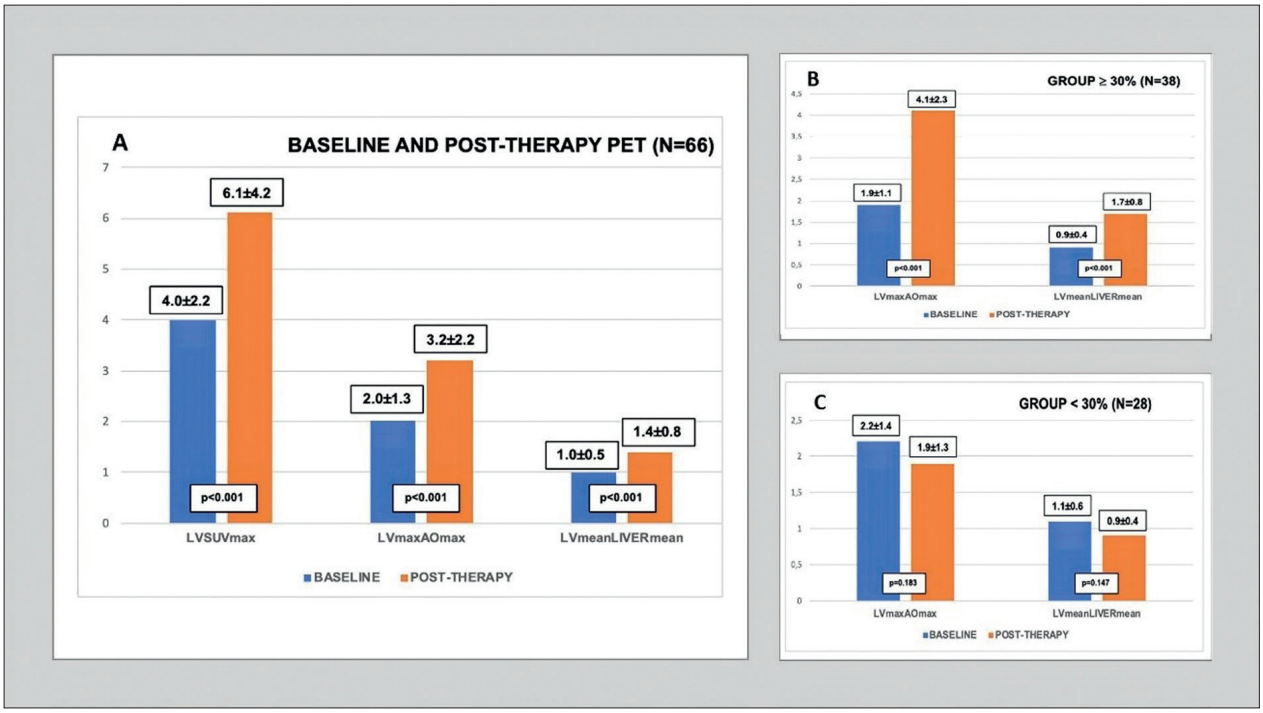


Figure 2 – *Group 02 – A) Comparison of LV SUVmax, LV SUVmax/Aorta SUVmax and LV SUVmean/Liver SUVmean ratios, between Baseline and Post-therapy PET. B) Comparison of LV SUVmax/Aorta SUVmax and LV SUVmean/Liver SUVmean ratios, between Baseline and Post-therapy PET in the Group with increase of LV SUVmax ≥ 30%. C) Comparison of LV SUVmax/Aorta SUVmax and LV SUVmean/Liver SUVmean ratios, between Baseline and Post-therapy PET in the Group with increase of LV SUVmax < 30%; LVmaxAOmax: LV SUVmax/Aorta SUVmax, LVmean LIVER mean: LV SUVmean/Liver SUVmean.*

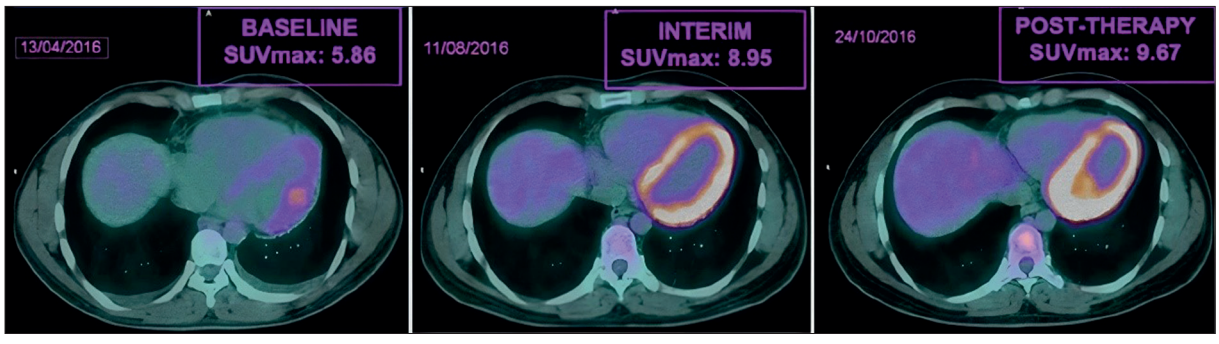


Figure 3 – *Case example - LV SUVmax in Baseline (5.86), Interim (8.95 / 52.73% percentage increase from baseline) and Post-therapy PET/CT (9.67 / 65.02% percentage increase from baseline). LV: Left Ventricle; PET/CT: Positron emission tomography associated with computed tomography scans; SUV: Standard Uptake Value; SUVmax: Maximum SUV.*

results are supported by recent evidence suggesting that it may be an early sign of CTX in response to the redox stress. The cardiac ^{18}F-FDG increase occurred in more than 50% of the patients and was observed in the interim PET and in the post-therapy scan. These results suffered no interference regarding the ^{18}F-FDG injected activity or any possible differences in exam preparation and timing.

The ^{18}F-FDG PET/CT is a well-established method in the diagnosis and staging of oncologic patients, especially with lymphoma, with a potential capacity to assess early manifestations of CTX in a way analogue to the ischemic cascade, as postulated in Figure 4.

Antineoplastic therapies have improved overall survival rates in oncologic patients. However, their cytotoxic effects have shown a wide spectrum of acute and chronic alterations to the cardiovascular system.[19] The cellular and molecular mechanisms of CTX are known to disrupt the redox homeostasis mostly in the myocardium and endothelium, significantly impairing cardiovascular health.[20]

CTX affects the cardiovascular system first by the inhibition of topoisomerase II and the formation of ROS. The intrinsic mitochondria-dependent and extrinsic death receptor pathways of apoptosis are then triggered. The cascade continues with the activation of caspase ^{3}, phosphatidylserine expression, DNA fragmentation, chromatin condensation, and phospholipid membrane metabolization.[21] The final stage is characterized by membrane blebbing and cell shrinkage.[22] This is the mechanism underlying subclinical CTX and it provides various opportunities to assess early signs of this entity.

The current recommendations and guidelines rely on imaging techniques focused on anatomy-based parameters, such as echocardiography, multigated radionuclide angiography (MUGA), and cardiac magnetic resonance imaging (CMRI).[23] However, these approaches detect late manifestations of CTX with low sensitivity for subclinical alterations.[24]

Nuclear medicine techniques may be a tool to assess specific points of the CTX pathway. The ^{18}F-FDG PET/CT, commonly used to detect tumoral glycolytic metabolism, has presented itself as an early marker of CTX. Initially, several studies pointed out that doxorubicin (DXR), one of the most utilized anthracyclines, can specifically affect myocardial metabolism, as showed by experimental study.[25]

Several experimental and clinical studies have shown that cardiotoxic therapy, such as sunitinib and anthracyclines, increases the cardiac ^{18}F-FDG uptake over time and is related to echocardiographic alterations.[26-33]

Although ^{18}F-FDG uptake has been commonly associated with glucose consumption, more recent data have shown otherwise. The redox stress and its antioxidant response have been characterized as a possible mechanism behind the progression of cardiac contractile impairment in CTX and in the ^{18}F-FDG uptake independently of the glycolytic metabolism.[34]

Redox stress to the endoplasmic reticulum (ER) environment might activate the local H6PD-triggered pentose phosphate pathway to fuel the NADPH levels needed for the antioxidant response, and is related to an increased ^{18}F-FDG uptake.[35]

In situations of oxidative stress, NADPH is a major source of electrons for reductive reactions.[36] It is generated intraluminally by H6PD, a bifunctional enzyme that catalyzes the first two steps of the pentose phosphate pathway, converting glucose-6-phosphate to 6-phosphogluconate with the concomitant production of NADPH.[37] H6PD has as substrate several hexoses such as 2-deoxyglucose and FDG.[38]

In the heart, there is a direct link between ER oxidative stress and myocardial uptake of 2-deoxyglucose,[39] that may be considered an early metabolic phase of contractile dysfunction by pressure overload.[40] Furthermore, Hrelia et al.[41] showed that the increase of 2-deoxyglucose uptake induced by DXR in cardiomyocytes can be reverted by the antioxidant effect of alpha-tocopherol.[41]

Baucknehet al.,[33] in 2019, analyzed the effect of DXR -induced oxidative damage on the correlation between myocardial ^{18}F-FDG uptake, overall glucose consumption and the H6PD-triggered metabolic response in mice. The study showed that myocardial redox stress persisted and directly correlated with the enhancement in ^{18}F-FDG uptake (SUV increase), and the activation of physiological antioxidant pathways such as the catalytic function of H6PD.[33] The study also showed that the metabolic alteration persisted after the disappearance of DXR, and it preceded the manifestation of contractile impairment.[33] Previous reports also showed a positive loop connecting ROS generation and ^{18}F-FDG uptake in cancer.[42]

In agreement with these findings, recent studies showed an increased ^{18}F-FDG uptake on PET/CT independent of glycolytic metabolism and linked to the enzymatic activity of H6PD in the brain.[43,44] Another analysis showed the link between ^{18}F-FDG uptake and ROS generation in hyperglycemia-induced redox stress involving H6PD activation.[45]

Despite its interesting results and background of the present study, its retrospective nature makes the assessment of the mechanisms underlying the increased myocardial ^{18}F-FDG uptake difficult. However, no other cardiotoxic factors, besides CTX, were identified between baseline and control exams in the largest sample of patients with lymphoma evaluated during and after chemotherapy. In addition, unlike the other studies, we measured not only the LV SUVmax, but also the LV uptake values corrected for liver and blood pool, as control, confirming the increase of the cardiac uptake. Furthermore, the ^{18}F-FDG PET/CT protocol and the possible factors of SUV variability were the same in all baseline and control scans.

More studies are necessary to correlate increased cardiac ^{18}F-FDG uptake with clinical outcomes, the class and dose of chemotherapy, troponin and NT-proBNP levels, and with other imaging methods such as echocardiography and CMRI.

Conclusion

The present study showed a clear increase in cardiac ^{18}F-FDG uptake in patients with lymphoma, verified by ^{18}F-FDG PET/CT during and/or after chemotherapy. The literature corroborates with these findings and suggests that it may be an important and early sign of CTX that can be easily assessed by a widely available method. With the progressive

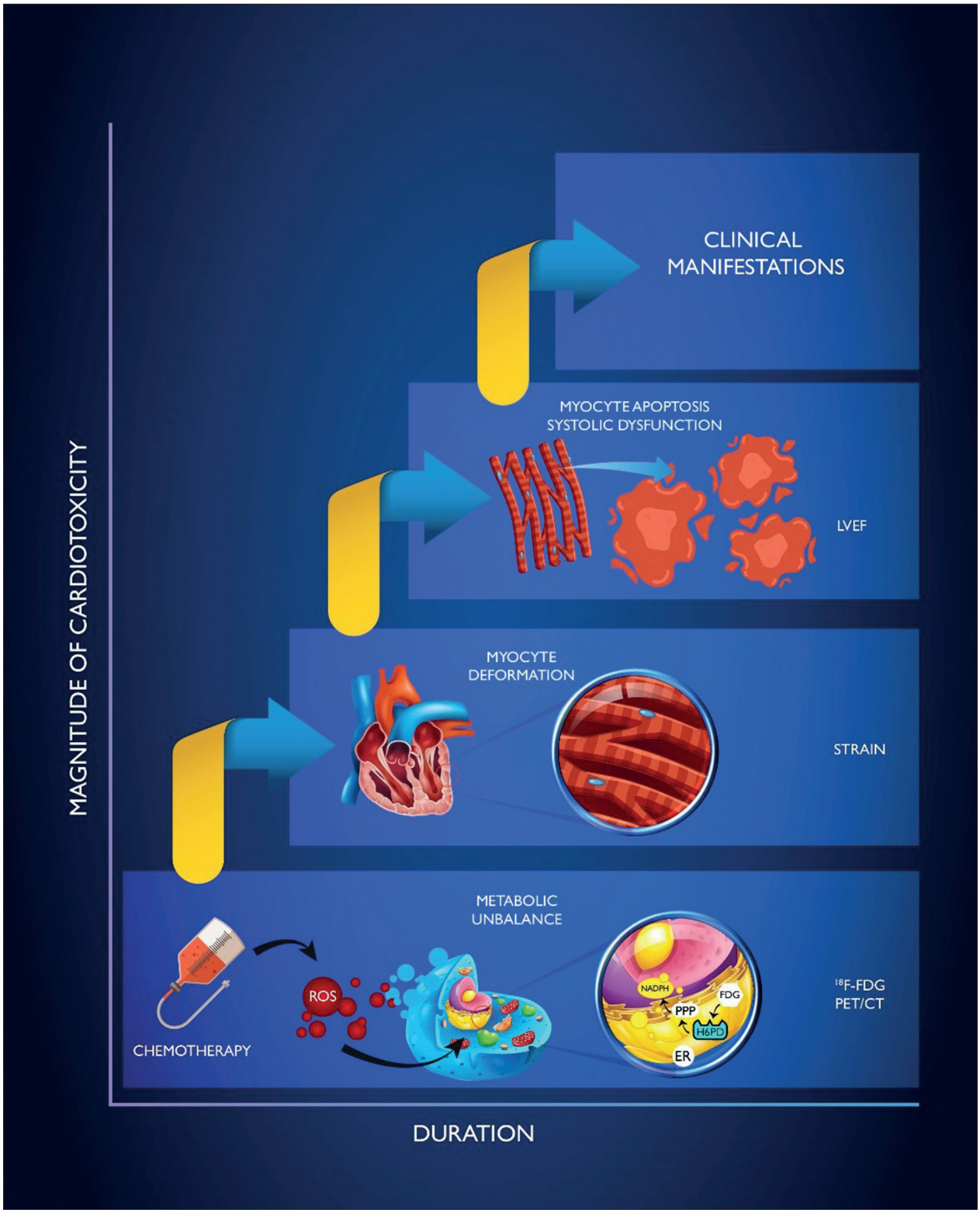


Figure 4 – *Cardiotoxicity cascade – Cardiotoxic injury triggers series of metabolic alterations in response to the oxidative stress, it is detectable by 18F-FDG PET/CT. The sustained injury and the failure of the myocyte self-healing contribute to cell dysfunction and mechanic alterations detected by strain rate imaging. Furthermore, the process continues with a decrease in the cardiac overall performance assessed by the LVEF. Signs of heart failure are then noticeable, suggesting that the heart no longer meet the body's demands, or do it at the expense of high ventricular filling pressures (ROS: reactive oxygen species; ER: endoplasmic reticulum; PPP: pentose phosphate pathway; H6PD: hexose-6-phosphate dehydrogenase; FDG: 18F-fluorodeoxy-glucose; LVEF: Left Ventricle Ejection Fraction).*

improvement in anticancer therapies, CTX is still a concern that requires further investigation and new diagnostic approaches.

Acknowledgements

We are pleased to acknowledge the support provided by all technicians and nuclear physicians of the Real Nuclear at the Real Hospital Português in hosting our study.

Author Contributions

Conception and design of the research: Dourado MLC, Leitão GM, Mourato FA, Almeida Filho PJ, Markman Filho B, Melo MDT, Brandão SCS; Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Dourado MLC, Dompieri LT, Leitão GM, Mourato FA, Santos RGG, Almeida Filho PJ, Markman Filho B, Melo MDT, Brandão SCS; Statistical analysis: Dourado MLC, Brandão SCS; Obtaining financing: Dourado MLC; Writing of the manuscript: Dourado MLC, Dompieri LT, Brandão SCS.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Mayara L. C. Dourado, from Universidade Federal de Pernambuco - UFPE.

References

1. Awadalla M, Hassan MZO, Alvi RM, Neilan TG. Advanced Imaging Modalities to Detect Cardiotoxicity. Curr Probl Cancer. 2018;42(4):386-96. doi: 10.1016/j.currproblcancer.2018.05.005.
2. Kalil Filho R, Hajjar LA, Bacal F, Hoff PM, Diz MP, Galas FR, et al. I Brazilian Guideline for Cardio-Oncology from Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011;96(2 Suppl 1):1-52.
3. Jain D, Russell RR, Schwartz RG, Panjrath GS, Aronow W. Cardiac Complications of Cancer Therapy: Pathophysiology, Identification, Prevention, Treatment, and Future Directions. Curr Cardiol Rep. 2017;19(5):36. doi: 10.1007/s11886-017-0846-x.
4. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience. J Clin Oncol. 2002;20(5):1215-21. doi: 10.1200/JCO.2002.20.5.1215.
5. Curigliano G, Cardinale D, Suter T, Plataniotis G, Azambuja E, Sandri MT, et al. Cardiovascular Toxicity Induced by Chemotherapy, Targeted Agents and Radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23(Suppl 7):155-66. doi: 10.1093/annonc/mds293.
6. Negishi T, Negishi K. Echocardiographic Evaluation of Cardiac Function After Cancer Chemotherapy. J Echocardiogr. 2018;16(1):20-7. doi: 10.1007/s12574-017-0344-6.
7. Barros-Gomes S, Herrmann J, Mulvagh SL, Lerman A, Lin G, Villarraga HR. Rationale for Setting up a Cardio-Oncology Unit: Our Experience at Mayo Clinic. Cardiooncology. 2016;2(1):5. doi: 10.1186/s40959-016-0014-2.
8. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying Causes and Long-Term Survival in Patients with Initially Unexplained Cardiomyopathy. N Engl J Med. 2000;342(15):1077-84. doi: 10.1056/NEJM200004133421502.
9. Simoni LJC, Brandão SCS. New Imaging Methods for Detection of Drug-Induced Cardiotoxicity in Cancer Patients. Curr Cardiovasc Imaging Rep. 2017;10(18):1-11. doi: 10.1007/s12410-017-9415-3.
10. Rix A, Drude NI, Mrugalla A, Baskaya F, Pak KY, Gray B, et al. Assessment of Chemotherapy-Induced Organ Damage with Ga-68 Labeled Duramycin. Mol Imaging Biol. 2020;22(3):623-33. doi: 10.1007/s11307-019-01417-3.
11. Kahanda MG, Hanson CA, Patterson B, Bourque JM. Nuclear Cardio-Oncology: From its Foundation to its Future. J Nucl Cardiol. 2020;27(2):511-8. doi: 10.1007/s12350-019-01655-6.
12. Wu X, Bhattarai A, Korkola P, Pertovaara H, Eskola H, Kellokumpu-Lehtinen PL. The Association Between Liver and Tumor [18F]FDG Uptake in Patients with Diffuse Large B Cell Lymphoma During Chemotherapy. Mol Imaging Biol. 2017;19(5):787-94. doi: 10.1007/s11307-017-1044-3.
13. Zhou Y, Zhao Z, Li J, Zhang B, Sang S, Wu Y, et al. Prognostic Values of Baseline, Interim and End-of Therapy 18F-FDG PET/CT in Patients with Follicular Lymphoma. Cancer Manag Res. 2019;11:6871-85. doi: 10.2147/CMAR.S216445.
14. Bascuñana P, Thackeray JT, Bankstahl M, Bengel FM, Bankstahl JP. Anesthesia and Preconditioning Induced Changes in Mouse Brain [18F] FDG Uptake and Kinetics. Mol Imaging Biol. 2019;21(6):1089-96. doi: 10.1007/s11307-019-01314-9.
15. Marini C, Ravera S, Buschiazzo A, Bianchi G, Orengo AM, Bruno S, et al. Discovery of a Novel Glucose Metabolism in Cancer: The Role of Endoplasmic Reticulum Beyond Glycolysis and Pentose Phosphate Shunt. Sci Rep. 2016;6:25092. doi: 10.1038/srep25092.
16. Clarke JL, Mason PJ. Murine Hexose-6-Phosphate Dehydrogenase: A Bifunctional Enzyme with Broad Substrate Specificity and 6-Phosphogluconolactonase Activity. Arch Biochem Biophys. 2003;415(2):229-34. doi: 10.1016/s0003-9861(03)00229-7.
17. Rogoff D, Black K, McMillan DR, White PC. Contribution of Hexose-6-Phosphate Dehydrogenase to NADPH Content and Redox Environment in the Endoplasmic reticulum. Redox Rep. 2010;15(2):64-70. doi: 10.1179/174329210X12650506623249.
18. Pinker K, Riedl C, Weber WA. Evaluating Tumor Response with FDG PET: Updates on PERCIST, Comparison with EORTC Criteria and Clues to Future Developments. Eur J Nucl Med Mol Imaging. 2017;44(Suppl 1):55-66. doi: 10.1007/s00259-017-3687-3.
19. Aggarwal S, Kamboj J, Arora R. Chemotherapy-related Cardiotoxicity. Ther Adv Cardiovasc Dis. 2013;7(2):87-98. doi: 10.1177/1753944712474332.
20. Vincent DT, Ibrahim YF, Espey MG, Suzuki YJ. The Role of Antioxidants in the Era of Cardio-Oncology. Cancer Chemother Pharmacol. 2013;72(6):1157-68. doi: 10.1007/s00280-013-2260-4.
21. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the Molecular Basis of Doxorubicin-Induced Cardiotoxicity. Nat Med. 2012;18(11):1639-42. doi: 10.1038/nm.2919.
22. Vangestel C, Peeters M, Mees G, Oltenfreiter R, Boersma HH, Elsinga PH, et al. In Vivo Imaging of Apoptosis in Oncology: An Update. Mol Imaging. 2011;10(5):340-58. doi: 10.2310/7290.2010.00058.

23. Markman TM, Markman M. Cardiotoxicity of Antineoplastic Agents: What is the Present and Future Role for Imaging? Curr Oncol Rep. 2014;16(8):396. doi: 10.1007/s11912-014-0396-y.

24. Wood PW, Choy JB, Nanda NC, Becher H. Left Ventricular Ejection Fraction and Volumes: It Depends on the Imaging Method. Echocardiography. 2014;31(1):87-100. doi: 10.1111/echo.12331.

25. Yang Y, Zhang H, Li X, Yang T, Jiang Q. Effects of PPAR/PGC-1 on the Energy Metabolism Remodeling and Apoptosis in the Doxorubicin Induced Mice Cardiomyocytes in Vitro. Int J Clin Exp Pathol. 2015;8(10):12216-24.

26. Borde C, Kand P, Basu S. Enhanced Myocardial Fluorodeoxyglucose Uptake Following Adriamycin-Based Therapy: Evidence of Early Chemotherapeutic Cardiotoxicity? World J Radiol. 2012;4(5):220-3. doi: 10.4329/wjr.v4.i5.220.

27. O'Farrell AC, Evans R, Silvola JM, Miller IS, Conroy E, Hector S, et al. A Novel Positron Emission Tomography (PET) Approach to Monitor Cardiac Metabolic Pathway Remodeling in Response to Sunitinib Malate. PLoS One. 2017;12(1):e0169964. doi: 10.1371/journal.pone.0169964.

28. Sourdon J, Lager F, Viel T, Balvay D, Moorhouse R, Bennana E, et al. Cardiac Metabolic Deregulation Induced by the Tyrosine Kinase Receptor Inhibitor Sunitinib is Rescued by Endothelin Receptor Antagonism. Theranostics. 2017;7(11):2757-74. doi: 10.7150/thno.19551.

29. Kim J, Cho SG, Kang SR, Yoo SW, Kwon SY, Min JJ, et al. Association Between FDG Uptake in the Right Ventricular Myocardium and Cancer Therapy-Induced Cardiotoxicity. J Nucl Cardiol. 2020;27(6):2154-63. doi: 10.1007/s12350-019-01617-y.

30. Sarocchi M, Bauckneht M, Arboscello E, Capitanio S, Marini C, Morbelli S, et al. An Increase in Myocardial 18-Fluorodeoxyglucose Uptake is Associated with Left Ventricular Ejection Fraction Decline in Hodgkin Lymphoma Patients Treated with Anthracycline. J Transl Med. 2018;16(1):295. doi: 10.1186/s12967-018-1670-9.

31. Bauckneht M, Ferrarazzo G, Fiz F, Morbelli S, Sarocchi M, Pastorino F, et al. Doxorubicin Effect on Myocardial Metabolism as a Prerequisite for Subsequent Development of Cardiac Toxicity: A Translational 18F-FDG PET/CT Observation. J Nucl Med. 2017;58(10):1638-45. doi: 10.2967/jnumed.117.191122.

32. Bauckneht M, Morbelli S, Fiz F, Ferrarazzo G, Piva R, Nieri A, et al. A Score-Based Approach to 18F-FDG PET Images as a Tool to Describe Metabolic Predictors of Myocardial Doxorubicin Susceptibility. Diagnostics. 2017;7(4):57 doi: 10.2967/jnumed.117.191122.

33. Bauckneht M, Pastorino F, Castellani P, Cossu V, Orengo AM, Piccioli P, et al. Increased Myocardial 18F-FDG Uptake as a Marker of Doxorubicin-Induced Oxidative Stress. J Nucl Cardiol. 2020;27(6):2183-94. doi: 10.1007/s12350-019-01618-x.

34. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-Induced Cardiomyopathy: from Molecular Mechanisms to Therapeutic Strategies. J Mol Cell Cardiol. 2012;52(6):1213-25. doi: 10.1016/j.yjmcc.2012.03.006.

35. Bánhegyi G, Benedetti A, Fulceri R, Senesi S. Cooperativity Between 11beta-Hydroxysteroid Dehydrogenase type 1 and Hexose-6-Phosphate Dehydrogenase in the Lumen of the Endoplasmic Reticulum. J Biol Chem. 2004;279(26):27017-21. doi: 10.1074/jbc.M404159200.

36. Fico A, Paglialunga F, Cigliano L, Abrescia P, Verde P, Martini G, et al. Glucose-6-Phosphate Dehydrogenase Plays a Crucial Role in Protection from Redox-Stress-Induced Apoptosis. Cell Death Differ. 2004;11(8):823-31. doi: 10.1038/sj.cdd.4401420.

37. Mason PJ, Stevens D, Diez A, Knight SW, Scopes DA, Vulliamy TJ. Human Hexose-6-Phosphate Dehydrogenase (glucose 1-dehydrogenase) Encoded at 1p36: Coding Sequence and Expression. Blood Cells Mol Dis. 1999;25(1):30-7. doi: 10.1006/bcmd.1999.0224.

38. Clarke JL, Mason PJ. Murine Hexose-6-Phosphate Dehydrogenase: A Bifunctional Enzyme with Broad Substrate Specificity and 6-Phosphogluconolactonase Activity. Arch Biochem Biophys. 2003;415(2):229-34. doi: 10.1016/s0003-9861(03)00229-7.

39. Sen S, Kundu BK, Wu HC, Hashmi SS, Guthrie P, Locke LW, et al. Glucose Regulation of Load-Induced mTOR Signaling and ER Stress in Mammalian Heart. J Am Heart Assoc. 2013;2(3):e004796. doi: 10.1161/JAHA.113.004796.

40. Zhong M, Alonso CE, Taegtmeyer H, Kundu BK. Quantitative PET Imaging Detects Early Metabolic Remodeling in a Mouse Model of Pressure-Overload Left Ventricular Hypertrophy in Vivo. J Nucl Med. 2013;54(4):609-15. doi: 10.2967/jnumed.112.108092.

41. Hrelia S, Fiorentini D, Maraldi T, Angeloni C, Bordoni A, Biagi PL, et al. Doxorubicin Induces Early Lipid Peroxidation Associated with Changes in Glucose Transport in Cultured Cardiomyocytes. Biochim Biophys Acta. 2002;1567(1-2):150-6. doi: 10.1016/s0005-2736(02)00612-0.

42. Chen L, Zhou Y, Tang X, Yang C, Tian Y, Xie R, et al. EGFR Mutation Decreases FDG Uptake in Non-Small Cell Lung Cancer via the NOX4/ROS/GLUT1 Axis. Int J Oncol. 2019;54(1):370-80. doi: 10.3892/ijo.2018.4626.

43. Cossu V, Marini C, Piccioli P, Rocchi A, Bruno S, Orengo AM, et al. Obligatory Role of Endoplasmic Reticulum in Brain FDG Uptake. Eur J Nucl Med Mol Imaging. 2019;46(5):1184-96. doi: 10.1007/s00259-018-4254-2.

44. Buschiazzo A, Cossu V, Bauckneht M, Orengo A, Piccioli P, Emionite L, et al. Effect of Starvation on Brain Glucose Metabolism and 18F-2-fluoro-2-deoxyglucose Uptake: An Experimental In-vivo and Ex-vivo Study. EJNMMI Res. 2018;8(1):44. doi: 10.1186/s13550-018-0398-0.

45. Bauckneht M, Cossu V, Castellani P, Piccioli P, Orengo AM, Emionite L, et al. FDG Uptake Tracks the Oxidative Damage in Diabetic Skeletal Muscle: An Experimental Study. Mol Metab. 2020;31:98-108. doi: 10.1016/j.molmet.2019.11.007.

Soluble Guanylate Cyclase Stimulators (Riociguat) in Pulmonary Hypertension: Data from Real-Life Clinical Practice in a 3-Year Follow-Up

Fernanda Brum Spilimbergo,[1] Taís Silveira Assmann,[1] Marcelo Bellon,[1] Laís Machado Hoscheidt,[1] Cássia Ferreira Braz Caurio,[1] Márcia Puchalski,[1] Bruno Hochhegger,[1] Gabriela Roncato,[1,2] Gisela Martina Bohns Meyer[1]

Centro de Hipertensão Pulmonar, Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre,[1] Porto Alegre, RS – Brazil
Bayer S.A.,[2] São Paulo, SP – Brazil

Abstract

Background: **Pulmonary hypertension (PH) is a rare and complex disease with poor prognosis, which requires lifelong treatment.**

Objective: **To describe 3-year follow-up real-life data on treatment with soluble guanylate cyclase stimulators (Riociguat) of patients with PH, measuring current risk assessment parameters.**

Methods: **This study retrospectively collected clinical and epidemiological data of patients with PH of group 1 (pulmonary arterial hypertension) and group 4 (chronic thromboembolic PH). Non-invasive and invasive parameters corresponding to the risk assessment were analyzed at baseline and follow-up. Statistical analyses were performed using the SPSS 18.0 software, and p-values < 0.050 were considered statistically significant.**

Results: **In total, 41 patients receiving riociguat were included in the study. Of them, 31 had already completed 3 years of treatment and were selected for the following analysis. At baseline, 70.7% of patients were in WHO functional class III or IV. After 3 years of treatment, the WHO functional class significantly improved in all patients. In addition, the median of the 6-minute walk test (6MWT) significantly increased from 394 ± 91 m at baseline to 458 ± 100 m after 3 years of follow-up (p= 0.014). The three-year survival rate was 96.7%.**

Conclusion: **In our real-life cohort, most patients with PH treated with riociguat showed stable or improved risk parameters, especially in the 6MWT, at 3 years of follow-up.**

Keywords: **Pulmonary Arterial Hypertension; Hypertension, Pulmonary; Pulmonary Wedge Pressure.**

Introduction

Pulmonary hypertension (PH) is a progressive clinical condition, characterized by the elevation of mean pulmonary arterial pressure (mPAP) to greater than 20 mmHg when at rest.[1] Prior to the modern era of PH therapy, the average life expectancy after diagnosis had been 2.8 years for adults with PH.2 The development and availability of new therapies have significantly improved the quality of life and the survival of PH patients.[3,4]

PH is classified into five clinical subgroups: pulmonary arterial hypertension (PAH), PH due to left-sided heart disease, PH due to chronic lung disease, chronic thromboembolic PH (CTEPH), and PH with an unclear and/or multifactorial mechanisms.[3] This categorization considers a similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy.[5] Specifically, PAH (group 1) and CTEPH (group 4) are characterized as pre-capillary PH, with pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood Units.[1] Although CTEPH originates from a chronic pulmonary thromboembolism, PAH and CTEPH diseases present loss and obstructive remodeling of the pulmonary vascular bed, resulting in elevated pulmonary arterial pressure and PVR, progressive right heart failure, and death.[6]

In addition to presenting pathophysiological similarities, PAH and CTEPH also have similarities in pharmacological treatment. Pulmonary endarterectomy remains the

Mailing Address: Gisela Martina Bohns Meyer •
Centro de Hipertensão Pulmonar – Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre – Av. Independência, 75, Centro Histórico. Postal Code 90035-074, Porto Alegre, RS – Brazil
E-mail: gimeyer@terra.com.br
Manuscript received June 02, 2020, revised manuscript August 09, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210492

treatment of choice for patients with surgical CTEPH; however, for those considered inoperable, scientific evidence supports the initiation of medical therapy and the consideration of balloon pulmonary angioplasty.[7]

The soluble guanylate cyclase stimulator (riociguat) has a dual mode of action: 1) it directly stimulates soluble guanylate cyclase independently of nitric oxide and 2) it increases the sensitivity of soluble guanylate cyclase to nitric oxide.[8,9] As it is known that patients with PAH or CTEPH have reduced levels of nitric oxide,[10] this mode of action is very important to improve the dynamics of the pulmonary vasculature. Previous studies have shown that riociguat significantly improved exercise capacity, as well as secondary endpoints, such as PVR, the World Health Organization (WHO) functional class, and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with PAH[11] and CTEPH.[12] Based on these results, riociguat was approved for the treatment of adults with PAH in monotherapy or in combination,[5] and it is the only medication approved by American, European, and Brazilian regulatory agencies for the treatment of inoperable CTEPH or residual PH.[13,14] In this context, the aim of this study was to describe real-life data on the treatment of patients with PH from group 1 (PAH) and group 4 (CTEPH) with riociguat in Brazil, measuring current risk assessment parameters.

Methods

Selection of patients

All patients with PAH and CTEPH who started the treatment with riociguat between 2010 and 2020 at the Centro de Hipertensão Pulmonar, Complexo Hospitalar Santa Casa de Porto Alegre were included and analyzed retrospectively (Figure 1). This is a Reference Center for PH treatment, which participates in the main multicenter clinical studies in the area since 2005. This study was approved by the local ethics committee (number: 30199714.6.0000.5335). Diagnosis of PH was confirmed by right heart catheterization (RHC) in all patients.

Procedures

Demographic and clinical characteristics were collected at baseline, 3 months, 1 year, and 3 years of follow-up. These parameters included the determination of PH etiology, the WHO functional class, the 6-minute walking test (6MWT), NT-proBNP, and hemodynamic measurements.

Baseline was defined as the time of stable medication before starting treatment with riociguat. The WHO functional class was determined by the treating physician at each visit. The 6MWT was carried out according to ATS guidelines.[15] RHC was performed using a Swan-Ganz catheter. Cardiac output was measured by thermodilution. Survival was established based on the electronic medical records.

Statistical analysis

Normal distribution was checked using the Shapiro-Wilk test. The continuous variables with normal distribution are presented as mean ± standard deviation (SD). Variables with skewed distribution were log-transformed before analyses and are presented as medians (25th – 75th percentiles).[16] Categorical data are shown as absolute number and percentages.

Clinical, laboratorial, and hemodynamics characteristics were compared between groups (PAH and CTEPH), using the unpaired Student's *t*-test[16] or χ^2 tests, as appropriate. Differences between baseline, 3 months, 1 year, and 3 years of follow-up were compared using the paired Student's *t*-test. Correlation analyses were performed

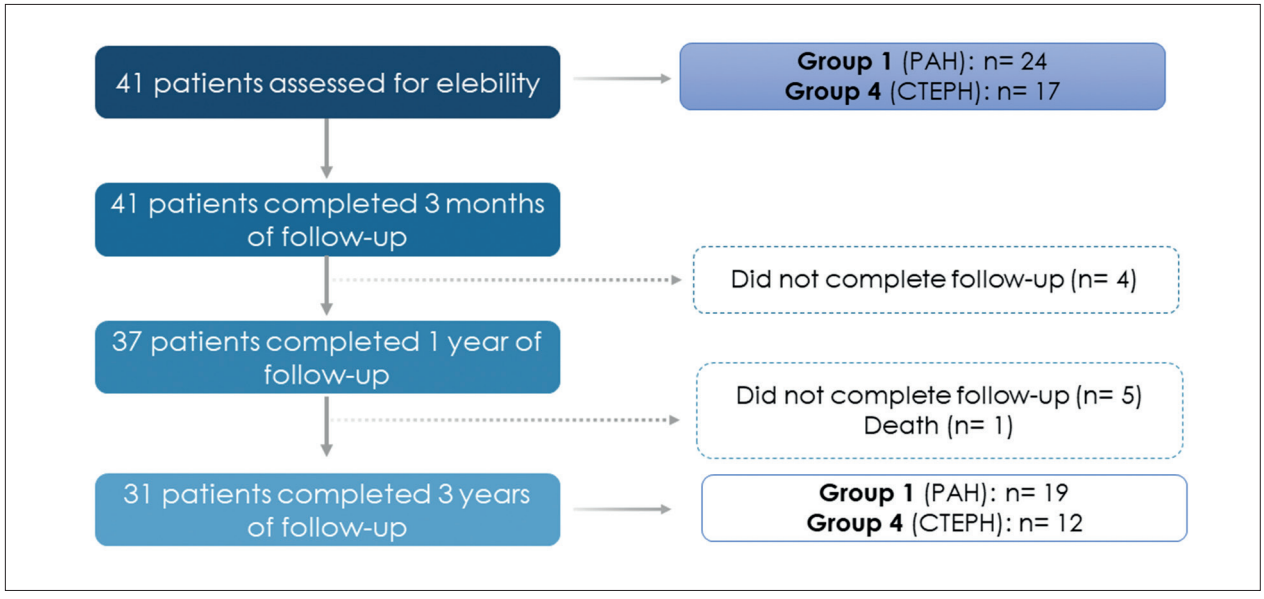


Figure 1 – *Flowchart of patients throughout the study. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.*

using Pearson's correlation tests. Statistical analyses were performed using the SPSS 18.0 software (SPSS, Chicago, IL), and p-values < 0.050 were considered statistically significant.

Results

A total of 41 patients who had been treated with riociguat were eligible for the analysis. Of these, 31 had completed 3 years of follow-up and were selected for the following analysis (Figure 1).

Baseline demographic and clinical characteristics of the study population are shown in Table 1. Of the 41 patients enrolled in this study, 24 patients were classified as PAH (group 1) and 17 patients as CTEPH (group 4). The most common PAH etiologies were idiopathic (67%). Patients were predominantly female (70.7%), with a mean age at PH diagnosis of 42.2 ± 3.5 years. Most participants showed moderate to severe disease manifestations at baseline, with 70.7% of the patients presenting WHO functional class III or IV. Overall, the median levels of NT-proBNP were 655 pg/ml, and the mean 6MWT was 386 meters. Hemodynamically, patients showed mPAP of 45.5 ± 11.7 mmHg; PVR of 9.8 ± 1.0 Wood; and a cardiac index (CI) of 2.7 ± 0.1 L/min (Table 1). It is important to note that no difference was found between the PAH and CTEPH groups regarding the analyzed characteristics (Table 1).

Table 1 – Baseline characteristics of patients treated with riociguat

Baseline characteristics	Total (n= 41)	PAH (n= 24)	CTEPH (n= 17)	p-value*
Gender, n (% male)	12 (29.3)	7 (29.1)	5 (29.4)	0.889
Age at diagnosis, years	42.2 ± 3.5	40.0 ± 4.3	55.7 ± 15.1	0.514
BMI (kg/m²)	27.3 ± 1.5	26.7 ± 4.6	29.0 ± 1.5	0.732
PAH classification (n)				
Idiopathic	-	16	-	-
Familiar	-	1	-	
Associated with connective-tissue disease	-	4	-	
Associated with congenital heart disease	-	1	-	
Associated with anorexigen or amphetamine use	-	1	-	
Associated with HIV	-	1	-	
WHO functional class, n (%)				
II	12 (29.3)	7 (29.2)	5 (29.5)	0.087
III	26 (63.4)	17 (70.8)	9 (52.9)	
IV	3 (7.3)	0 (0.0)	3 (17.6)	
Concomitant PH medications, n (%)				
Endothelin-receptor antagonist	18	14 (77.8)	4 (22.2)	0.080
Prostanoid	2	1 (50.0)	1 (50.0)	0.999
Anticoagulant	17	10 (58.8)	7 (41.2)	0.999
Diuretics	15	9 (60.0)	6 (30.0)	0.999
6-min walking distance (m)	386.1 ± 99.2	410.4 ± 72.4	346.5 ± 136.5	0.201
NT-proBNP (pg/ml)	655 (127 - 1191)	190 (90 – 1028)	793 (259 - 2554)	0.570
Systolic PAP (mmHg)	81.1 ± 3.0	79.9 ± 18.3	82.9 ± 21.3	0.487
Diastolic PAP (mmHg)	36.2 ± 1.7	38.8 ± 11.7	33.8 ± 6.6	0.121
mPAP (mmHg)	45.5 ± 11.7	55.4 ± 13.4	44.6 ± 8.4	0.410
PAWP (mmHg)	7.8 ± 0.4	7.3 ± 0.5	9.5 ± 0.3	0.131
PVR	9.8 ± 1.0	11.4 ± 0.8	9.0 ± 0.5	0.211
Cardiac index (L/min)	2.7 ± 0.1	2.7 ± 0.8	2.5 ± 0.8	0.921
Cardiac output (L/min)	4.9 ± 0.3	4.7 ± 1.3	4.9 ± 0.7	0.778

*Results are presented as mean ± SD, n (%), or median (25^{th} - 75^{th}), as appropriate. CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; BMI: body mass index; PAH: pulmonary arterial hypertension; PAP: pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WHO: World Health Organization. *p-value computed using χ^2 test or unpaired Student's t-test to compare the baseline characteristics between PAH and CTEPH groups, as appropriate.*

During a 3-year patient follow-up, a functional capacity improvement was noted, as illustrated in Figure 2. During the follow-up, the number of patients in functional class III decreased, and that of functional class II increased (Figure 2a). Considering only the patients who completed 3 years of follow-up (n= 31), at baseline, 61% patients were functional class III, and after 3 years of treatment with riociguat, 10% of patients continued as functional class III. In the same way, at baseline, 32% of the patients were functional class II, and after treatment, 71% of the patients were in functional class II. In particular, the number of patients in functional class I increased from 0 at baseline to 5 patients after 3 years of treatment (Figure 2b).

Clinical characteristics of the 31 patients who completed the 3 years of follow-up are described in Table 2. Our results showed a significant improvement of 64 m after 3 years of treatment with riociguat when compared to the baseline (p= 0.014). After stratification by PH etiology, a reduction of 59 m was observed in PAH (p= 0.045) and of 70 m in CTEPH patients (p= 0.080). Moreover, as shown in Figure 3, 6MWT significantly improved in 3 months, 1 year, and 3 years when compared to baseline results. Although the decrease in NT-proBNP levels is not statically significant, a clinically important reduction of 663 pg/ml could be observed in NT-proBNP levels after treatment with riociguat (Table 2 and Figure 4). Moreover, there is a negative correlation between 6MWT and NT-proBNP levels after 3 years of follow-up (r= -0.520, p= 0.027). No significant changes were observed in RAP and CI in baseline measurements when compared to 3 years of follow-up. According to the French non-invasive risk stratification, no patient was at low risk at baseline and 7 patients achieved low risk status after 3 years of treatment. During the follow-up period, a total of one (3.2%) patient died of PH-related causes; and this death occurred in patient with functional class III at baseline.

Additionally, our center also observed the results of a sub-group of 10 patients who have completed 10-years

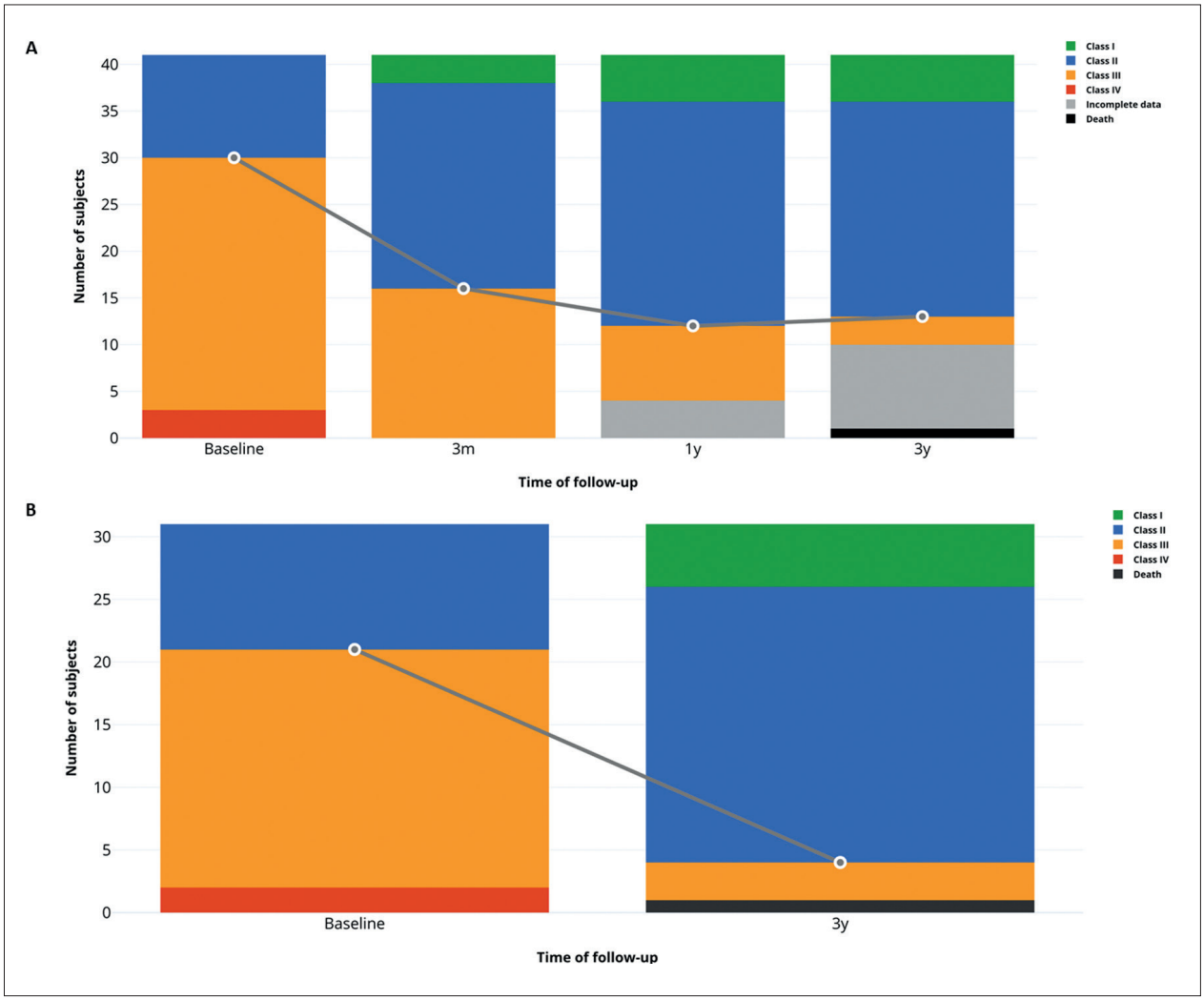


Figure 2 – *Change of WHO functional class over time in patients with pulmonary hypertension. A) Data from all 41 patients in baseline and follow-up periods. B) Data from the 31 patients who completed 3 years of follow-up.*

using riociguat. In the same line of 3 years of follow-up results, the clinical status of these patients was also satisfactory, with low risk and good treatment tolerability.

Discussion

To the best of our knowledge, this is the first study to detail the real-life experience of treating PAH and CTEPH with riociguat for at least 3 years. In this real-life cohort, we show an improvement in 6MWT and WHO functional class in both groups, PAH and CTEPH.

The 6MWT is a simple tool for the evaluation of functional exercise capacity, which reflects the capacity of the individual to perform activities of daily living. Moreover, it is familiar to patients[5] and has been the most employed primary endpoint in clinical trials of PH therapies.[17] Among exercise tests, the 6MWT has proven to have the best ability to capture changes in exercise capacity and has regularly proven to be an independent predictor of morbidity and mortality in PH.[18-20]

Our results showed a significant improvement of 64 m after 3 years of treatment with riociguat, which is in accordance with the findings of improvements in 6MWT of many studies, both randomized controlled trials[11,12] as well as extension,[21,22] open-label[23,24] and real-life studies.[25] In addition, our data presented a gradual increase in 6MWT distance, from 3 months to 3 years after the start of treatment, with a final median greater than 440m, which is considered a low-risk status for patients.[5]

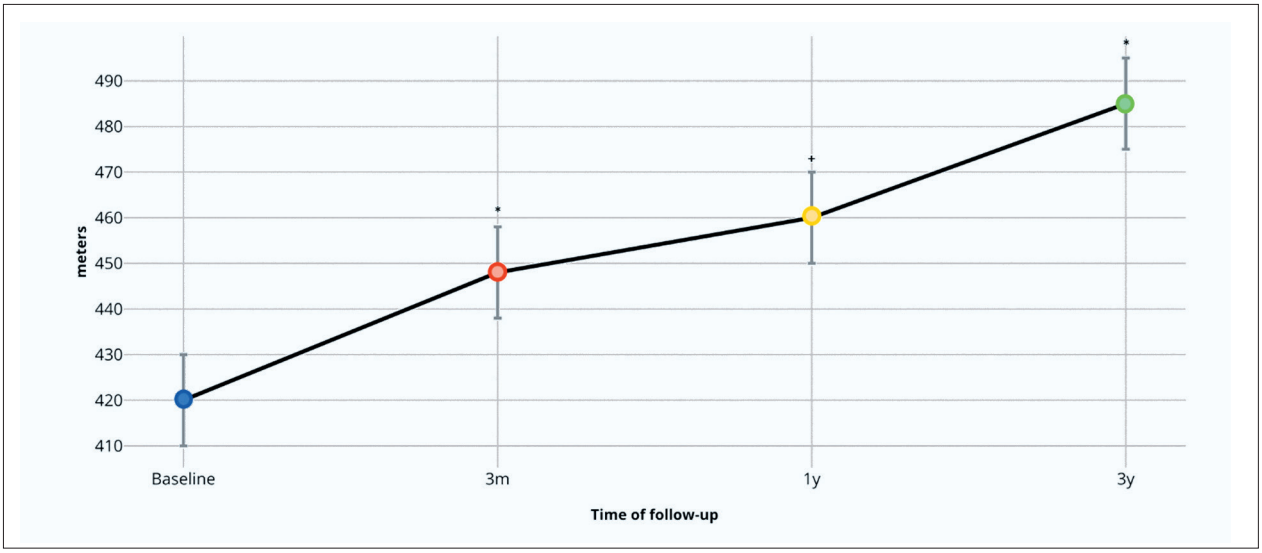


Figure 3 – *Change of 6-min walking test (6MWT) over time in patients with pulmonary hypertension. *p-value< 0.05; +p-value< 0.10; Paired Student's t-test compared to Baseline.*

Table 2 – Changes in clinical and laboratorial measurements after 3 years of treatment with riociguat

Characteristic	Baseline (n= 31)	3 years (n= 31)	Δ	p-value*
Systolic PAP (mmHg)	81.6 ± 16.1	78.2 ± 14.2	-3.4	0.500
Diastolic PAP (mmHg)	35.1 ± 5.2	34.2 ± 4.7	-0.9	0.618
mPAP (mmHg)	43.5 ± 9.0	39.6 ± 3.4	-3.9	0.253
PAWP (mmHg)	7.3 ± 1.8	9.6 ± 3.1	2.3	0.013
PVR	9.3 ± 3.0	7.9 ± 3.1	-1.4	0.157
Cardiac Index (L/min)	2.9 ± 0.8	2.7 ± 0.7	-0.2	0.170
Cardiac output (L/min)	5.2 ± 1.5	5.0 ± 1.5	-0.2	0.504
6-min walk distance (m)	394 ± 91	458 ± 100	64	0.014
NT-proBNP (pg/ml)	793 (145 - 1235)	130 (58 - 980)	-663	0.197

*Results are presented as mean ± SD or median (25^{th} - 75^{th}), as appropriate. mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance. *p-value computed using paired Student's t-test compared to Baseline.*

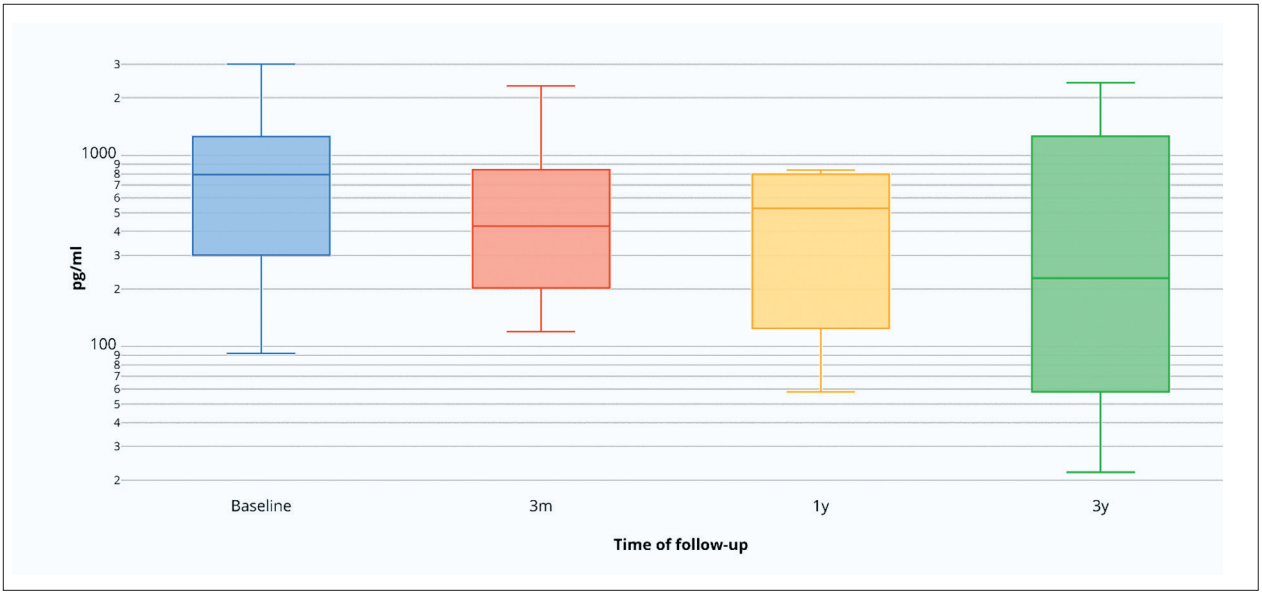


Figure 4 – *Change of N-terminal pro-brain natriuretic peptide (NT-proBNP) over time in patients with pulmonary hypertension.*

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) treatment guidelines recommend regular risk assessment in PAH patients, to manage the patients, focusing on low risk.[5] This risk assessment is performed using a multidimensional approach, but there are abbreviated versions, such as the French registry non-invasive method, which evaluate 6MWT, NT-ProBNP, and WHO functional class.[17] In this context, we also found improvements in NT-ProBNP and WHO functional class in our patients treated with riociguat. Moreover, seven patients achieved the low-risk status. These results emphasize the benefits of medication to the achievement of treatment goals and, perhaps, to reduce the estimated 1-year mortality. Previous reports found significant improvements in these parameters[11,12] and in the low-risk score achievement[17] after treatment with riociguat. It is likely that our data did not reach statistical significance because of the small sample size.

Our study has some limitations. First, due to the real-life cohort design of this study, the number of patients at each visit varied. Second, this is a retrospective study with a reduced sample size. Third, the results are from a single center. Therefore, these limitations should be considered when interpreting the results.

Conclusion

In our real-life cohort, most patients with PH treated with riociguat showed stable or improved risk parameters, especially the 6MWT, at 3 years of follow-up. Moreover, our data was able to reproduce the results of pivotal studies during our follow-up.

Acknowledgments

Gabriela Roncato was an employee of Bayer SA during the writing of the study as a former researcher at Centro de Hipertensão Pulmonar, Complexo Hospitalar Santa Casa de Porto Alegre.

Author Contributions

Conception and design of the research: Spilimbergo FB, Meyer GMB; Acquisition of data: Spilimbergo FB, Assmann TS, Bellon M; Analysis and interpretation of the data: Spilimbergo FB, Assmann TS, Puchalski M, Hochhegger B, Roncato G, Meyer GMB; Statistical analysis: Assmann TS; Obtaining financing: Meyer GMB; Writing of the manuscript: Spilimbergo FB, Assmann TS, Roncato G, Meyer GMB; Critical revision of the manuscript for intellectual contente: Bellon M, Hoscheidt LM, Caurio CFB, Puchalski M, Hochhegger B.

Potential Conflict of Interest

Fernanda Brum Spilimbergo - Lecture and consultation fees from: Bayer, Eli Lilly e GSK.

Marcelo Bellon - Lecture and consultation fees from: Bayer, Eli Lilly e GSK.

Gabriela Roncato - Bayer employee.

Gisela Martina Bohns Meyer - Lecture and consultation fees from: Bayer, Eli Lilly e GSK.

Sources of Funding

There were no external funding sources for this study.

Study Association

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

References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension. Eur Respir J. 2019;53(1):1801913. doi: 10.1183/13993003.01913-2018.
2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in Patients with Primary Pulmonary Hypertension. Results from a National Prospective Registry. Ann Intern Med. 1991;115(5):343-9. doi: 10.7326/0003-4819-115-5-343.
3. Poch D, Mandel J. Pulmonary Hypertension. Ann Intern Med. 2021;174(4):49-64. doi: 10.7326/AITC202104200.
4. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An Evaluation of Long-term Survival from Time of Diagnosis in Pulmonary Arterial Hypertension from the REVEAL Registry. Chest. 2012;142(2):448-56. doi: 10.1378/chest.11-1460.
5. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi: 10.1093/eurheartj/ehv317.
6. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, et al. Pathology and Pathobiology of Pulmonary Hypertension: State of the Art and Research Perspectives. Eur Respir J. 2019;53(1):1801887. doi: 10.1183/13993003.01887-2018.
7. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic Thromboembolic Pulmonary Hypertension. Eur Respir J. 2019;53(1):1801915. doi: 10.1183/13993003.01915-2018.
8. Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, et al. First Acute Haemodynamic Study of Soluble Guanylate Cyclase Stimulator Riociguat in Pulmonary Hypertension. Eur Respir J. 2009;33(4):785-92. doi: 10.1183/09031936.00039808.
9. Stasch JP, Pacher P, Evgenov OV. Soluble Guanylate Cyclase as an Emerging Therapeutic Target in Cardiopulmonary Disease. Circulation. 2011;123(20):2263-73. doi: 10.1161/CIRCULATIONAHA.110.981738.
10. Ghofrani HA, Humbert M, Langleben D, Schermuly R, Stasch JP, Wilkins MR, et al. Riociguat: Mode of Action and Clinical Development in Pulmonary Hypertension. Chest. 2017;151(2):468-80. doi: 10.1016/j.chest.2016.05.024.
11. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2013;369(4):330-40. doi: 10.1056/NEJMoa1209655.
12. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. N Engl J Med. 2013;369(4):319-29. doi: 10.1056/NEJMoa1209657.
13. Fernandes CJCS, Ota-Arakaki JS, Campos FTAF, Corrêa RA, Gazzana MB, Jardim C, et al. Brazilian Thoracic Society Recommendations for the Diagnosis and Treatment of Chronic Thromboembolic Pulmonary Hypertension. 2020;46(6): e20200204. doi:10.36416/1806-3756/e20200204.
14. Klinger JR, Chakinala MM, Langleben D, Rosenkranz S, Sitbon O. Riociguat: Clinical Research and Evolving Role in Therapy. Br J Clin Pharmacol. 2021;87(7):2645-62. doi: 10.1111/bcp.14676.
15. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the Six-minute Walk Test. Am J Respir Crit Care Med. 2002;166(1):111-7. doi: 10.1164/ajrccm.166.1.at1102.
16. Winter JCF. Using the Student's t-test with Extremely Small Sample Sizes. Practical Assessment, Research & Evaluation. 2013;18(10):1-11. doi: 10.7275/e4r6-dj05.
17. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk Assessment, Prognosis and Guideline Implementation in Pulmonary Arterial Hypertension. Eur Respir J. 2017;50(2):1700889. doi: 10.1183/13993003.00889-2017.
18. Mainguy V, Malenfant S, Neyron AS, Bonnet S, Maltais F, Saey D, et al. Repeatability and Responsiveness of Exercise Tests in Pulmonary Arterial Hypertension. Eur Respir J. 2013;42(2):425-34. doi: 10.1183/09031936.00107012.
19. Deboeck G, Scoditti C, Huez S, Vachiéry JL, Lamotte M, Sharples L, et al. Exercise Testing to Predict Outcome in Idiopathic Versus Associated Pulmonary Arterial Hypertension. Eur Respir J. 2012;40(6):1410-9. doi: 10.1183/09031936.00217911.
20. Nagel C, Prange F, Guth S, Herb J, Ehlken N, Fischer C, et al. Exercise Training Improves Exercise Capacity and Quality of Life in Patients with Inoperable or Residual Chronic Thromboembolic Pulmonary Hypertension. PLoS One. 2012;7(7):e41603. doi: 10.1371/journal.pone.0041603.
21. Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension: A Long-term Extension Study (CHEST-2). Eur Respir J. 2015;45(5):1293-302. doi: 10.1183/09031936.00087114.
22. Souza R, Kawut SM. What is New About Rio? Eur Respir J. 2015;45(5):1211-3. doi: 10.1183/09031936.00032715.
23. Hoeper MM, Simonneau G, Corris PA, Ghofrani HA, Klinger JR, Langleben D, et al. RESPITE: Switching to Riociguat in Pulmonary Arterial Hypertension Patients with Inadequate Response to Phosphodiesterase-5 Inhibitors. Eur Respir J. 2017;50(3):1602425. doi: 10.1183/13993003.02425-2016.
24. Frantz RP. REPLACE and the Role of Riociguat in Pulmonary Arterial Hypertension Therapy. Lancet Respir Med. 2021;9(6):546-7. doi: 10.1016/S2213-2600(20)30567-1.
25. McLaughlin VV, Jansa P, Nielsen-Kudsk JE, Halank M, Simonneau G, Grünig E, et al. Riociguat in Patients with Chronic Thromboembolic Pulmonary Hypertension: Results from an Early Access Study. BMC Pulm Med. 2017;17(1):216. doi: 10.1186/s12890-017-0563-7.

Should we Consider the Stimulation of Soluble Guanylyl Cyclase as Beneficial for Treating Pre-Capillary Pulmonary Hypertension?

Allan Kardec Nogueira de Alencar[1]

Faculdade de Medicina de Petrópolis,[1] *Petrópolis, RJ – Brazil*

Short Editorial related to the article: Soluble Guanylate Cyclase Stimulators (Riociguat) in Pulmonary Hypertension: Data from Real-Life Clinical Practice in a 3-Year Follow-Up

One of the rarest and most complex group of diseases that affects the cardiopulmonary system is known as pulmonary hypertension (PH), a life-threatening clinical condition that in advanced stages eventually results in irreversible dysfunction of the right heart chamber and sudden cardiac death.[1] Pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) are two different groups within the PH clinical classification system, in which loss and obstructive remodeling of the lung vessels is responsible for a significant rise in pulmonary arterial (PA) pressure and pulmonary vascular resistance (PVR), resulting in a functional decline of the heart performance and progressive right ventricle (RV) failure.[1]

PAH is a pre-capillary-type PH (Group 1), hemodynamically defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg, PA wedge pressure ≤15 mmHg, and PVR ≥3 Wood units.[2] Remodeling of pulmonary vessels in PAH is depicted by the accumulation of pulmonary artery smooth muscle (PASMCs) and endothelial cells (PAECs), fibroblasts, myofibroblasts, and pericytes in the PA walls. In addition, this remodeling process results in a loss of pre-capillary arteries and exacerbates perivascular inflammation.[1] The excessive loss of PAECs is a key pathobiological feature of PAH.[3] This phenomenon triggers the development of an apoptosis-resistant and hyperproliferative phenotype of PAECs.[3] Subsequently, an intense proliferation of PAECs induces the formation of plexogenic lesions in the lung vessels, a histopathologic hallmark of PAH.[4]

Patients with thromboembolic disease may consequently develop CTEPH (Group 4 in the PH classification)[2] due to a persistent pulmonary vascular obstruction after an embolic event.[2] Pathophysiologically, CTEPH can be multifactorial as it involves both large pulmonary vessels and microcirculation.[5] 75% of patients with PH in chronic thromboembolic disease have a history of acute pulmonary embolism,[6] and it was suggested that the remaining 25% had recurrent and silent emboli.[6] Pointing out the histopathological characteristics of CTEPH, mainly thrombotic materials with a large amount of collagen, elastin, rarely calcifications, and commonly inflammatory cells adhere to the pulmonary vessel walls and obliterate this small vascular bed.[7] Similarly to PAH, CTEPH is another example of pre-capillary PH, in which patients can be hemodynamically diagnosed with a pulmonary arterial wedge pressure ≤15 mmHg, PVR ≥3 Wood units and mPAP ranging from 15 to 24 mmHg.[2]

Available treatments for PH specifically target the reduction of PA vasoconstriction and the pressure-overloaded RV.[1,8,9] It was reported that stimulation of the soluble guanylyl cyclase (sGC) enzyme with a drug named riociguat is beneficial in the clinical setting of PAH.[10] In the context of CTEPH, pulmonary endarterectomy is the recommended treatment.[11] However, up to 40% of patients are technically inoperable, and 17-31% develop persistent or recurrent PH following the pulmonary endarterectomy.[11] Importantly, riociguat was the first substance to be approved for the treatment of two distinct groups of pre-capillary PH: PAH and inoperable or persistent/recurrent CTEPH.[11]

Molecularly, in PASMCs from patients with PAH and CTEPH, the nitric oxide (NO)-sGC-cyclic GMP (cGMP) axis is deregulated, which results in pulmonary vascular inflammation, thrombosis and exacerbated vasoconstriction.[1,4,5] Riociguat modifies the cGMP signaling pathway by increasing its cytosolic levels after stimulation of sGC. It should be addressed that this mechanism is independent of the paracrine roles of NO in the pulmonary vascular cells.[12] Increased cytosolic levels of cGMP lead to vasodilation and inhibition of PASMCs proliferation and fibrosis, with further antithrombotic and anti-inflammatory effects.[12] Additionally, the increasing content of cGMP after administration of riociguat could lead to inhibition of the phosphodiesterase type 3 in cardiomyocytes, which consequently augments the intracellular levels of cyclic AMP and promotes a positive inotropic effect in the heart.[12] Riociguat may also exert cardioprotective effects and improve the RV function when it potentiates the activation of protein kinase G, following the rise of cGMP levels.[12] This biomolecular signaling is mainly explained by the opening of mitochondrial K_{ATP} channels in cardiac cells.[12]

In their groundbreaking paper of 2022, Spilimbergo et al.[13] were the first researchers to retrospectively investigate the effects of riociguat in patients with PAH and CTEPH through a 3-year follow-up real-life study.[13] These scientists measured current risk assessment parameters and found interesting data which may help to prove the beneficial effects of riociguat in PAH and CTEPH subjects.[13]

Firstly, they have shown that riociguat significantly increased the 6-minute walking distance (6MWD) after at least 3 years of therapy, compared with the baseline data, in both patients with PAH and CTEPH.[13] The authors also found a gradual increase

Keywords

Pulmonary hypertension; Pulmonary Ciruculation; Pulmonary Arterial Wedge Pressure; Soluble Guanylyl Cyclase Stimulators; Riociguat.

Mailing Address: Allan Kardec Nogueira de Alencar •
Faculdade Arthur Sá Earp Neto Faculdade de Medicina de Petrópolis - Av. Barão do Rio Branco, 1003. Postal Code 25680-120, Petrópolis, RJ - Brazil
E-mail: allankdc@gmail.com

DOI: https://doi.org/10.36660/abc.20220261

in the 6MWD from 3 months to 3 years after the beginning of the treatment of diseased subjects with riociguat, with a final median greater than 440 meters.[13]

Importantly, after 3 years of investigation, the authors did not observe significant changes in the following parameters: systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, mPAP, PVR, cardiac index, cardiac output and N-terminal (NT)-prohormone BNP (NT-pro BNP) levels.[13] However, 3 years of treatment with riociguat significantly increased the pulmonary arterial wedge pressure.[13]

In accordance with the findings mentioned above, the authors have shown that the stimulation of sGC in this cohort decreased the number of patients in the World Health Organization (WHO) functional class III, who were then classified as functional class II after the follow-up.[13] Considering only the patients who completed 3 years of follow-up, at baseline, 61% of patients were functional class III, and after 3 years of treatment with riociguat, 10% of patients continued as functional class III.[13] Similarly, at baseline, 32% of the patients were in functional class II, and after treatment, 71% of the patients were in functional class II.[13] It was also shown that the three-year survival rate among PAH and CTEPH patients treated with riociguat was 96.7%.[13] Therefore, we might understand that riociguat has improved the functional exercise capacity, increased the pulmonary arterial wedge pressure and preserved the other clinical and laboratorial measurements after 3 years of treatment, which probably have transferred most patients to a better WHO functional class.

Finally, according to the French non-invasive risk stratification, the researchers found that no patient was at low risk at baseline, but 7 patients achieved low-risk status after 3 years of therapy with riociguat.[13]

In my opinion, the authors have conducted this investigation appropriately and have shown the study's limitations in the discussion section. Accordingly, this work can add important data on the therapy for pre-capillary PH, although we still understand that there is a lack of pleiotropic agents in the context of these diseases, mainly when we highlight the need for new pharmacological approaches that promote beneficial actions on the pulmonary vascular bed (attenuation of the proliferative phenotype of endothelial, smooth muscle and fibroblast cells) with a further potential cardioprotective effect.

References

1. Humbert M, Guignabert C, Bonnet S, Dorfmuller P, Klinger JR, Nicolls MR, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019;53(1):1801-87. doi: 10.1183/13993003.01887-2018.
2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):180913. doi: 10.1183/13993003.01913-2018.
3. Voelkel NF, Cool C, Taraceviene-Stewart L, Geraci MW, Yeager M, Bull T, et al. Janus face of vascular endothelial growth factor: the obligatory survival factor for lung vascular endothelium controls pre-capillary artery remodeling in severe pulmonary hypertension. Crit Care Med. 2002;30(5 Suppl):S251-6. doi: 10.1097/00003246-200205001-00013.
4. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease: pulmonary arterial hypertension. Nat Rev Cardiol. 2011;8(8):443-55. doi: 10.1038/nrcardio.2011.87.
5. Kim NH. Group 4 Pulmonary Hypertension: Chronic Thromboembolic Pulmonary Hypertension: Epidemiology, Pathophysiology, and Treatment. Cardiol Clin. 2016;34(3):435-41. doi: 10.1016/j.ccl.2016.04.011.
6. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973-81. doi: 10.1161/CIRCULATIONAHA.110.015008.
7. Albani S, Biondi F, Stolfo D, Lo Giudice F, Sinagra G. Chronic thromboembolic pulmonary hypertension (CTEPH): what do we know about it? A comprehensive review of the literature. J Cardiovasc Med (Hagerstown). 2019;20(4):159-68. doi: 10.2459/JCM.0000000000000774.
8. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53(1):1802148. doi: 10.1183/13993003.02148-2018.
9. Fernandes CJ, Calderaro D, Assad APL, Salibe-Filho W, Kato-Morinaga LT, Hoette S, et al. Update on the Treatment of Pulmonary Arterial Hypertension. Arq Bras Cardiol. 2021;117(4):750-64. doi: 10.36660/abc.20200702.
10. Rubin LJ, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). Eur Respir J. 2015;45(5):1303-13. doi: 10.1183/09031936.00090614.
11. Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur Respir J. 2015;45(5):1293-302. doi: 10.1183/09031936.00087114.
12. Watanabe H. Treatment Selection in Pulmonary Arterial Hypertension: Phosphodiesterase Type 5 Inhibitors versus Soluble Guanylate Cyclase Stimulator. Eur Cardiol. 2018;13(1):35-7. doi: 10.15420/ecr.2017:22:2.
13. Spilimbergo FB, Assmann TS, Bellon M, Caurio LMB, Puchalski M, Hochehegger B, et al. Estimuladores de Guanilato Ciclase Solúvel (Riociguate) na Hipertensão Pulmonar: Dados da Prática Clínica Real em 3 Anos de Acompanhamento. Arq Bras Cardiol. 2022; 118(6):1059-1066.

Angiotensin Receptor Blockers Evaluated by Office and Home Blood Pressure Measurements. TeleHBPM Study

Weimar Kunz Sebba Barroso,[1] Andréa Araujo Brandão,[2] Priscila Valverde de Oliveira Vitorino,[3] Audes Diógenes de Magalhães Feitosa,[4,5] Eduardo Costa Duarte Barbosa,[6] Roberto Dischinger Miranda,[7] Josep Redon,[8] Miguel Camafort-Babkowski,[9] Antonio Coca,[10] Marco Antônio Mota Gomes[11]

Universidade Federal de Goiás - Liga de Hipertensão Arterial,[1] Goiânia, GO – Brazil
Universidade do Estado do Rio de Janeiro – Cardiologia,[2] Rio de Janeiro, RJ – Brazil
Pontifícia Universidade Católica de Goiás - Escola de Ciências Sociais e da Saúde,[3] Goiânia, GO – Brazil
Universidade de Pernambuco,[4] Recife, PE – Brazil
Universidade Católica de Pernambuco,[5] Recife, PE – Brazil
Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre – Cardiologia,[6] Porto Alegre, RS – Brazil
Universidade Federal de São Paulo - Escola Paulista de Medicina,[7] São Paulo, SP – Brazil
University of Valencia – Hypertension,[8] Valencia, Comunitat Valenciana – Spain
University of Barcelona - Hospital Clínic. Hypertension Unit,[9] Barcelona, Catalunya – Spain
Hypertension and Vascular Risk Unit. Hospital Clinic. University of Barcelona,[10] Barcelona – Spain
Centro Universitário CESMAC - Hospital do Coração,[11] Maceió, AL – Brazil

Abstract

Background: Adequate treatment of arterial hypertension and achieving arterial hypertension goals in are important in reducing cardiovascular outcomes.

Objectives: To describe angiotensin receptor blockers in monotherapy or double combination therapy and the rate of arterial hypertension control.

Methods: This cross-sectional study evaluated patients who were using angiotensin receptor blockers between 2017 and 2020. Those using three or more antihypertensive drugs were excluded. The analyzed variables included sex, age, body mass index, valid home blood pressure monitoring (HBPM) measurements, casual and HBPM systolic and diastolic blood pressure measurements, blood pressure variability, and antihypertensive and angiotensin receptor blocker class. Paired t, chi-square, and Fisher's exact tests were used, as well as overlapping 95% confidence intervals and a significance level of 5% ($p < 0.05$).

Results: Of 17,013 patients, 12,813 met the inclusion criteria, 62.1% of whom were female. The mean number of valid measurements was 23.3 (SD, 2.0). The mean HBPM and casual measurements for systolic blood pressure were 126.8 (SD, 15.8) mmHg and 133.5 (SD, 20.1) mmHg ($p < 0.001$), respectively, while those for diastolic blood pressure were 79.1 (SD, 9.7 mmHg) and 83.6 (SD, 11.9) mmHg ($p < 0.001$), respectively. Losartan was the most common angiotensin receptor blocker and resulted in the highest blood pressure values. Combinations of angiotensin receptor blockers with diuretics or calcium channel antagonists resulted in lower blood pressure values.

Conclusions: More than half of the patients used losartan, although it was the least efficient drug for reducing and controlling blood pressure.

Keywords: Hypertension; Angiotensin II Type 1 Receptor Blockers; Losartana; Antihypertensive Agents/therapeutic use; Age; Sex; Body Weights and Measures.

Introduction

Adequate treatment and control is one of the great challenges in arterial hypertension, which is the leading cause of death worldwide. Aligning treatment strategies with the most current scientific is one way to optimize these results.[1-3] Drugs that effectively reduce blood pressure (BP) also protect against the main outcomes of hypertensive disease, and the best results can be expected of drugs with a long half-life (thus, a single daily dose) that do not negatively interfere in metabolic parameters. It is also known that small BP reductions, even in the early stages of arterial hypertension, can lead to reductions in the main cardiovascular outcomes.[1,4,5]

On the other hand, despite such evidence, the Brazilian Unified Health System provides medications with a short half-life that are used in monotherapy and require several doses a day. Such characteristics can negatively impact adherence and hinder adequate BP control. It should be emphasized that

Mailing Address: Weimar Kunz Sebba Barroso •
Universidade Federal de Goiás - Liga de Hipertensão Arterial – Av. Universitária Hospital das Clínicas. Postal Code 74605-220, Goiânia, GO – Brazil
E-mail: sebbabarroso@gmail.com
Manuscript received June 07, 2021, revised manuscript August 08, 2022, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210504

the Brazilian Unified Health System reflects the drug strategy used for 75% of the hypertensive patients in our country.[1,6]

A 2021 study evaluated a database of 22,446 individuals who underwent home and office BP measurement, 11,337 of whom were being treated for hypertension by cardiologists with antihypertensive drugs. In 74.6% of the cases, renin-angiotensin-aldosterone system blockade was used, including angiotensin receptor blockers (ARBs) in 58.7%, either in monotherapy or combination therapy.[7]

The objectives of the present study were: (i) to verify the distribution of ARB prescription in monotherapy and combined therapy according to sex, geographic region, and diabetes status; (ii) to compare BP control according to casual and home BP monitoring measurement (HBPM) for all ARB treatment strategies; (iii) to compare BP control in casual and HBPM measurements; and (iv) to compare mean systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and BP variability obtained through ARBs in monotherapy or double combination therapy, considering the class as a whole and individual types.

Methods

This study was approved by the Human Research Ethics Committee of the Hospital das Clínicas of the Federal University of Goiás (opinion 99691018.7.0000.5078) and evaluated patients who were examined on the TeleHBPM platform (www.telemrpa.com) between May 2017 and October 2020.

The platform was developed as a remote reporting tool for telemonitoring, including features that allow the database to be analyzed and filtered according to research questions. The mathematical algorithm allows analysis while protecting the personal data of patients and health facilities, whether interpreting exams or developing research projects. Since it is not software, but a platform accessible on any device via an Internet connection, BP measurements can be uploaded quickly and remotely.[8]

The database search was limited to patients who used ARBs. Patients aged at least aged 18 years on monotherapy or double combination therapy were included. Patients on a combination of three or more antihypertensives, antihypertensives in combination with angiotensin-converting enzyme inhibitors, or antihypertensives in double combination therapy with infrequently used antihypertensives (eg, spironolactone, direct vasodilators, alpha2 agonists) were excluded (Figure 1). We also excluded irbesartan from the results due to its rarity in the overall sample.

The following data were collected from the TeleHBPM platform: sex, age (in years), body mass index, number of valid HBPM measurements, casual and HBPM SBP and DBP measurements, blood pressure variability based on HBPM measurements obtained through the standard deviation of the 24 household measurements taken during the protocol, drug class used, and type of ARB. The regional distribution of the sample was also evaluated, as was the prevalence of individuals who used medications to treat diabetes mellitus (oral antidiabetics and/or insulin).

The Quetelet formula was used to calculate body mass index based on weight and height data.[9] HBPM was performed with the provided device; patients were instructed about proper handling and BP measurement on the day the device was delivered.[1] On that day, two measurements were taken in a clinical/office environment and, over the next 4 days, the patient (and/or caregiver/companion) performed the measurements at home according to protocol. The mean of the two measurements taken on the first day was considered the casual measurement, and the mean of the 24 measurements taken from the second to the fifth day was considered the HBPM measurement.[8,10] Only validated automatic devices (Omron, Geratherm, and Microlife) were used.

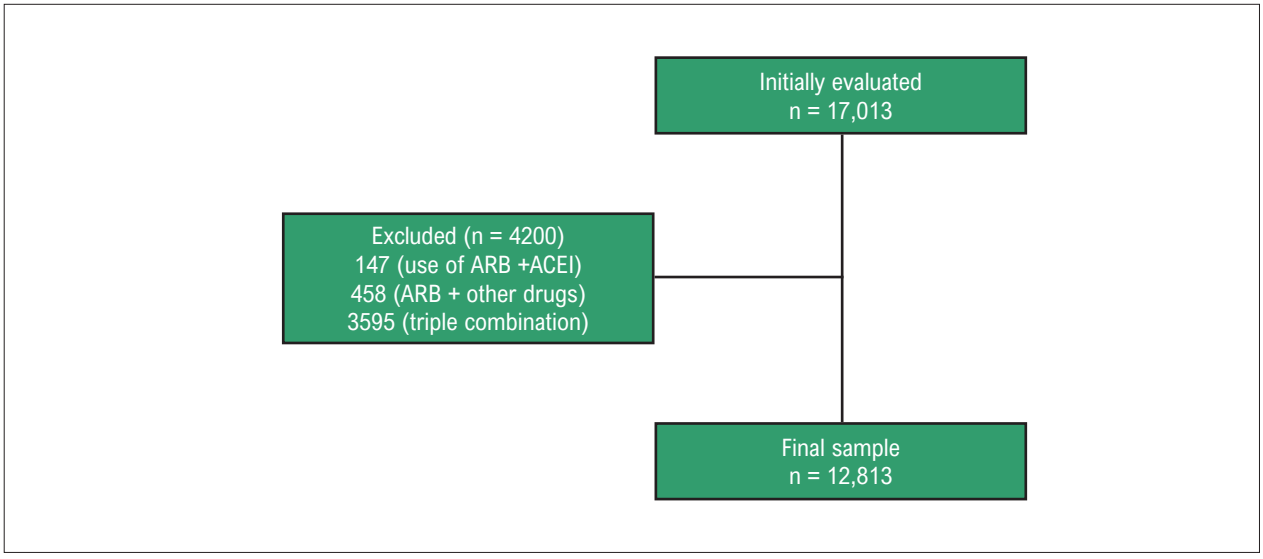


Figure 1 – *Sample selection flowchart. ARB: angiotensin receptor blockers; ACEI: angiotensin-converting enzyme inhibitors.*

The data were exported from the TeleHBPM platform to Microsoft Excel. All drug classes described on the platform were reviewed and coded by two work teams. The databases were then cross-referenced to identify discrepant data, which, when present, were reviewed by the entire team. Individuals whose SBP/DBP values were <140/90 mmHg in casual measurement and <130/80 mmHg in HBPM, respectively, were considered to have controlled BP.[1]

Statistical analysis

Statistical analysis was performed in Stata 14.0. Quantitative variables were expressed as mean and standard deviation, and qualitative variables were expressed as absolute and relative frequencies. The Kolmogorov-Smirnov test was used to verify the normality of the data.

The mean SBP, DBP and PP values obtained in casual and HBPM measurements were compared using a paired Student's *t*-test. The chi-square test or Fisher's exact test was used to compare BP control rates according to the casual and HBPM measurements, as well as to compare the rates of BP control for each drug strategy.

Overlapping 95% confidence intervals were used to compare the differences in mean SBP, DBP, PP and BP variability obtained with ARB monotherapy or double combination therapy, considering the class as a whole and individual types. P-values <0.05 were considered significant.

Results

A total of 12,813 patients were evaluated, the majority of whom were female. The Northeast was the most prominently represented region, with approximately half of the patients. The prevalence of diabetes was 6.2% (Table 1).

Double combination therapy was slightly more prevalent than monotherapy (51.2% vs. 48.5%). The following types of ARBs were used: losartan (57.2%), olmesartan (18.8%), valsartan (15.0%), telmisartan (4.8%), candesartan (3.8%), and irbesartan (0.4%).

The mean number of valid HBPM measurements was 23.3(SD, 2.0). The differences in mean casual and HBPM values for SBP and DBP were 6.7 mmHg ($p < 0.001$) and 4.5 mmHg ($p < 0.001$), respectively. These differences characterize the white-coat effect and were maintained across all treatment strategies. This behavior was repeated in all ARBs, whether in monotherapy or combination therapy. We also compared the rate of BP control by casual and HBPM measurements in monotherapy and combination therapy (Table 2).

Table 3 describes the mean casual and HBPM BP values and the BP control rate with different ARBs in monotherapy, while Tables 4, 5 and 6 compare these values for ARBs combined with diuretics, calcium channel antagonists (CCA), and beta-blockers, respectively.

According to the goals of <140/90 mmHg (casual) and <130/80 mmHg (HBPM) recommended by current guidelines,[1] overall BP control was better in casual measurement. In HBPM, BP control was lower in ARB monotherapy and in ARBs combined with beta-blockers. Among the ARB types used in monotherapy or combination therapy, BP control was lower with losartan and higher with long half-life ARBs. This trend was repeated in the casual measurements.

The control rates of different ARBs in combination with CCA, BB, or diuretics were lower in combinations with losartan and higher in ARBs with a long half-life in both HBPM and casual measurements. In HBPM, the mean SBP for ARB + CCA and ARB + diuretics was lower than that of ARB monotherapy.

Table 1 – Description of hypertensive patients using ARBs, n = 12,813

Variable	Total n (%)	ARB n (%)	ARB + DIU n (%)	ARB + BB n (%)	ARB + CCA n (%)
	12,813 (100)	**6225 (48.6)**	**3006 (23.5)**	**1433 (11.2)**	**2.149 (16,8)**
Sex					
Female	7953 (62.1)	3749 (60.2)	2006 (66.7)	980 (68.4)	1218 (56.7)
Male	4860 (37.9)	2476 (39.8)	1000 (33.2)	453 (31.6)	931 (43.3)
Region					
Unidentified	37 (0.3)	12 (0.2)	16 (0.5)	5 (0.3)	4 (0.1)
Northeast	6347 (49.6)	3187 (51.2)	1355 (45.1)	698 (48.7)	1107 (51.5)
North	802 (6.3)	326 (5.2)	194 (6.5)	52 (3.6)	230 (10.7)
Midwest	1003 (7.8)	478 (7.7)	232 (7.7)	162 (11.3)	131 (6.1)
Southeast	4028 (31.4)	1961 (31.5)	1026 (34.1)	444 (31.0)	597 (27.8)
South	596 (4.7)	261(4.2)	183 (6.1)	72 (5.0)	80 (37)
Diabetes					
No	12,015 (93.8)	5877 (94.4)	2811 (93.5)	1294 (90.3)	2033 (94.6)
Yes	798 (6.2)	348 (5.6)	195 (6.5)	139 (9.7)	116 (5.4)

CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; DUI: diuretics.

Table 2 – Sample description and comparison of blood pressure control by casual measurement and by HBPM according to the use of ARB in monotherapy and combinations, n = 12,813

Variable	HBPM	Casual	p*
Total (n = 12,813)			
SBP	126.8±15.8	133.5±20.1	< 0.001
DBP	79.1±9.7	83.6±11.9	< 0.001
PP	52.2±14.4	49.9±16.1	< 0.001
ARB monotherapy (n = 6225)			
SBP	126.9±15.6	133.5±19.8	< 0.001
DBP	79.7±9.6	84.3±11.7	< 0.001
PP	51.7±14.0	49.215.7	< 0.001
ARB + DIU (n = 3006)			
SBP	125.0±15.8	132.3±20.3	< 0.001
DBP	78.6±9.5	83.3±11.9	< 0.001
PP	50.7±14.3	49.1±16.1	< 0.001
ARB + CCA (n = 2149)			
SBP	127.0±14.9	133.8±19.2	< 0.001
DBP	78.4±9.9	82.8±11.9	< 0.001
PP	53.2±14.0	51.0±15.8	< 0.001
ARB + BB (n = 1433)			
SBP	129.4±17.9	136.0±22.2	< 0.001
DBP	78.3±10.4	82.6±12.4	< 0.001
PP	56.016.2	53.417.7	< 0.001
Variable	**Controlled**	**Not controlled**	**p****
Total			
HBPM	5695 (44.5)	7118 (55.5)	< 0.001
Casual measurement	7211 (56.3)	5602 (43.7)	
ARB monotherapy			
HBPM	2691 (43.2)	3534 (56.8)	0.007
Casual measurement	3485 (56.0)	2740 (44.0)	0.513
ARB + DIU			
HBPM	1441 (48.0)	1565 (52.1)	< 0.001
Casual measurement	1751 (58.3)	1255 (41.7)	0.013
ARB + CCA			
HBPM	960 (44.7)	1189 (55.3)	0.818
Casual measurement	1204 (56.0)	945 (44.0)	0.796
ARB + BB			
HBPM	603 (42.1)	830 (57.9)	0.056
Casual measurement	771 (53.8)	662 (46.2)	0.045

**Paired t-test; **Chi-square or Fisher's exact test. CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; DUI: diuretics; HBPM: home blood pressure monitoring; BPD: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.*

Table 3 – Sample description and comparison of blood pressure control in casual and HBPM measurements according to ARB type in monotherapy, n = 6225

Variable	HBPM	Casual measurement	p*
Losartan (n = 3.861)			
SBP	128.3 ±15.8	135.4± 20.3	< 0.001
DBP	80.6±9.7	85.5±11.8	< 0.001
PP	52.1±14.1	50.0±16.0	< 0.001
Valsartan (n = 818)			
SBP	126.8±15.3	132.4±19.5	< 0.001
DBP	78.6±9.5	82.4±10.8	< 0.001
PP	52.7±14.3	50.0±16.0	< 0.001
Candesartan (n = 221)			
SBP	124.0±12.9	129.0±17.0	< 0.001
DBP	77.5±7.8	81.4±9.5	< 0.001
PP	50.9±13.4	47.6±14.8	< 0.001
Olmesartan (n = 1.032)			
SBP	123.0±14.9	128.418.1	< 0.001
DBP	77.9±9.4	82.0±11.9	< 0.001
PP	49.8±13.0	46.414.1	< 0.001
Telmisartan (n = 287)			
SBP	126.2±14.8	132.6±18.0	< 0.001
DBP	79.6±9.1	84.0±11.3	< 0.001
PP	51.1±13.9	48.3±15.1	< 0.001
Variable	Controlled	Not controlled	p**
Losartan			
HBPM	1517 (39.3)	2344 (60.7)	< 0.001
Casual	1984 (51.4)	1877 (48.6)	< 0.001
Valsartan			
HBPM	369 (45.1)	449 (54.9)	0.693
Casual	489 (59.8)	329 (40.2)	0.037
Candesartan			
HBPM	111 (50.2)	110 (49.8)	0.081
Casual	150 (67.9)	71 (32.1)	< 0.001
Olmesartan			
HBPM	559 (54.2)	473 (45.8)	< 0.001
Casual	682 (66.1)	350 (33.9)	< 0.001
Telmisartan			
HBPM	130 (45.3)	157 (54.7)	0.770
Casual	172 (59.9)	115 (40.1)	0.207

**Paired t-test; **Chi-square or Fisher's exact test. ARB: angiotensin receptor blockers; HBPM: home blood pressure monitoring; BPD: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.*

Table 4 – Comparison of blood pressure control in casual and HBPM measurement according to ARB type in double combination therapy with DUIs, n = 3006

Variable	HBPM	Casual measurement	p
Olmesartan + DIU (n = 530)			
SBP	122.1±15.8	128.4±20.2	< 0.001
DBP	77.0±9.6	81.112.0	< 0.001
PP	49.5±15.1	47.3±16.3	< 0.001
Candesartan + DIU (n = 151)			
SBP	123.1±5.0	130.920.8	< 0.001
DBP	77.6±9.1	82.4±12.1	< 0.001
PP	49.6±14.1	48.5±15.1	0.199
Telmisartan + DIU (n = 123)			
SBP	124.9±16.7	132.5±20.1	< 0.001
DBP	78.3±8.5	83.6±11.1	< 0.001
PP	51.1±15.9	48.9±16.8	< 0.001
Valsartan + DIU (n = 1.920)			
SBP	126.9±15.5	132.7±20.1	< 0.001
DBP	78.3±9.7	82.1±11.7	< 0.001
PP	53.2±14.3	50.6±16.1	< 0.001
Losartan + DIU (n = 1.715)			
SBP	125.7±15.7	133.8±20.1	< 0.001
DBP	79.2±9.4	84.2±11.7	< 0.001
PP	50.9±14.1	49.6±16.1	< 0.001
Variable	Controlled	Not controlled	p**
Olmesartan + DIU			
HBPM	288 (54.3)	242 (45,7)	< 0,001
Casual	335 (63.2)	195 (36,8)	0,001
Candesartan + DIU			
HBPM	80 (53.0)	71 (47,0)	0,034
Casual	99 (65.6)	52 (34,4)	0,021
Telmisartan + DIU			
HBPM	59 (48.0)	64 (52,0)	0,430
Casual	73 (59.4)	50 (40,6)	0,490
Valsartan + DIU			
HBPM	887 (46.2)	1.033 (53,8)	0,094
Casual	1.136 (59.2)	784 (40,8)	0,006
Losartan + DIU			
HBPM	779 (45.4)	936 (54,6)	0,382
Casual	965 (56.3)	750 (43,7)	0,992

**Paired t-test; **Chi-square or Fisher's exact test. ARB: angiotensin receptor blocker; DUI: diuretic; HBPM: home blood pressure monitoring; BPD: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.*

Table 5 – Sample description and comparison of blood pressure control in casual and HBPM measurement according to ARB type in double combination therapy with CCAs, n = 2,149

Variable	HBPM	Casual measurement	p*
Olmesartan + CCA (n = 626)			
SBP	125.0±14.9	131.7±19.4	< 0.001
DBP	77.8±10.2	81.8±12.5	< 0.001
PP	51.9±14.5	49.9±15.9	< 0.001
Candesartan + CCA (n = 419)			
SBP	127.4±14.6	135.1±18.4	< 0.001
DBP	78.6±10.2	83.6±11.6	< 0.001
PP	53.4±13.9	51.5±15.4	< 0.001
Telmisartan + CCA (n = 136)			
SBP	128.7±15.8	132.4±18.8	0.003
DBP	78.6±10.3	81.8±11.7	< 0.001
PP	55.1±13.6	50.7±14.1	< 0.001
Valsartan + CCA (n = 433)			
SBP	127.0±15.2	132.6±19.5	< 0.001
DBP	77.4±9.6	80.7±11.6	< 0.001
PP	54.2±13.6	51.8±15.4	< 0.001
Losartan + CCA (n = 903)			
SBP	128.2±14.5	135.9±18.7	< 0.001
DBP	79.6±9.6	84.7±11.3	< 0.001
PP	53.1±3.7	51.1±15.9	< 0.001
Variable	Controlled	Not controlled	p**
Olmesartan + CCA			
HBPM	302 (48.2)	324 (51.8)	0.050
Casual	378 (60.4)	248 (39.6)	0.034
Candesartan + CCA			
HBPM	173 (41.3)	246 (58.7)	0.186
Casual	218 (52.0)	201 (48.0)	0.075
Telmisartan + CCA			
HBPM	69 (50.7)	67 (49.3)	0.138
Casual	84 (61.8)	52 (38.2)	0.195
Valsartan + CCA			
Casual	270 (62.4)	163 (37.6)	0.010
HBPM	206 (47.6)	227 (52.4)	0.183
Losartan + CCA			
HBPM	361 (40.0)	542 (60.0)	0.005
Casual	451 (49.9)	452 (50.1)	< 0.001

**Paired t-test; **Chi-square or Fisher's exact test. CCA: calcium channel antagonists; ARB: angiotensin receptor blockers; HBPM: home blood pressure monitoring; BPD: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.*

Table 6 – Sample description and comparison of blood pressure control in casual and HBPM measurement according to ARB type in double combination therapy with BBs, n = 1,433

Variable	HBPM	Casual	p*
Olmesartan + BB (n = 230)			
SBP	126.3±17.0	132.0±20.6	< 0.001
DBP	77.6±10.4	80.911.5	< 0.001
PP	53.6±14.8	51.1±17.0	< 0.001
Candesartan + BB (n = 65)			
SBP	129.8±17.3	133.8±21.0	< 0.001
DBP	75,8±11.8	79.114.2	0.012
PP	59.0±17.1	54.716.6	0.002
Telmisartan + BB (n = 75)			
SBP	128.4±16.5	132.6±21.9	0.01
DBP	78.0±10.7	82.0±13.9	< 0.001
PP	55.2±15.3	50.6±16.3	< 0.001
Valsartan + BB (n = 213)			
SBP	130.0±16.8	137.021.9	< 0.001
DBP	77.9±10.3	82.5±12.5	< 0.001
PP	57.0±15.7	54.5±18.0	< 0.001
Losartan + BB (n = 851)			
SBP	130.2±18.5	137.3±22.7	< 0.001
DBP	78.8±10.3	83.4±12.3	< 0.001
PP	56.2±16.7	53.8±17.9	< 0.001
Variable	Controlled	Not controlled	p**
Olmesartan + BB			
HBPM	114 (49.6)	116 (50.4)	0.115
Casual	138 (60.0)	92 (40.0)	0.251
Candesartan + BB			
HBPM	31 (47.7)	34 (52.3)	0.598
Casual	40 (61.5)	25 (38.5)	0.391
Telmisartan + BB			
HBPM	36 (48.0)	39 (52.0)	0.535
Casual	46 (61.3)	29 (38.7)	0.376
Valsartan + BB			
HBPM	91 (42.7)	122 (57.3)	0.610
Casual	113 (53.1)	100 (46.9)	0.338
Losartan + BB			
HBPM	331 (38.9)	520 (61.1)	0.001
Casual	433 (50.9)	418 (49.1)	0.001

**Paired t-test; **Chi-square or Fisher's exact test. BB: beta-blockers; ARB: angiotensin receptor blockers; HBPM: home blood pressure monitoring; DBP: diastolic blood pressure; SBP: systolic blood pressure; PP: pulse pressure.*

In monotherapy, the BP values were progressively higher for olmesartan, candesartan, telmisartan, valsartan and losartan (Figure 2). In combined therapy, the mean SBP values for HBPM were progressively higher with diuretics, CCA and BB, and combinations with losartan tended to have higher values than those with longer half-life ARBs (Figure 3). The mean DBP measurements were higher in ARB monotherapy than any double combination therapy. In HBPM, the ARB type with the highest mean DBP values in monotherapy was losartan (Figure 4). No difference was found in DBP values between the different possible combinations of ARB types (Figure 5).

PP was higher with ARB + BB than any other combination or ARB monotherapy. Losartan in monotherapy or in double combination therapy resulted in a higher mean PP than candesartan or telmisartan.

BP variability was greater with ARB + CCA than in combinations with diuretics or BB or in monotherapy. Whether in monotherapy or combination therapy, BP variability was lower with telmisartan than valsartan. Losartan + CCA had lower mean variability than other combinations. Candesartan + BB showed greater variability than candesartan + CCA. There was no difference in BP variability between combinations with valsartan, olmesartan and telmisartan

Discussion

The present study, a further development of an analysis published in 2020, found that, in hypertensive patients treated with monotherapy or double combination therapy, different possible combinations of ARB types resulted in significantly lower mean SBP and DBP in HBPM than in casual measurements, as well as that ARBs were the most common treatment option.[7] Thus, it makes sense to assess BP behavior in response to various ARB types in both clinical and home settings.

Our sample population had a mean age of approximately 60 years and a high body mass index. The patients were also predominantly women, and most resided in the Northeast and Southeast regions. It is important to consider that advanced age and excess weight can impede achieving recommended arterial hypertension treatment goals.[1,11-13]

It should also be noted that in the last year, as a result of HBPM evidence published in the national database, the reference values for normality were lowered from 135/85 mmHg to 130/80 mmHg.[1,14-16] This change explains the difference in BP control rates found in casual and HBPM measurements in this analysis compared to our previous article.[7]

Regarding the treatment strategies used in this sample, 48.5% received ARB monotherapy, 23.4% received ARBs combined with diuretics, 16.8% received ARBs combined with CCAs, and 11.2% received ARBs combined with BBs. Interestingly, although hypertension guidelines unanimously recommend drug combinations for most cases of hypertension, monotherapy was still quite frequent.[1-3] Dual combination therapy with diuretics and CCAs was preferred, which is in line with current recommendations.[1,7,17-19]

Another relevant aspect in selecting arterial hypertension drugs is a long half-life, which allows a single daily dose; these characteristics directly interfere with treatment adherence and adequate BP control. Drugs with a short half-life must be taken twice or more daily to maintain their plasma level and efficacy in reducing BP levels.[1,7,20-22]

It is interesting to note that, from a pharmacological point of view, there are important differences between these drugs, and the different half-lives of ARBs (losartan, 2 h; valsartan, 6 h; candesartan, 9 h; olmesartan, 12 h; and telmisartan, 24 h) may be related to the differences we found in BP behavior.[23]

When evaluating the BP control rate by casual and HBPM measurements, we found that 56.3% and 44.5% of the patients, respectively, were within the goals. We found different percentages of patients with controlled BP among the different ARB types and combinations.

For a more refined analysis of this behavior, we determined the mean HBPM measurements and confidence intervals of SBP, DBP, and pressure variability. Combinations with BBs resulted in higher mean SBP values and variability than combinations with diuretics or CCAs. In monotherapy, losartan had the highest mean SBP and DBP values of the longer half-life ARBs.

This observational study was limited by the fact that it did not assess the dosage of each drug, and the sample was not representative of the Brazilian population. On the other hand, it analyzed data from a large database that reflected ARB usage strategies in hypertensive patients, allowing important parameters to be determined regarding BP behavior with different drugs in monotherapy and combination therapy.

These findings are consistent with those of previously published randomized studies that evaluated the antihypertensive efficacy of different ARBs[24-28] and, more importantly, they reflect the need to review the Brazilian Unified Health System's strategy for antihypertensive drugs,[6] since it is known that small BP reductions in hypertensive patients have important repercussions on cardiovascular morbidity and mortality.

Conclusions

In hypertensive patients treated with ARBs, monotherapy is still frequent. In combined therapy, diuretics and CCAs are preferred. Among ARBs, losartan is still used in more than half of patients, whether in monotherapy or double combination therapy, despite being the least efficient medication for reducing and controlling BP. There are clear differences in the half-life of ARBs, which was seen in BP behavior through both casual and HBPM measurements. These differences may reflect the effectiveness of blood pressure control.

National co-investigators

Adriana Siqueira Serpa de Menezes, SAVE, Recife, PE. Andréa Araújo Brandão, Universidade do Estado do Rio de Janeiro, RJ. Anibal Prata Barbosa, Prog de Hip. Arterial Secretaria de Saúde de Duque de Caxias, RJ. Antonio Almeida Braga, PROCAPE, UPE, Recife, PE. Antonio Eduardo de Melo Filho, Clínica de Saúde Dr Antonio Eduardo de Melo, Triunfo, PE. Átila de Oliveira Melo, Liga de Hipertensão Arterial UFG, Goiânia, GO. André K Vidigal de Vasconcellos, Instituto de Cardiologia do Agreste, Caruaru, PE. Audes D. M. Feitosa, Unidade de Hipertensão e Cardiologia Preventiva,

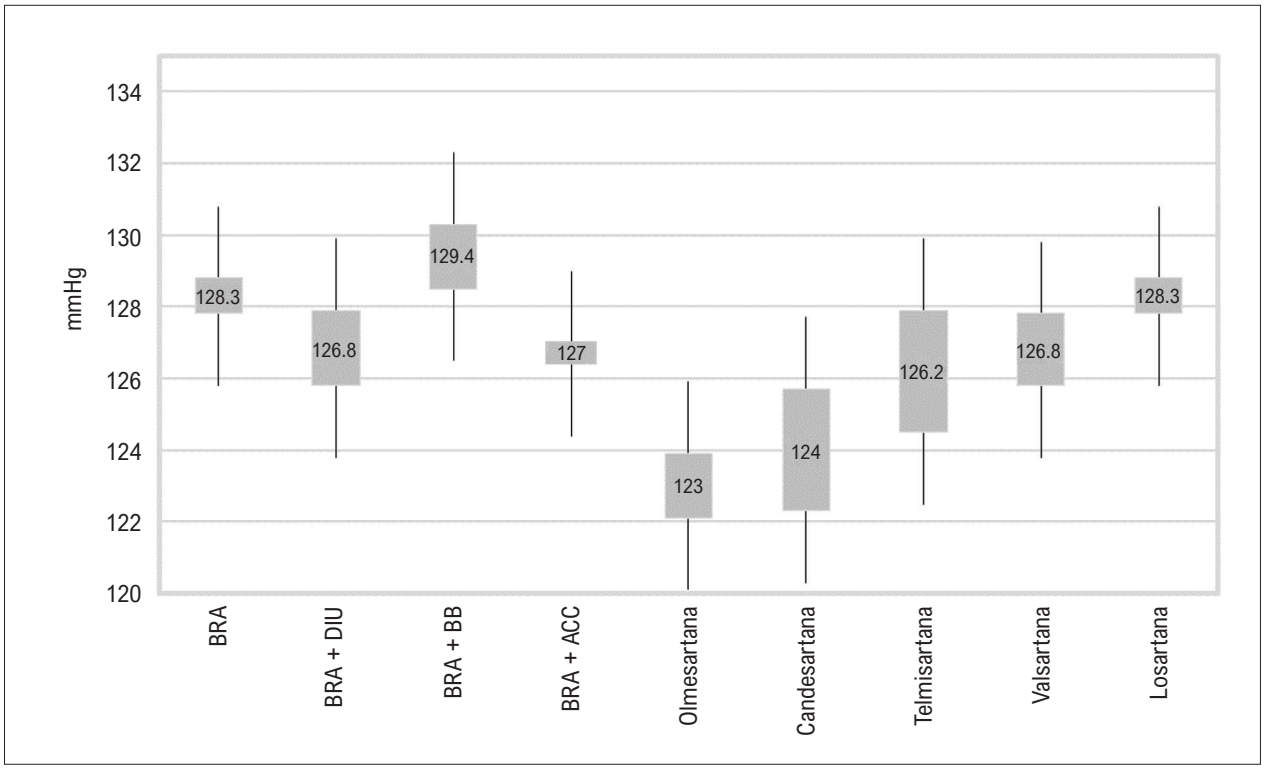


Figure 2 – *Comparison of mean SBP (HBPM) obtained using ARB (classes and types) in monotherapy or in double combination therapy. CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; DUI: diuretics; HBPM: home blood pressure monitoring; SBP: systolic blood pressure. Differences are significant when 95% confidence intervals do not overlap.*

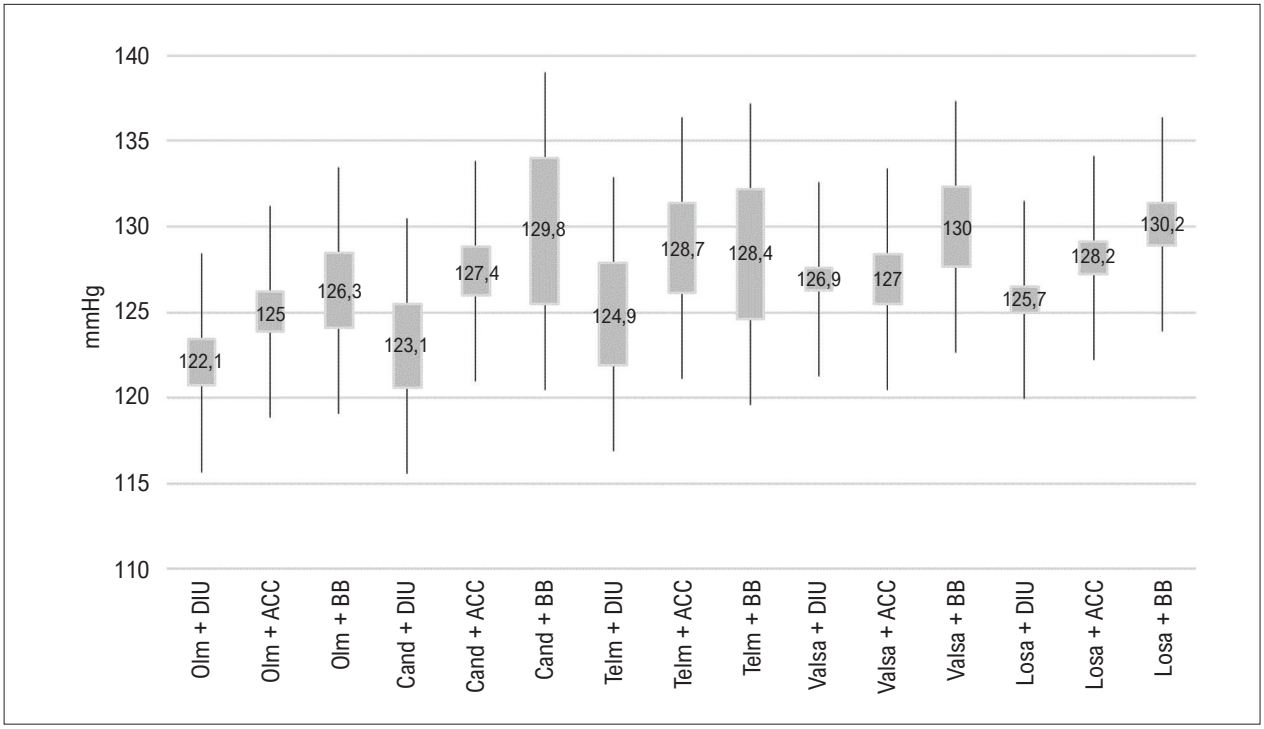


Figure 3 – *Comparison of mean SBP (HBPM) obtained using different types of ARB in double combination therapy. CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; Cand: candesartan; DUI: diuretics; Losa: losartan; HBPM: home blood pressure monitoring; Olm: olmesartan; SBP: systolic blood pressure; Telm: telmisartan; Valsa: valsartan. Differences are significant when 95% confidence intervals do not overlap.*

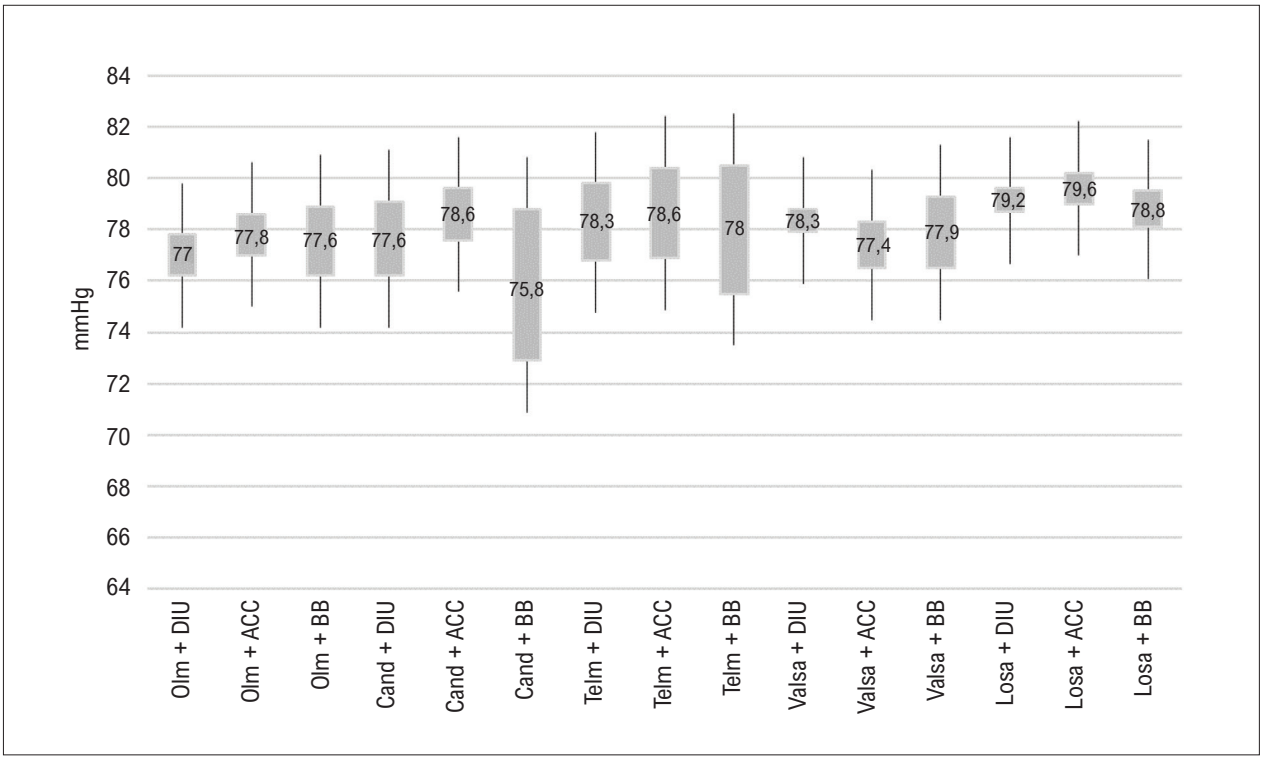


Figure 4 – *Comparison of mean DBP (HBPM) obtained using ARB (classes and types) in double combination therapy. CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; Cand: candesartan; DUI: diuretics; Losa: losartan; HBPM: home blood pressure monitoring; Olm: olmesartan; DBP: diastolic blood pressure; Telm: telmisartan; Valsa: valsartan.*
Differences are significant when 95% confidence intervals do not overlap.

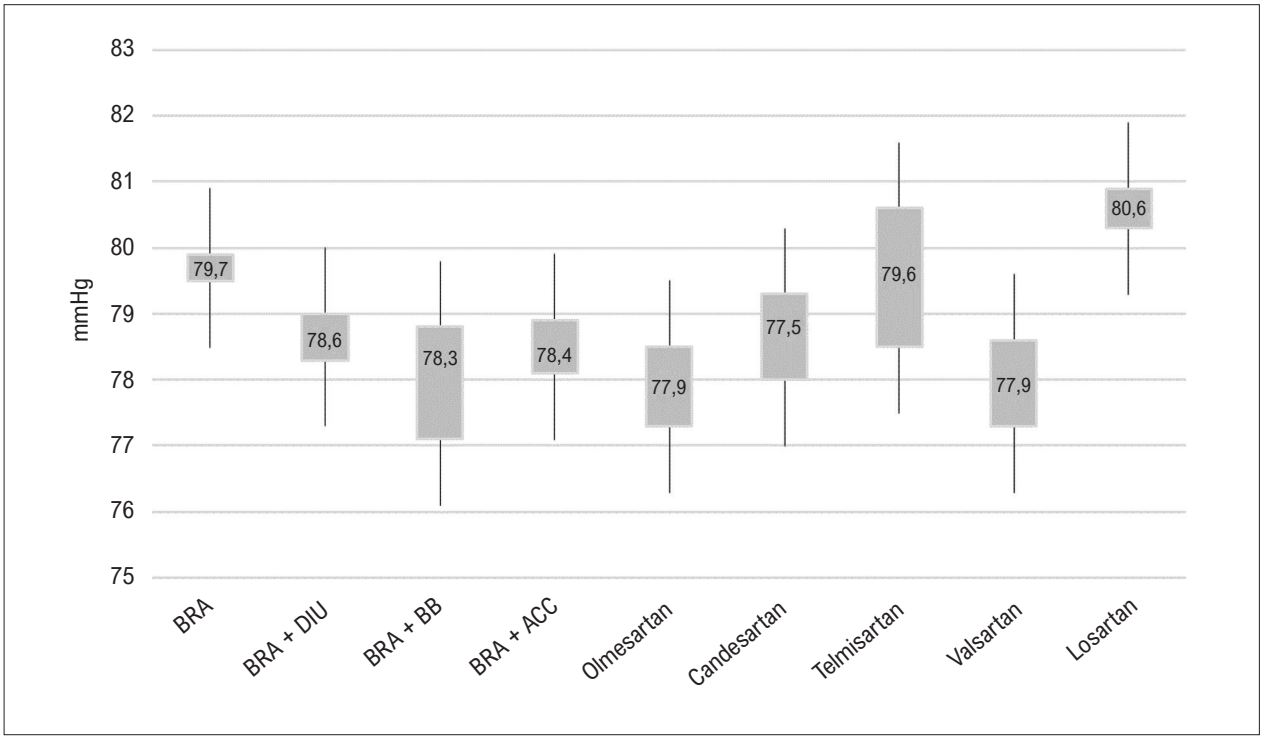


Figure 5 – *Comparison of mean DBP (HBPM) obtained using ARB (classes and types) in monotherapy or in double combination therapy. CCA: calcium channel antagonists; BB: beta-blockers; ARB: angiotensin receptor blockers; DUI: diuretics; HBPM: home blood pressure monitoring; DBP: diastolic blood pressure. Differences are significant when 95% confidence intervals do not overlap.*

PROCAPE/UPE, Recife, PE. Breno Gontijo de Camargos, AngioCor, Taguatinga, DF. Bruno Alencar Fonseca, Clínica Blues, Belo Horizonte, MG. Bruno Daniel Ferrari, Fundação Educacional do Município de Assis, FEMA, SP. Bruno José Peixoto Coutinho, Cardiologia Hospital Oswaldo Cruz, Universidade de Pernambuco, PE. Carlo Bonasso, Clínica Médica Carlo Bonasso SS Ltda, São Paulo, SP. Carlos José Mota de Lima, Centro Cardiológico São Camilo, CE. Carlos Filinto de Almeida, Instituto do Coração de Mato Grosso do Sul, Campo Grande, MS. Claudinelli Alvarenga Aguilar, Clínica do Esporte, Goiânia, GO. César Ricardo Soares Medeiros, Clínica de Cardiologia Dr César Medeiros, Ribeirão Preto, SP. Cristiano Pederneiras Jaeger, Instituto de Medicina Vascular - Coracentro, Porto Alegre/RS. Daniel Lages Dias, Novacordis, Paulínia, SP. Diogo da Silva Amorim, Liga de Hipertensão Arterial UFG, Goiânia, GO. Ednaldo M. Fontes Segundo, Cardiologista pela SBC, Instituto Paulo Gomes (IPG) em Estância, SE. Eduardo C. D. Barbosa, Dept Hipertensão e Cardiometabolismo Hospital São Francisco, Santa Casa Porto Alegre, RS. Eduardo Érico Zen, Hospital Cardiológico Costantini, Curitiba, PR. Elder Gil A. Cruz, Clínica do Coração Dr. Elder Gil, Salgueiro, PE. Esther G. Diôgo de Lima de B. Carvalho, Clínica São Lucas, Guarabira, PB. Fábio Argenta, Mediodonto, Cuiabá, MT. Fabiano de Souza Ramos, MEDCOR Cardiologia, Nova Iguaçu- RJ. Flávia Karina Silva e Oliveira, Centro de Cardiologia, São José dos Campos, SP. Flávio H. A. P. Véras, Clínica do Coração, Mossoró, RN. Francisco Deoclecio Pinheiro, Clínica de Especialidades Médicas de Itapipoca, Itapipoca, CE. Frank Land L. de Carvalho, Cardiovasf, Petrolina, PE. Germano Granja, Clínica do Coração, Ouricuri, PE. Giovanni Saraiva, Imedi e Icordis, Recife, PE. Gleidson Junio Oliveira de Souza, Liga de Hipertensão Arterial UFG, Goiânia, GO. Gustavo Barros - MCOR / Recife-PE. Gustavo Guimarães Moreira de Castro, ITACORDIS e Universidade Iguaçu – UNIG, Itaboraí e Nova Iguaçu, RJ. Jadil Francisco Fusturath Júnior, Cardio Service, Porto Velho, RO. José Wladimir Tambelli Pires, Clínica de Cardiologia, Itapetininga/SP. João Evaristo de Oliveira Dantas, Cardiomed/Multimed, São Luís, MA. João Félix de Morais Filho, Clínica Angiocárdio, Natal / RN. João Francisco Martins Pacheco, Endocardio, Belém, PA. Jonathan Scapin Zagatti, Cardio Ritmo Diagnósticos, Jales, SP. José Joaquim Raposo, Serviço de Cardiologia da Santa Casa de Limeira, SP. José Roberto Moya, Biocardios, Cuiabá, MT. Josafá de Oliveira Costa, Clínica Vitta, Igarassu, PE. Josiedson Pontes de Farias, Cardio Diagnósticos, Caruaru, PE. Juan Carlos Yugar Toledo. Endocor, Rio Preto, SP. Lilian Mesquita, Ergo Med Setor De Cardiologia/Geriatria, RJ. Lola Helbingen Santos, Cardiodiagnósticos, Goiania, GO. Luam Vieira de Almeida Diógenes, Procardiaco, Teresina, PI. Luiz Kencis Júnior, Lapacor, São Paulo, SP. Marcelo Júlio de Oliveira, Clínica Cardiograficos, Ribeirão Preto, SP. Marco Antônio de M Alves, Escada Clinical Center, Escada, PE. Marco A. M. Gomes, Centro de Pesquisas Clínicas do Cesmac/Hospital do Coração de Alagoas. Marcos Alberto Pires Meira Júnior, Clincar João Pessoa PB. Maria Christina Cavalcanti Ballut, MEDCENTRO, Manaus, AM. Marcus Vinícius de Oliveira, Cardiodiagnósticos, Goiânia-GO. Maria Beatriz M. B. L. Rodrigues, Cardiovida, Porto Velho, RO. Mayara Cedrim Santos, Instituto UNICAP de Pesquisa Clínica, Recife, PE. Naiara Pedrassi Engracia Garcia Caluz, Centro de Medicina Avançada Dr Luiz Kencis, São Paulo, SP. Nelson Dinamarco, Ambulatório de Hipertensão Arterial, Colegiado de Medicina, Universidade Estadual Santa Cruz – UESC. Nildo Magalhães, SOBAM Jundiaí, SP. Paulo Roberto Pereira de Sant'Ana, MEDCOR Cardiologia, Nova Iguaçu- RJ. Rafael Nogueira de Macedo, Centro Cardiológico São Camilo, CE. Paulo Sérgio Lopes Soares, Universidade De Vassouras - Hospital Universitário de Vassouras, RJ. Ricardo Mesquita de Freitas, Cardiocenter, Barreiras, BA. Roberto de A. Dultra, Clinicor, Itabuna, Bahia, BA. Roberto Dischinger Miranda, Serviço de Cardiologia, Disciplina de Geriatria e Gerontologia, Escola Paulista de Medicina, Universidade Federal de São Paulo. Rodrigo Cunha de Sousa, Centro Integrado de Medicina Invasiva – CIMI, Uberaba, MG. Rogério Krakauer, Santa Casa de SP. Rogerio Ruiz, HD HomeDoctor, SP. Ruy Morando, Cincor - Centro Integrado do Coração, Americana, SP. Sérgio Augusto Vieira Simões, Consultório Médico Integrado, Tássia Tâmara Silva Feitosa, Ok Doutor, Recife, PE. Tobias Barreto, SE. Sheyla Cristina Tonheiro Ferro da Silva, CLINSAUDE e CEMISE, Aracaju, SE. Vanderlei Magalhães da Silveira, Cardiologista, Faculdade de Medicina, Universidade de Passo Fundo. Vanildo Guimarães, Diagnóstico Cardíaco, Recife, PE. Vilma Helena Burlamaqui, Consultório de Cardiologia, Niterói, RJ. Vitor Bruno Teixeira de Holanda, Climile, Ananindeua, PA. Walmir de Vasconcelos Ratier Thomaz, Rio de Janeiro, RJ. Weimar Sebba Barroso, Liga de Hipertensão Arterial UFG, Goiânia, GO. Wenderson Tavares dos Santos, Hospital Biocor, Belo Horizonte, MG

Author Contributions

Conception and design of the research: Barroso WKS, Brandão AA, Vitorino PVO, Feitosa A, Barbosa ECD, Gomes MM; Acquisition of data: Barroso WKS, Brandão AA, Feitosa A, Barbosa ECD, Gomes MM; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Barroso WKS, Brandão AA, Vitorino PVO, Feitosa A, Barbosa ECD, Miranda RD, Redon J, Camafort-Babkowski M, Coca A, Gomes MM; Statistical analysis: Barroso WKS, Vitorino PVO; Obtaining financing: Barroso WKS; Writing of the manuscript: Barroso WKS, Brandão AA, Vitorino PVO, Feitosa A, Barbosa ECD, Coca A.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by Indústria Farmacêutica EMS.The study was supported by the Brazilian National Council for Scientific and Technological Department (CNPq; 313481/2020-2) for Dr. Barroso.

Study Association

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

References

1. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Diretrizes Brasileiras de Hipertensão Arterial – 2020. Arq. Bras. Cardiol. 2021;116(3):516-658.
2. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. J Hypertens. 2017; 35: 1529-45.
3. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-104.
4. Departamento da Sociedade Brasileira de Cardiologia. I Posicionamento Brasileiro sobre Fármacos Anti-hipertensivos. Arq Bras Cardiol. 2014; 102: 203-10.
5. The Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant level data meta-analysis. LANCET. 2021; 397: 1625 - 1636.
6. Relação Nacional de Medicamentos Essenciais: Rename 2020 [recurso eletrônico] / Ministério da Saúde, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde, Departamento de Assistência Farmacêutica e Insumos Estratégicos. Brasília: Ministério da Saúde, 2020. http://portalms.saude.gov.br/assistencia-farmaceutica/medicamentos-rename ISBN 978-85-334-2748-8
7. Barroso WKS, Feitosa ADM, Barbosa ECD, Brandão AA, Miranda RD, Vitorino PVO, et al. Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleHBPM Study. Arq Bras Cardiol. 2021; [online]. ahead print, PP.0-0 doi.org/10.36660/abc.20200073.
8. Barroso WKS. MRPA no Diagnostico e Controle da Hipertensão Arterial. 1a ed. ed. São Paulo: DDS Comunicação e Serviços Editoriais, 2019.
9. Calle EE, Thun MJ, Petrelli JM, Rodriguez C and Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. The New England journal of medicine. 1999; 341: 1097-105.
10. Brandão AA, Alessi A, Feitosa AM, Machado CA, Figueiredo CEP, Amodeo C, et al. 6a Diretrizes de monitorização ambulatorial da pressão arterial e 4a Diretrizes de monitorização residencial da pressão arterial. Arq Bras Cardiol. 2018;110(5 suppl 1):1-29.
11. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol. 2011; 57: 2037-114.
12. Aprahamian, I, Sassaki, E, dos Santos, MF, et al. Hypertension and frailty in older adults. J Clin Hypertens. 2018; 20: 186– 192.
13. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. Nat Rev Nephrol. 2019;15(6):367-85.
14. Feitosa ADM, Mota-Gomes MA, Nobre F, Mion Jr. D, Argenta F, et al. What are the Optimal Reference Values for Home Blood Pressure Monitoring? Arq. Bras. Cardiol. 2021; 116(3): 501-503.
15. Feitosa ADM, Mota-Gomes MA, Barroso WS, Miranda RD, Barbosa ECD, Pedrosa RP. Correlation between office and home blood pressure in clinical practice:a comparison with 2017 American College of Cardiology/American Heart Association Hypertension Guidelines recommendations. Journal of Hypertension 2020, 38:176–181.
16. Feitosa ADM, Mota-Gomes MA, Barroso WS, MD, Miranda RD MD, Barbosa ECD, Brandão AA, et al. The impact of changing home blood pressure monitoring cutoff from 135/85 to 130/80 mmHg on hypertension phenotypes J Clin Hypertens. 2021;00:1–5.
17. Departamento da Sociedade Brasileira de Cardiologia. I Posicionamento Brasileiro sobre Fármacos Anti-hipertensivos. Arq Bras Cardiol. 2014; 102: 203-10.
18. Feitosa AD, Gomes MM, Passarelli Júnior O, Barroso WKS, Miranda RDS, Barbosa EDB, et al. Pharmacological Treatment of Hypertension: From the Golden Trio to the Octet. Arq Bras Cardiol. 2020; 115(2):270-2.
19. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet (London, England). 2016; 388: 2665-712.
20. Gianfranco Parati, Sverre Kjeldsen, Antonio Coca, William C. Cushman, Jiguang Wang. Adherence to Single-Pill Versus Free-Equivalent Combination Therapy in Hypertension. Hypertension.2021; 77: 692-705.
21. Thomopoulos C, Parati G and Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--overview and meta-analyses. J Hypertens. 2015; 33: 195-211.
22. Brunstrom M, Carlberg B. Association of blood pressure lowering with mortal- ity and cardiovascular disease across blood pressure levels: a systematic review and meta-analysis. JAMA Intern Med. 2018;178(1):28–36.
23. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384(9943):591-598.
24. Abraham HMA, White CM, White WB, The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases. :Drug Saf. 2015 Jan; 38(1): 33–54. doi: 10.1007/s40264-014-0239-7
25. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative Efficacy of Olmesartan, Losartan, Valsartan, and Irbesartan in the Control of Essential Hypertension. The Journal of Clinical Hypertension 2001; 3:283-292.
26. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD001841. DOI: 10.1002/14651858.CD001841.pub3.
27. Julius S, Weber MA, Kjeldsen SE, McInnes GT, Zanchetti A, Brunner HR, Laragh J. The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial. Outcomes in Patients Receiving Monotherapy. Hypertension 2006, 48: 385-391.
28. Kondrack R , Mohiuddin S. Valsartan/hydrochlorothiazide: pharmacology and clinical efficacy. Expert Opin Drug Metab Toxicol. 2009 Sep;5 (9):1125-34.doi: 10.1517/17425250903136730
29. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al.. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358: 1547 - 1559.

Differences among Angiotensin Receptor Blockers (BRA) in the Treatment of Arterial Hypertension

José Geraldo Mill[1,2]

Departamento de Ciências Fisiológicas, Universidade Federal do Espírito Santo,[1] *Vitória, ES – Brazil*
Hospital Universitário Cassiano Antônio Moraes,[2] *Vitória, ES – Brazil*

Short Editorial related to the article: Angiotensin Receptor Blockers Evaluated by Office and Home Blood Pressure Measurements. TeleHBPM Study

Cardiovascular diseases (CVD) are the main cause of death and disability in Brazil, and arterial hypertension (AH) is the main risk factor for cardiovascular morbidity and mortality.[1] Early diagnosis and correct treatment are priority actions to face the problem.[2] The National Health Survey conducted by the Ministry of Health in 2013 (PNS-2013) determined the prevalence of AH by direct measurement of blood pressure (BP) and use of antihypertensive drugs in a representative sample of the Brazilian adult population. Prevalence of 32.3% (95%CI: 31.7 - 33.0) indicated nearly 50 million hypertensive patients.[3] Around 70% depend on the Unified Health System (SUS) for both diagnosis and pharmaceutical care, an essential aspect of the Chronic Noncommunicable Diseases (NCD) plan.[2]

According to the current guidelines, the initial treatment of AH should be carried out with general measures, including regular aerobic physical activity, reduction of salt intake, increased consumption of fruits and vegetables and weight reduction when obesity or overweight is present.[4] These measures benefit everyone and not only hypertensive patients indeed. Even adopting these strategies, many patients still depend on the regular use of drugs to get high BP control. Thus, the use of these drugs shows great importance because, given the dimension of the problem, even small pressure reductions generate a positive impact for millions of individuals affecting the morbidity and mortality rates due to CVD.[5] Thus, the search for effective treatments for BP control has paramount importance to adopt public policies in this area.

The public health system provides at least one drug among the seven classes of antihypertensive medicines most often used in clinical routine, contributing to the high drug coverage in hypertensive patients in Brazil compared to other countries. A nationwide survey carried out in 2016 showed that 93.8% of individuals who knew their hypertensive state used at least one antihypertensive drug.[6] High treatment indexes(>80%) were also reported in the PNS-2013 and in the ELSA-Brasil cohort, where most participants are attended by private health insurance.[7,8] An important finding in the PNS was to show that the frequency of use was independent of schooling and income, confirming the universality of access, one of the objectives of the national policy to face CNCD in Brazil.[2]

Angiotensin receptor blockers (BRA) are Brazil's most used antihypertensive drug.[7,8] After the introduction of losartan, the prototype compound of BRA in the therapeutic arsenal of AH over 30 years ago, a series of other compounds with the same mechanism of action were available to use. The effectiveness of these compounds in BP control is the central theme of the article by Barroso et al.[9] published in this issue of *Arquivos Brasileiros de Cardiologia*. This robust study included 12,813 hypertensive patients to compare the therapeutic efficacy of BRA used as monotherapy or in combination with other antihypertensive drugs. Additionally, they correlated the BP effect with the half-life of each BRA. The effect on BP was assessed by office BP assessment and by home BP monitoring (HBPM). The latter allows more accurate information on the long-term BP effect of any antihypertensive drug. On average, each patient obtained more than 20 BP records along three treatment days. It is worth mentioning that the prescription was open to any BRA at the doctor's discretion. As expected, losartan was the most BRA prescribed, both as monotherapy and in different combinations. Despite being the drug with the lowest cost among BRA, one disadvantage is its short half-life, requiring shorter intervals between pill uses, thus reducing adherence to treatment. The study showed that the control rates of BP were higher, both in the office and in-home measurement, when longer-live ARB was used. As stated before, the rate of antihypertensive drugs by patients in Brazil is reasonable. The same cannot be said concerning BP control which still shows insufficient rates,[6-8] mainly in those attended by the public health system and in use of monotherapy even though current recommendations[4,7] since the mechanism of hypertension remains unknown for most patients.[4]

The results showed by Barroso et al.[9] are important because they allow two main conclusions. One has a direct impact on the therapeutic approach to hypertension. Regardless of the BRA chosen, it is more effective for BP control when combined with other antihypertensive classes. The other impacts on the public policies for coping with CNCD point to the need to evaluate the inclusion of at least one longer half-life BRA in the SUS, improving the BP management of hypertensive patients. Even with more expensive drugs, lower and stable BP levels are cost-effective as they increase the prevention of events that negatively impact the quality of life and the economic and social costs of CVD

Keywords

Hypertension; Angiotensin-Converting Enzyme Inhibitors; Losartana;Early Diagnosis

Mailing Address: José Geraldo Mill •
Depto. Ciências Fisiológicas da UFES – Av. Marechal Campos 1468. Postal Code 29040-090, Vitória, ES – Brazil
E-mail: josegmill@gmail.com

DOI: https://doi.org/10.36660/abc.20220281

References

1. Oliveira GMM, Brant LCC, Polanczyk CA, Malta DC, Biolo A, Nascimento BR, et al. Cardiovascular Statistics - Brazil 2021. Arq Bras Cardiol. 2022; 118(1):115-373. doi.org/10.36660/abc.20211012.
2. Brasil. Ministério da Saúde. Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DNCT) no Brasil, 2011-2022. Brasilia;2011.p.30-160. (Textos Básicos de Saúde.Série B).
3. Malta DC, Gonçalves RPF, Machado IE. Freitas MIF, Azeredo C, Szwarcwald CL. Prevalence of arterial hypertension according to different diagnostic criteria, National Health Survey. Rev Bras Epidemiol. 2018;21(Supp. l1):e180021.
4. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian Guidelines of Hypertension - 2020. Arq Bras Cardiol. 2021;116(3):516-658. doi: 10.36660/abc.20201238
5. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;5;387(10022):957-67. doi:10.1016/S0140-6736(15)01225-8.
6. Mengue SS, Bertoldi AD, Ramos LR, Farias MR, Oliveira MA, Tavares NUL, et al. Acesso e uso de medicamentos para hipertensão arterial no Brasil. Rev Saúde Pública 2016;50(supl 2):1S-8S. doi:1.159S15188787.21656154
7. Monteiro CN, Lima MG, Szwarcwald CL, Bastos TF, Barros MBA. Use of antihypertensive and antidiabetic medications in Brazil: an analysis of socioeconomic differences. National Health Survey, 2013. Rev Bras Epidemiol. 2019; 22;(Suppl 02):E190014. doi: 10.1590/1980-549720190014.supl.2.eCollection 2019.
8. Chór D, Ribeiro ALP, Carvalho MS, Duncam BB, Lotufo PA, Nobre AA, et al. Prevalence, Awareness, Treatment and Influence of Socioeconomic Variables on Control of High Blood Pressure: Results of the ELSA-Brasil Study. PLoS One. 2015;10(6):e0127382. doi: 10.1371/journal.pone.0127382. eCollection 2015.
9. Barroso WKS, Brandão AA, Vitorino PVO, Feitosa ADM, Barbosa ECD, Miranda RD, et al. Bloqueadores do Receptor de Angiotensina Avaliados por Medida de Consultório e Residencial da Pressão Arterial. Estudo TeleMRPA. Arq Bras Cardiol. 2022; 118(6):1069-1082.

Recent Developments and Current Status of Transcatheter Aortic Valve Replacement Practice in Latin America – the WRITTEN LATAM Study

Fernando Luiz de Melo Bernardi,[1] Henrique Barbosa Ribeiro,[1,2,3] Luis Nombela-Franco,[4] Enrico Cerrato,[5] Gabriel Maluenda,[6] Tamim Nazif,[7] Pedro Alves Lemos,[8] Matias Sztejfman,[9] Pablo Lamelas,[10] Dario Echeverri,[11] Marcelo Antonio Cartaxo Queiroga Lopes,[12] Fábio Sândoli de Brito Jr.,[1,3] Alexandre A. Abizaid,[1] José A. Mangione,[13] Helene Eltchaninoff,[14] Lars Søndergaard,[15] Josep Rodes-Cabau[16]

Universidade de São Paulo – Faculdade de Medicina Hospital das Clínicas – Instituto do Coração,[1] São Paulo, SP – Brazil
Hospital Samaritano Paulista,[2] São Paulo, SP – Brazil
Hospital Sírio-Libanês – Hemodinâmica e Cardiologia Intervencionista,[3] São Paulo, SP – Brazil
Hospital Clínico San Carlos,[4] Madrid – Spain
San Luigi Gonzaga University Hospital,[5] Orbassano – Italy
Hospital Clínico San Borja Arriarán,[6] Santiago – Chile
Columbia University Medical Center,[7] New York – USA
Hospital Israelita Albert Einstein,[8] São Paulo, SP – Brazil
Sanatorio Finochietto,[9] Buenos Aires – Argentina
Instituto Cardiovascular de Buenos Aires,[10] Buenos Aires – Argentina
Fundacion Cardioinfantil Instituto de Cardiologia,[11] Bogota, Cundinamarca – Colombia
Hospital Alberto Urquiza Wanderley,[12] Cabedelo, João Pessoa, PB – Brazil
Beneficência Portuguesa de São Paulo,[13] São Paulo, SP – Brazil
Hôpital Charles Nicolle,[14] Rouen, Normandy – France
Copenhagen University Hospital[15] Kobenhavn – Denmark
Institut Universitaire de Cardiologie Et de Pneumologie de Québec,[16] Quebec – Canada

Abstract

Background: **Transcatheter aortic valve replacement (TAVR) is a worldwide adopted procedure with rapidly evolving practices. Regional and temporal variations are expected to be found.**

Objective: **To compare TAVR practice in Latin America with that around the world and to assess its changes in Latin America from 2015 to 2020.**

Methods: **A survey was applied to global TAVR centers between March and September 2015, and again to Latin-American centers between July 2019 and January 2020. The survey consisted of questions addressing: i) center's general information; ii) pre-TAVR evaluation; iii) procedural techniques; iv) post-TAVR management; v) follow-up. Answers from the 2015 survey of Latin-American centers (LATAM15) were compared with those of other centers around the world (WORLD15) and with the 2020 updated Latin-American survey (LATAM20). A 5% level of significance was adopted for statistical analysis.**

Results: **250 centers participated in the 2015 survey (LATAM15=29; WORLD15=221) and 46 in the LATAM20. Combined centers experience accounted for 73 707 procedures, with WORLD15 centers performing, on average, 6- and 3-times more procedures than LATAM15 and LATAM20 centers, respectively. LATAM centers performed less minimalistic TAVR than WORLD15 centers, but there was a significant increase in less invasive procedures after 5 years in Latin-American centers. For postprocedural care, a lower period of telemetry and maintenance of temporary pacing wire, along with less utilization of dual antiplatelet therapy was observed in LATAM20 centers.**

Conclusion: **Despite still having a much lower number of procedures, many aspects of TAVR practice in Latin-American centers have evolved in recent years, followingthe trend observed in developed country centers.**

Keywords: **Transcatheter Aortic Valve Replacement; Aortic Valve Stenosis; Latin America.**

Mailing Address: Henrique Barbosa Ribeiro •
Universidade de São Paulo Instituto do Coração - Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: hbribeiro@gmail.com, henrique.ribeiro@hc.fm.usp.br
Manuscript received December 08, 2020, revised manuscript June 04, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210327

Introduction

Transcatheter aortic valve replacement (TAVR) has been adopted worldwide for severe symptomatic aortic stenosis with various risk profiles. This achievement has been built on more than a decade of advancements in technology and patient care. As a consequence, TAVR practices have been evolving rapidly, resulting in a significant improvement in clinical outcomes.[1–4]

In Latin America, the first TAVR procedures were performed in 2008 in Brazil and Colombia.[5,6] Although a steady growth of cases has been observed since then, there have been concerns in the adoption of the most up-to-date practices in Latin America.[8–10] In developing countries, disparities in practice of a high-cost medical procedure can be exacerbated due to several factors, such as lower-income health systems, lower center volumes, less experienced operators, unavailability of certain devices, among others. Understanding such differences is crucial to better comprehend the contemporary practices and seek for further standardization. Moreover, it could aid in developing policies by the local regulators to achieve more widespread adoption of TAVR in such underserved populations, since published data in Latin America are limited.

Therefore, the general and secondary objectives of the study were: i) to compare TAVR practice between Latin-American centers and centers from the rest of the world based on data obtained from the 2015 WRITTEN survey; ii) to assess the changes in TAVR practice in Latin America after 5 years through reapplication of the survey in the continent.

Methods

The WRITTEN survey was an internet-based questionnaire designed to investigate the practices in TAVR centers around the world. The survey design has been described previously.[7] In summary, at least one regional TAVR expert from each country or region was contacted and invited to distribute the survey locally. The survey was promoted through general interventional cardiology mailing lists, announcements by official societies of interventional cardiology, website advertisements, and personalized emails to TAVR operators. Invitations were distributed in different geographic areas simultaneously over 6 months (March 2015 to September 2015). A second enquiry was performed from July 2019 to January 2020, with similar methods, involving only Latin-American centers without a specific cutoff on the number of procedures performed by the center (Figure 1). The survey consisted of an online platform hosted on the collaborative research website (www.cardiogroup.org/TAVI/) with 59 questions addressing five domains of TAVR (Supplemental Table 1): (i) general information about the program at each institution, (ii) patient selection, (iii) procedural techniques and imaging, (iv) postprocedural management, and (v) follow-up. It was requested that only one individual from each TAVR center completed the survey, and only one questionnaire per center was accepted.

Statistical analysis

For the study analysis, the answers corresponding to the TAVR practices of the Latin-American centers in 2015 (LATAM15 centers) were used as reference. Categorical variables were expressed as absolute frequencies and percentages, and continuous variables as median and interquartile range (IQR). For comparison of categorical variables, Fisher's exact test was used to assess the association between dependent (centers group) and independent variables (results from the questionnaire) for dichotomous answers with a two-tailed P value. For questions with more than two possible answers, the association between independent and dependent variables was tested with the chi-square test. Continuous variables were compared with the Mann-Whitney test due to the non-normal distribution of the variables, confirmed by the Shapiro-Wilk test, also with a two-tailed P value. A 5% level of significance was adopted for all statistical analyses. All analyses were performed with the software GraphPad Prism version 7.0 (GraphPad Software, USA).

Results

As previously published, 250 centers completed the questionnaire properly and were included in the 2015 survey.[7] Of these, 29 (11.6%) were from LATAM15 centers. Figure 1 illustrates the global distribution of the centers. Figure 2 summarizes the enrollment of the 46 centers participating in the Latin-American survey in 2020 (LATAM20). Out of the 296 questionnaires, 263 (88.8%) were fully answered, while the remaining had more than 80% of their questions responded. The very few missing data were considered as completely at random, and no special treatment was made. The names of the cities and countries of all centers are listed in the Supplemental Tables 2 and 3.

By the time of the surveys' completion, the sum of all TAVR performed by the participating centers in Latin America in 2015 and 2020 (LATAM15 and LATAM20) and worldwide (WORLD) accounted for 73 707 procedures combined. In comparison to LATAM15, WORD15 centers had performed a much higher number of procedures in their whole experience (median of 34, IQR: 12 to 101 vs. 200, IQR: 84 to 453, $p<0.001$), as well as in the year before survey completion (median of 12, IQR: 5 to 23 vs. 60, IQR: 27 to 110, $p<0.001$). Compared to LATAM15, the LATAM20 total experience was ~2-fold larger (median of 62, IQR: 22 to 138, $p=0.08$), but only slightly higher in the year before the survey (median of 16, IQR: 6 to 30, $p=0.29$). The complete survey results are found in Supplemental Tables 4-7.

Pre-procedural evaluation

In all three groups, the majority of TAVR patients treated in their current practice were at high or prohibited surgical risk. Nonetheless, when comparing LATAM15 to LATAM20, an increase over time was observed in the proportion of intermediate and low surgical risk patients (Figure 3). WORLD15 centers had a higher median number of heart-team meetings monthly than LATAM15 centers (4, IQR: 2 to 4 vs. 1, IQR: 1 to 2, $p=0.001$), with a slight increase in LATAM20 centers (1.5, IQR: 1 to 4, $p=0.27$). The Society of Thoracic Surgeons (STS) score was the most common risk-stratification tool, used routinely by 90%, 69%, and 98% of the LATAM15, WORDL15, and LATAM20 centers, respectively. Meanwhile,

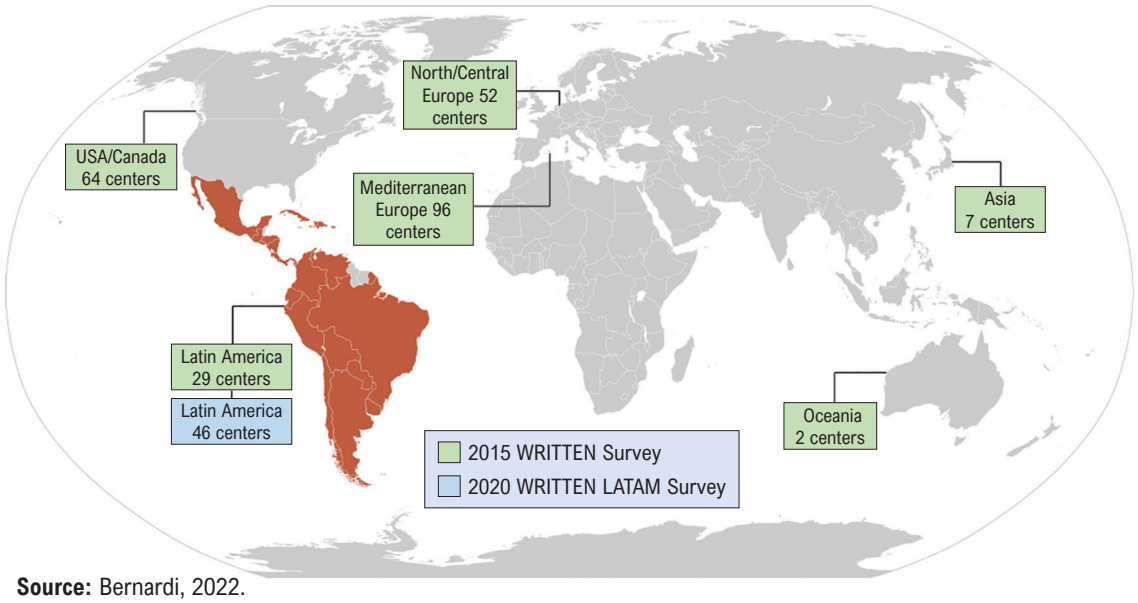


Figure 1 – *Geographical distribution of the participating centers in the 2015 and 2020 surveys.*

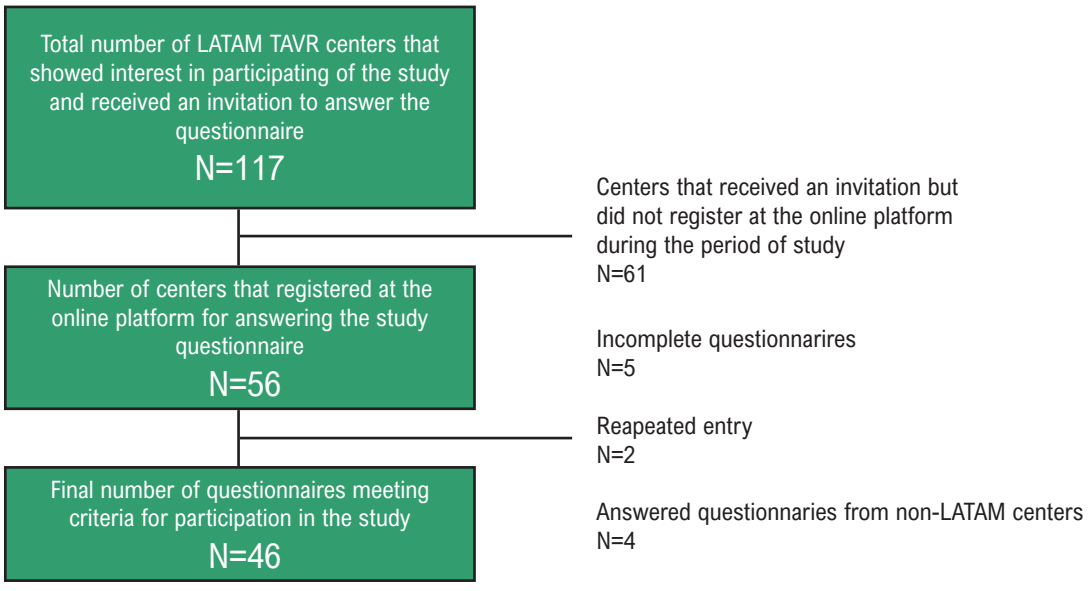
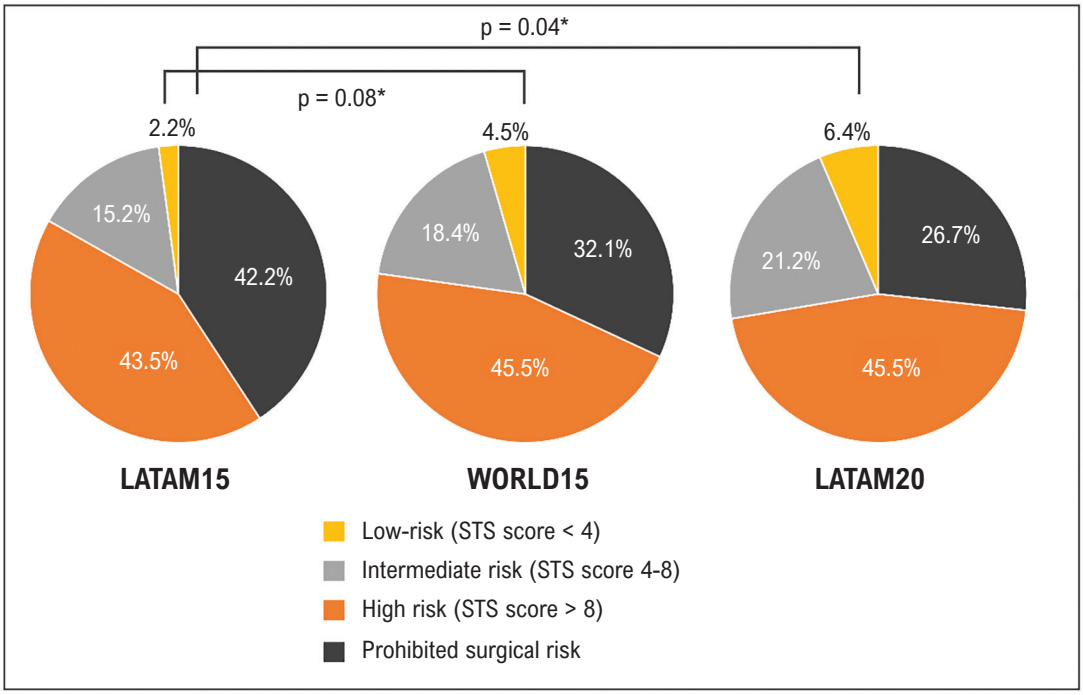


Figure 2 – *Enrollment flowchart of the 2020 WRITTEN LATAM survey.*

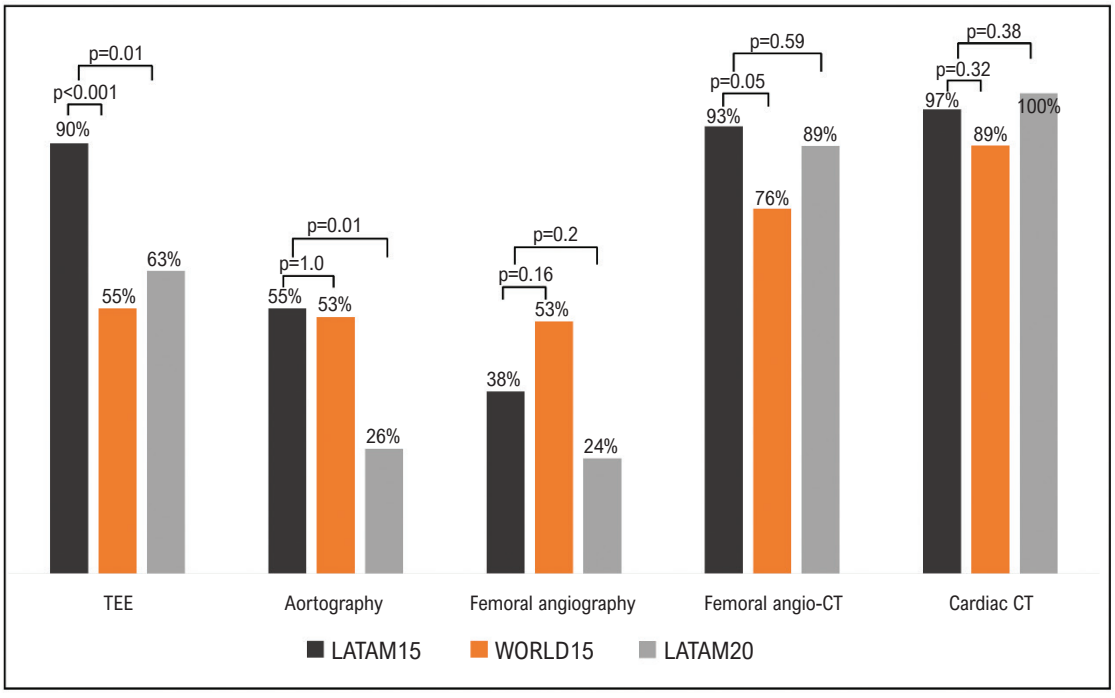
only 28%, 47%, and 39% of the centers, respectively, applied frailty tests routinely. Regarding pre-TAVR imaging (Figure 4), almost all centers performed cardiac computed tomography in their practice. Transesophageal echocardiography as a routine before the procedure was performed more often by LATAM15 centers.

A lower proportion of WORLD15 and LATAM20 centers regularly administered dual-antiplatelet therapy (DAPT) before transfemoral procedures in comparison to LATAM15 centers (45% and 56% vs. 83%, $p<0.001$ and $p=0.02$, respectively). Regarding the time of percutaneous coronary intervention



*P value for the comparison of the mean proportions of low/intermediate-risk patients between the groups (Mann-Whitney test)
Source: Bernardi, 2022

Figure 3 – *Mean proportions of treated patients according to the risk profile.*



Source: Bernardi, 2022

Figure 4 – *Routinely performed preprocedural imaging studies (% of centers). TEE: transesophageal echocardiogram; CT: computed tomography*

(PCI) when a severe proximal coronary lesion was detected, the most common approach by the centers from all groups was to perform PCI before TAVR. In cases deemed risky for coronary obstruction, the three groups agreed the most frequent strategy was to have a PCI protection wire during TAVR (Supplemental Table 4). Regarding antibiotic prophylaxis, more than 90% of the centers administer antibiotics as a routine, with half of them administering 1 dose and the other half ≥ 2 doses.

Procedural management

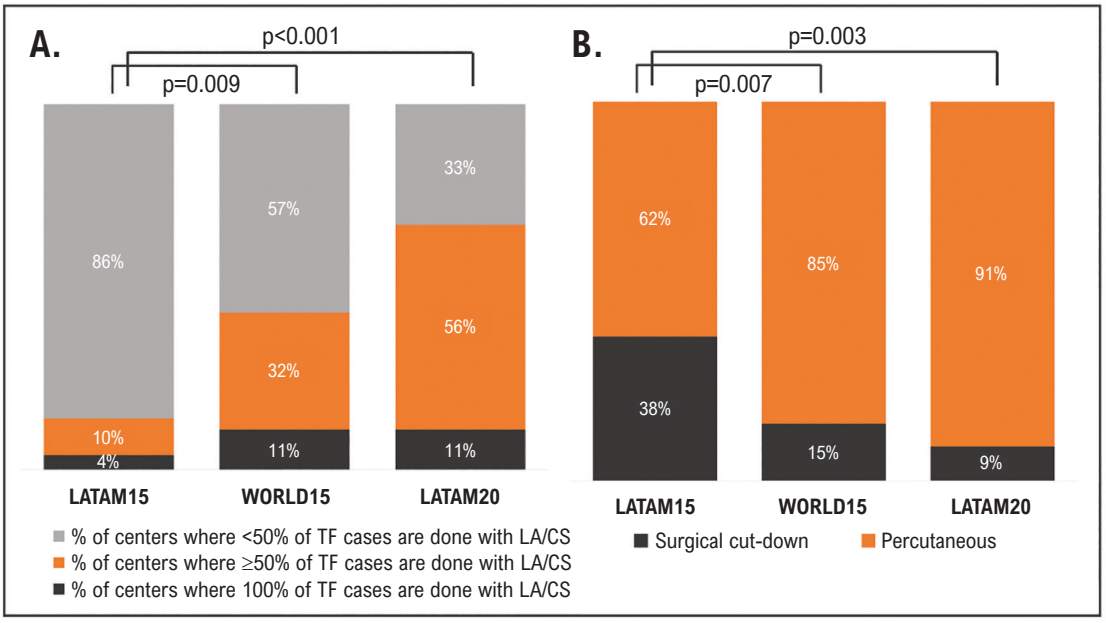
The comparison of answers to procedural management questions is summarized in Table 1. Transfemoral TAVR was the preferred approach by all centers, but a higher proportion of LATAM15 over WORLD15 centers performed ≥ 90% of their cases via the transfemoral route (72% vs. 42%, respectively, p=0.003). No significant change was noted after 5 years (LATAM20 87%, p=0.14). Almost all centers reported having an anesthesiologist to assist in transfemoral procedures, but LATAM15 centers more commonly performed these procedures under general anesthesia compared to WORLD15 and LATAM20 centers (Figure 5). Additionally, 86% of LATAM15 centers reported having a cardiac surgeon assisting transfemoral TAVR vs. 61% for WORLD15 (p=0.01) and 52% for LATAM20 (p=0.005). Meanwhile, interventional cardiologists regularly assisted transapical/transaortic procedures in most LATAM15 (88%) and WORLD15 (88%) centers, with a significant reduction after 5 years in LATAM20 centers (56%, p=0.008). Regarding procedural transesophageal echocardiography guidance, 83% of LATAM15 centers reported always relying on it, compared to 41% for WORLD15 and 15% for LATAM20 centers (Table 1).

In transfemoral cases, TAVR with a fully percutaneous approach was more frequently performed by the WORLD15

Table 1 – Comparison of technical procedural management between the LATAM15, WORLD15, and LATAM20 centers

	LATAM15 (N=29)	WORLD15 (N=221)	p value	LATAM20 (N=46)	p value#
Site where TAVR is routinely performed (% centers)					
Operating room	3%	9%	0.48	0	0.38
Cath lab	83%	63%	0.04	83%	1.0
Hybrid room	24%	45%	0.04	19%	0.77
TEE during TAVR (% of centers)					
Always	83%	41%	<0.001	15%	<0.001
Only in certain patients	10%	42%		63%	
Never	7%	17%		22%	
Type of closure device routinely used in transfemoral percutaneous access (% centers)					
1 Perclose	0	1%	0.03	9%	0.17
2 or more Perclose	90%	59%		83%	
Prostar	10%	40%		2%	
Protection guidewire from contralateral artery in femoral percutaneous cases (% of centers)					
Always	33%	35%	0.06	32%	1.0
Never	4.8%	25.2%		4%	
Only in challenging iliofemoral access	62%	40%		61%	
Peripheral balloon during access closure in percutaneous cases (% centers)					
Routinely	10%	12.9%	1.0	4%	0.6
Just in case of complication	90%	87.1%		96%	
In case of femoral perforation in percutaneous cases (% centers)					
Usually implant self-expandable or balloon-expandable covered stent	70%	78%	0.99	78%	0.54
Usually assisted by vascular surgeons or an interventional radiologist	30%	22%		22%	
Embolic protection device as a routine (% centers)	0	16%	0.02	0	1.0

Notes: # P-values for the LATAM20 in comparison to the LATAM15 results. TAVR: transcatheter aortic valve replacement; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.



Source: Bernardi, 2022.

Figure 5 – *A) Percentages of transfemoral procedures performed with conscious sedation/local anesthesia (% of centers). TF: transfemoral; LA: local anesthesia; CS: conscious sedation. B) Type of vascular access routinely performed for transfemoral cases (% of centers).*

and LATAM20 centers (Figure 5). For these, the Perclose (Abbott Vascular, Abbott Park, IL) was the most utilized device in all groups (Table 1). When asked about protective strategies in percutaneous transfemoral access, the most common approach by all groups was to leave a protection guidewire from the collateral artery only in challenging iliofemoral access and use of a peripheral balloon during access closure only when a complication ensues. In the case of femoral perforation, the most common approach consisted of using self- or balloon-expandable covered stent by the operator himself (Table 1).

The Corevalve system (Medtronic, Minneapolis, MN) and Edwards valves (Edwards Lifesciences, Irvine, CA) were reported as being regularly used by most centers from all three groups. Nonetheless, in 2015 a higher proportion of Latin-American centers implanted a self-expanding valve in > 50% of their patients compared to the other centers in the world without a significant change after 5 years in Latin-American centers. Of note, in 2015, only the Corevalve and Sapien XT transcatheter heart valves were commercially available in Latin America for these families of valves. In contrast, for LATAM20, most centers used the Evolut R and the Sapien 3 systems. The WORLD15 centers more routinely employed predilatation valvuloplasty than LATAM15 and LATAM20 centers (Table 2). Neither LATAM15 nor LATAM20 centers reported using embolic protection devices as a routine as compared to 16% of the WORLD15 centers (Table 1).

Postprocedural management and follow-up

The main findings on postprocedural care are shown in Table 3. Maintenance of telemetry after TAVR varied widely among institutions, with no difference between LATAM15 and WORLD15 centers (72% vs. 59%, during 48 hours), although a significant reduction in the period of surveillance was observed in LATAM20 centers (72% of centers maintained telemetry for just 24 hours). When a self-expandable valve was implanted, LATAM15 centers tended to remove the temporary pacemaker wire (TPW) later than WORLD15 and LATAM20 centers, whereas no difference was seen with balloon-expandable valves. The preferred initial management of transient atrioventricular block by all groups was to keep the TPW and watch, regardless of the type of valve. Centers also agreed on the management of a new left bundle branch block, most opting to keep telemetry or TPW for a longer period while waiting for any other indication of permanent pacemaker implantation (Supplemental Table 5).

Concerning the antithrombotic therapy at discharge, when no indication for anticoagulation existed, DAPT with aspirin and clopidogrel was the strategy of choice for most institutions. However, within the past 5 years, more Latin-American centers discharged their patients with a single antiplatelet agent (Figure 6). For the duration of DAPT, there was heterogeneity in practice, but ~90% of the centers suspended one of the agents within 6 months. In patients with an indication for anticoagulants, antithrombotic therapy varied considerably, being the association of an oral anticoagulant with only one antiplatelet agent the preferred choice by most centers from all groups. In these cases, the utilization of novel oral anticoagulants (NOACs) increased significantly from 4% to 28% in Latin-American centers during the 5-year period (Figure 6).

Table 2 – Comparison of the type of transcatheter heart valve implanted between groups

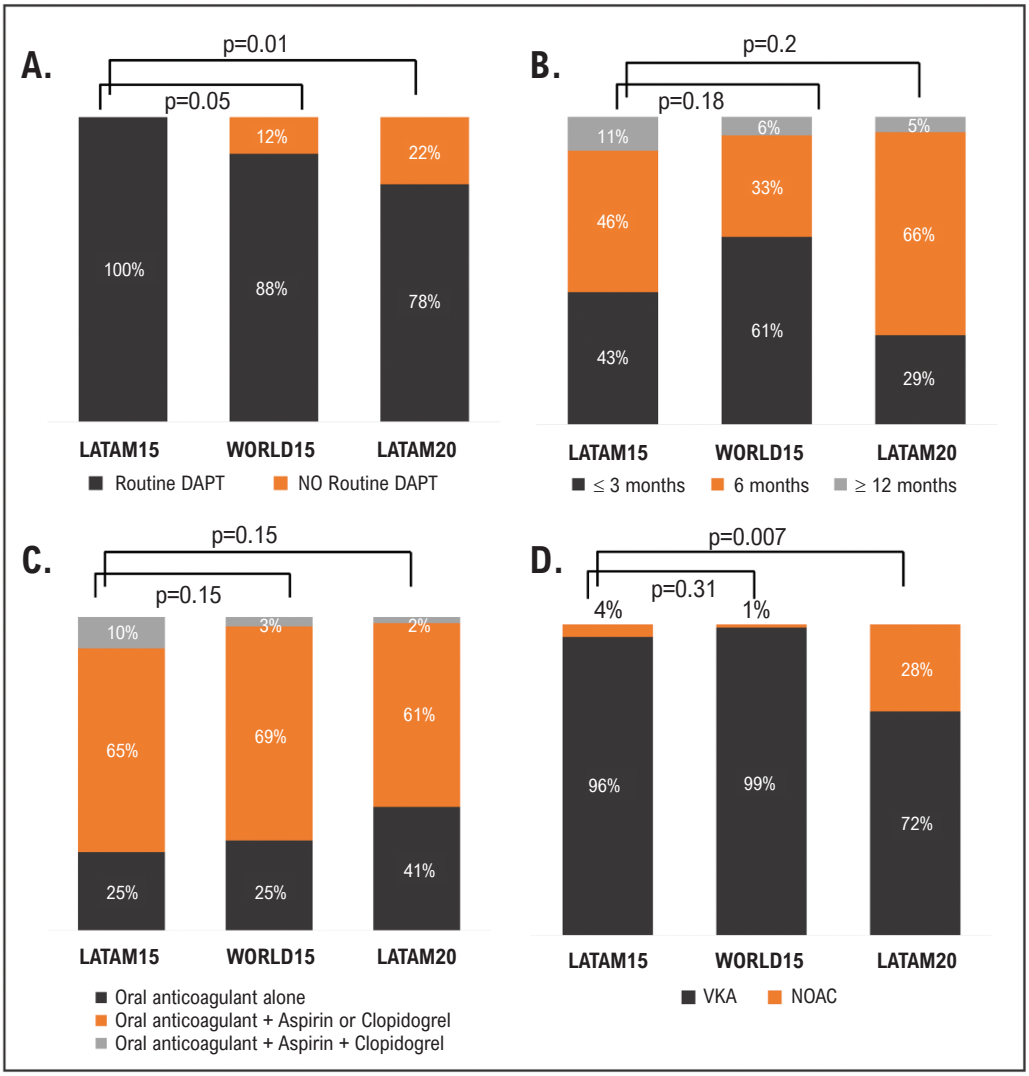
	LATAM15 (N=29)	WORLD15 (N=221)	p value	LATAM20 (N=46)	p value#
Type of THV routinely implanted (% centers)					
Corevalve system	86%	79%		91%	
Edwards valve	72%	84%		93%	
Acurate valve	10%	4%		41%	
Lotus valve	3%	26%		11%	
Portico valve	0	1%		0	
Centers where >50% of cases are done with self-expanding THV (% centers)	52%	33%	0.06	46%	0.64
Routine balloon predilatation valvuloplasty (% centers)					
For self-expanding valves	44%	50%	0.68	47%	0.81
For balloon-expandable valves	52%	68%	0.13	37%	0.23
In no case	30%	14%	0.04	44%	0.32

Notes: # P-values for the LATAM20 in comparison to the LATAM15 results. THV: transcatheter heart valve.

Table 3 – Comparison of answers regarding postprocedural care between LATAM15, WORLD15, and LATAM20 centers

	LATAM15 (N=29)	WORLD15 (N=221)	p value	LATAM20 (N=46)	p value#
Maintenance of telemetry after TAVR (% center)					
24h	36%	20%		72%	
48h	36%	39%	0.13	24%	0.002
>48h	28%	41%		4%	
Maintenance of TPW after self-expanding THV (if no AV block or new conduction disorder)					
Always remove at the end of procedure	0	11%		24%	
At least 12-24h	30%	40%	0.004	59%	<0.001
At least 48h	59%	27%		4%	
No standardized protocol	11%	22%		13%	
Maintenance of TPW after balloon-expandable THV (if no AV block or new conduction disorder)					
Always remove at the end of procedure	71%	46%		70%	
At least 12-24h	10%	24%	0.08	15%	0.17
At least 48h	10%	6%		0	
No standardized protocol	10%	24%		15%	
Management of transient AV block in self-expanding THV (% centers)					
Direct permanent pacemaker implantation	4%	13%		7%	
TPW and watch	81%	66%	0.31	63%	0.26
Depends on existence of prior conduction disorders	11%	14%		28%	
Other	4%	6%		2%	
Management of transient AV-block in balloon-expandable THV (% centers)					
Direct permanent pacemaker implantation	4.5%	7%		4%	
TPW and watch	87%	66%	0.06	63%	0.04
Depends on existence of prior conduction disorders	0	17%		26%	
Other	9%	10%		2%	

Notes: # P-values for the LATAM20 in comparison to the LATAM15 results. TAVR: transcatheter aortic valve replacement; THV: transcatheter heart valve; AV-block: atrioventricular block; TPW: temporary pacing wire.



Source: Bernardi, 2022.

Figure 6 – *Antithrombotic therapy after TAVR. A) Routine DAPT after TAVR when no other indication for anticoagulation exists (% of centers). DAPT: dual-antiplatelet therapy; B) Routine duration of DAPT (% of centers); C) Routine antithrombotic therapy in cases where there is an indication for anticoagulation (% of centers); D. Type of oral anticoagulant utilized when an indication for anticoagulation exists (% of centers). VKA: vitamin K antagonist; NOAC: novel oral anticoagulant.*

Discussion

In the present study, the current TAVR practices in Latin-American centers and their changes between 2015 and 2020 were evaluated, having for comparison the practice status at centers from developed countries in 2015. The main findings can be summarized as: 1) overall, Latin-American centers had a much lower cumulative experience and annual volume in comparison to centers from the rest of the world; 2) there has been an increase in the proportion of low and intermediate surgical risk patients now being treated with TAVR in Latin America; 3) the adoption of minimalistic TAVR approaches has increased in Latin-American centers from 2015 to 2020, a trend already observed in centers around the world in 2015; 4) postprocedural care varied considerably among institutions, but some significant changes in the TAVR practice have been observed in Latin-American centers over the studied period, such as a reduction in the time of telemetry and TPW after the procedure, less frequent administration of DAPT, and more frequent use of NOACs when anticoagulation was clinically recommended.

Center volume

Recent studies have highlighted the importance of center volume and experience as indicators in TAVR, linking them

to improved outcomes and better practices.[8–11] In the present study, we observed that the volume of procedures in Latin-American centers is still much lower than that in developed countries. Even in 2020, the median number of procedures performed in Latin-American institutions corresponded to a third of the volume performed in centers around the world 5 years earlier. Our data corroborate an estimate from 2017 on the geographical dispersion of TAVR across the world, showing that Latin-American countries implant less than 10 valves per 1 000 000 inhabitants, while the numbers for nations, such as the United States, France, and Germany, were above 100 implants per 1 000 000 people.[12] When considering the proportion of centers per elderly inhabitants, this discrepancy is even more evident. Currently, Latin America has an estimate of 200 active TAVR centers for an elderly population of ~56 million (3.6 centers/million) vs. 698 centers in the United States (according to the National Cardiovascular Data Registry[13]) for ~52 million elderly (13.4 centers/million).[14] Economic factors are most probably one of the most significant in explaining this disparity.

Over the past decades, despite economic growth and improvement in social indicators, wealth inequality is still a major issue in Latin America, directly impacting population well-being and health systems.[15] Developing countries often lag behind wealthier nations in implementing high-cost technological medical procedures in their health systems, which is the case of TAVR and cardiovascular surgery in general.[16] With demographic changes in Latin America towards population aging, the demand for TAVR is expected to rise accordingly. For the health systems to afford such demand, governments and local leaders will need to find ways to improve the cost-effectiveness of TAVR in the continent. Implementation of policies targeting a reduction in procedural costs will be key, primarily by lowering device prices that today represent on average ~70% of the procedure's total cost. This could be achieved by subsidizing or reducing importation taxes, stimulating more medical industries to come to Latin America, and creating incentives for manufacturing the high-cost prosthesis locally, which has been the case of Brazil recently. On the effectiveness side, the present study signals to a reduction in the disparities between Latin-American countries and the current TAVR practices compared to the rest of the world. In addition, data from the Brazilian TAVR registry from 2016 showed similar clinical outcomes as compared with the literature, even though more contemporary data is lacking.[17] This development in practice can be attributed mainly to a strong support of the local medical societies and industries, promoting scientific and hands-on training sessions, along with strong proctoring programs in Latin America over the recent years.

Periprocedural management

In addition to a volume-outcomes relationship, a volume-practice relationship exists, as centers with a higher number of TAVR change their routine practice over time. Recent analysis from the North American Transcatheter Valve Therapy (TVT) Registry on the TAVR learning curve demonstrates that, as an institution's cumulative experience progresses, TAVR procedures are more likely to be performed with conscious sedation, local anesthesia, and fully percutaneous vascular access. The so-called minimalistic approach.[8,11] Although there is no definitive data in the literature showing that these less invasive techniques are directly associated with improvements in hard clinical outcomes,[18–21] they surely represent incremental expertise of the heart teams.

The present study captured this phenomenon. In 2015, a higher proportion of centers around the world had already adopted the routine use of the minimalistic TAVR when compared to their Latin-American counterparts. But interestingly, after 5 years, even though Latin-American centers continue to have low volumes overall, with a median of only 16 cases yearly, there has been consistent incorporation of these more current techniques. The proportion of centers that performed more than half of cases with local anesthesia and conscious sedation increased ~6-fold. A similar trend has been observed in the TVT Registry during the latest years, where a steady increase in conscious sedation procedures has been reported, currently accounting for 64% of the North American cases.[22] Similarly, a fully percutaneous approach as a routine practice increased from 62% to 91% of the Latin-American centers, showing that TAVR practices are evolving in the continent despite the struggle to improve procedural volume.

Postprocedural management and follow-up

Proper postprocedural care is another fundamental, but sometimes overlooked, factor in a TAVR program. Of note, most clinical trials to date have aimed to assess intraprocedural aspects of TAVR. Consequently, there is a scarcity of definitive data on the best management of patients after the procedure. Not surprisingly, the present study showed heterogeneity in practice among centers in this domain. Yet, some significant changes in practice have been noted in Latin-American centers in the last 5 years. The routine prescription of DAPT on hospital discharge was less frequent and NOACs were more often used in patients with an indication for oral anticoagulation therapy. These changes in practice are probably attributed to data published between the two surveys showing a potential benefit of single oral antiplatelet therapy in reducing bleeding complications[23] and to a more widespread use of NOACs in general cardiology due to safety profile in elderly patients. Still, the optimal antithrombotic regimen and the utilization of NOACs after TAVR remain open to debate, particularly after the dismal results from a recent large randomized trial with rivaroxaban.[24] Hence, data from future randomized trials are warranted to define the optimal postprocedural care.

Finally, the progression of Latin-American practices reveals that even centers from developing and underserved countries can follow along with the rapid ongoing progressions in the field. This has been catalyzed thanks to a deep engagement of the medical societies in spreading the knowledge in Latin America. For instance, in Brazil, a formal TAVR certification has been adopted since 2017. Through multi-faceted and multilevel educational programs, the country has already trained more than 700 cardiologists. Likewise, similar initiatives in other countries, such as Argentina, Chile, Colombia, and Mexico, have also been adopted. All these efforts have contributed to a steady increase in new centers performing TAVR in Latin America and have played a significant role in the development of the most modern

techniques and adherence to them. However, continous efforts should be implemented for diminishing the gap to developed nations. As the number of TAVR centers increases, expansion of proctoring and continuing medical education programs will be necessary. In the post-COVID-19 era, innovations, like teleproctoring, can be an invaluable asset. The creation of virtual simulation programs to soften the learning curve of lower volume centers/operators seems another attractive emerging option.[25] Finally, improving publication of scientific content by Latin-American centers is urgently warranted, accompanied by the creation of nationwide databanks in all Latin-American countries to determine the actual clinical outcomes and further define the potential gaps for improvement.

Limitations

Although this study was a unique opportunity to capture variations in practice among centers and regions of the world, as well as the changes in Latin-American centers over the past 5 years, some limitations must be mentioned. First, this was a self-reported voluntary survey, which, by its nature, makes it prone to biases. Results from such studies can under- or overestimate the actual reality of the participating centers. Reports on the differences in the baseline characteristics of the patients treated by each center, which could influence the adoption of different practices, were not available. Moreover, the study did not include information on clinical outcomes. Thus, it is impossible to draw conclusions on whether the differences in practice impacted patients' outcomes. In addition, there is big heterogeneity among Latin-American countries, regions, and institutions. It is difficult to assume that one survey can precisely represent the whole continent's reality, even though we estimate ~15% of Latin-American centers participated in the latest inquiry. Nevertheless, the results give us a notion of which direction we are moving to and the gaps that still need to be filled, in addition to serving as a guide for the less experienced centers in defining their protocols. Finally, since the WRITTEN survey was not reconducted in the rest of the world during 2019-2020, a direct comparison of the current TAVR practice in Latin America with other centers through the survey's responses was not possible.

Conclusion

In conclusion, differences in TAVR practice exist between the Latin America and other developed nations of the world, with an at least 5-year delay in the widespread adoption of some techniques in Latin America. Some of these differences in practice seem to be linked to a lower procedural volume in Latin-American centers, while others could be merely associated with a lack of global consensus and regional variability. Nevertheless, the gap appears to be diminishing since this volume-practice relationship has softened in the latest years due to practice development and the adoption of more refined techniques even by lower volume centers in Latin America. Future studies in the continent are warranted to evaluate the impact of such changes in practice on patients' clinical outcomes.

Author Contributions

Conception and design of the research: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Nazif T, Rodes-Cabau J; Acquisition of data: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Maluenda G, Nazif T, Lemos PA, Sztejfman M, Lamelas P, Echeverri D, Brito Jr. FS, Mangione JA, Søndergaard L, Rodes-Cabau J; Analysis and interpretation of the data: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E; Statistical analysis, Obtaining financing and Writing of the manuscript: Bernardi FLM, Ribeiro HB; Critical revision of the manuscript for intellectual content: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Maluenda G, Nazif T, Lemos Neto PA, Sztejfman M, Lamelas P, Echeverri D, Lopes MACQ, Brito Jr. FS, Abizaid AA, Mangione JA, Eltchaninoff H, Søndergaard L, Rodes-Cabau J.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Fernando Luiz de Melo Bernardi, from Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo.

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. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med. 2010;363(17):1597-607. doi: 10.1056/NEJMoa1008232.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med. 2011;364(23):2187-98. doi: 10.1056/NEJMoa1103510.
3. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017;376(14):1321-31. doi: 10.1056/NEJMoa1700456.
4. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705. doi: 10.1056/NEJMoa1814052.

5. Brito FS Jr, Carvalho LA, Sarmento-Leite R, Mangione JA, Lemos P, Siciliano A, et al. Outcomes and Predictors of Mortality After Transcatheter Aortic Valve Implantation: Results of the Brazilian Registry. Catheter Cardiovasc Interv. 2015;85(5):153-62. doi: 10.1002/ccd.25778.

6. Dager AE, Nuis RJ, Caicedo B, Fonseca JA, Arana C, Cruz L, et al. Colombian Experience with Transcatheter Aortic Valve Implantation of Medtronic CoreValve. Tex Heart Inst J. 2012;39(3):351-8.

7. Cerrato E, Nombela-Franco L, Nazif TM, Eltchaninoff H, Søndergaard L, Ribeiro HB, et al. Evaluation of Current Practices in Transcatheter Aortic Valve Implantation: The WRITTEN (WoRldwIde TAVI ExperieNce) Survey. Int J Cardiol. 2017;228:640-7. doi: 10.1016/j.ijcard.2016.11.104.

8. Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F, et al. Procedural Experience for Transcatheter Aortic Valve Replacement and Relation to Outcomes: The STS/ACC TVT Registry. J Am Coll Cardiol. 2017;70(1):29-41. doi: 10.1016/j.jacc.2017.04.056.

9. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, et al. Procedural Volume and Outcomes for Transcatheter Aortic-Valve Replacement. N Engl J Med. 2019;380(26):2541-50. doi: 10.1056/NEJMsa1901109.

10. Wassef AWA, Rodes-Cabau J, Liu Y, Webb JG, Barbanti M, Muñoz-García AJ, et al. JACC Cardiovasc Interv. 2018;11(17):1669-79. doi: 10.1016/j.jcin.2018.06.044.

11. Russo MJ, McCabe JM, Thourani VH, Guerrero M, Genereux P, Nguyen T, et al. Case Volume and Outcomes After TAVR with Balloon-Expandable Prostheses: Insights from TVT Registry. J Am Coll Cardiol. 2019;73(4):427-40. doi: 10.1016/j.jacc.2018.11.031.

12. Pilgrim T, Windecker S. Expansion of Transcatheter Aortic Valve Implantation: New Indications and Socio-Economic Considerations. Eur Heart J. 2018;39(28):2643-5. doi: 10.1093/eurheartj/ehy228.

13. National Cardiovascular Data Registry. Washington: American College of Cardiology. 2020 [cited 2020 Apr 3]. Available from: https://www.ncdr.com/WebNCDR/tvt/publicpage.

14. United Nations. Department of Economic and Social Affairs. World population ageing 2019: Highlights. v. 40, New York: Department of Economic and Social Affairs; 2019. p.40-1307.

15. United Nations. Inequality Matters: Report on the World Social Situation. New York: Department of Economic and Social Affairs; 2013.

16. Reichert HA, Rath TE. Cardiac Surgery in Developing Countries. J Extra Corpor Technol. 2017;49(2):98-106.

17. Bernardi FL, Ribeiro HB, Carvalho LA, Sarmento-Leite R, Mangione JA, Lemos PA, et al. Direct Transcatheter Heart Valve Implantation Versus Implantation with Balloon Predilatation: Insights from the Brazilian Transcatheter Aortic Valve Replacement Registry. Circ Cardiovasc Interv. 2016;9(8):e003605. doi: 10.1161/CIRCINTERVENTIONS.116.003605.

18. Holper EM, Kim RJ, Mack M, Brown D, Brinkman W, Herbert M, et al. Randomized Trial of Surgical Cutdown Versus Percutaneous Access in Transfemoral TAVR. Catheter Cardiovasc Interv. 2014;83(3):457-64. doi: 10.1002/ccd.25002.

19. Mayr NP, Michel J, Bleiziffer S, Tassani P, Martin K. Sedation or General Anesthesia for Transcatheter Aortic Valve Implantation (TAVI). J Thorac Dis. 2015;7(9):1518-26. doi: 10.3978/j.issn.2072-1439.2015.08.21.

20. Husser O, Fujita B, Hengstenberg C, Frerker C, Beckmann A, Möllmann H, et al. Conscious Sedation Versus General Anesthesia in Transcatheter Aortic Valve Replacement: The German Aortic Valve Registry. JACC Cardiovasc Interv. 2018;11(6):567-78. doi: 10.1016/j.jcin.2017.12.019.

21. Bernardi FL, Gomes WF, Brito FS Jr, Mangione JA, Sarmento-Leite R, Siqueira D, et al. Surgical Cutdown Versus Percutaneous Access in Transfemoral Transcatheter Aortic Valve Implantation: Insights from the Brazilian TAVI Registry. Catheter Cardiovasc Interv. 2015;86(3):501-5. doi: 10.1002/ccd.25820.

22. Butala NM, Chung M, Secemsky EA, Manandhar P, Marquis-Gravel G, Kosinski AS, et al. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement: Variation in Practice and Outcomes. JACC Cardiovasc Interv. 2020;13(11):1277-87. doi: 10.1016/j.jcin.2020.03.008.

23. Rodés-Cabau J, Masson JB, Welsh RC, Del Blanco BG, Pelletier M, Webb JG, et al. Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement with a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. JACC Cardiovasc Interv. 2017;10(13):1357-65. doi: 10.1016/j.jcin.2017.04.014.

24. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. N Engl J Med. 2020 Jan 9;382(2):120–9.

25. Aggarwal S, Choudhury E, Ladha S, Kapoor P, Kiran U. Simulation in cardiac catheterization laboratory: Need of the hour to improve the clinical skills. Ann Card Anaesth. 2016;19(3):521–6.

*Supplemental Materials

For additional information, please click here.

Transcatheter Aortic Valve Implant in Latin America – We will Get There!

Silvio Gioppato[1] and Rodrigo Modolo[2]

Departamento de Medicina Interna – Divisão de Cardiologia, Faculdade de Ciências Médicas. Universidade de Campinas – UNICAMP,[1] Campinas, SP – Brazil

Boston Scientific Corporation,[2] Maple Grove – USA

Short Editorial related to the article: Recent Developments and Current Status of Transcatheter Aortic Valve Replacement Practice in Latin America – the WRITTEN LATAM Study

As with percutaneous coronary intervention, the Transcatheter Aortic Valve Implantation (TAVI) is making great strides toward overcoming the surgical approach and becoming the predominant procedure in treating aortic stenosis. Since the first percutaneous implantation made by Dr. Alain Cribier, who turns 2 decades old this year, TAVI has demonstrated, study after study, robust evidence of its efficacy and safety.[1] At each stage of this journey, the challenges were successively overcome both by the improvement of the devices and the skills acquired by the operators, which allowed us to move consistently from the prohibitive surgical risk scenario to the low-risk scenario in just over 15 years.[2-7] Furthermore, evolution is unfolding[8-10] – ongoing studies investigate the expansion of TAVI for young patient populations, bicuspid aortic valve, asymptomatic and even pure aortic regurgitation.

Today the million-dollar question is about the durability of devices that, in part, starts to be answered. In 2019, Thyregod et al.[11] published the 5-year result of the NOTION study (The Nordic Aortic Valve Intervention Trial), showing no differences in either the primary composite endpoint of death from any cause, stroke or heart attack (TAVR 38% vs. SAVR 36%; p=0.86) as in individual events. More recently, at the American College of Cardiology Congress (ACC 2022), Michael Reardon presented the 5-year results combining the CoreValve US Pivotal and SURTAVI studies showing that in intermediate- or high-risk patients, the rate of valve structural deterioration was significantly lower in the TAVI group compared to the surgical group (2.57% x 4.38%; p=0.0095). Nevertheless, these data are still insufficient to answer whether TAVI will be the Gold Standard for treating aortic valve diseases, regardless of etiology, age or type of dysfunction.

Another important aspect is the financing of technology. Whenever a technological advance appears with safety and efficacy proven by clinical studies, there is a clash between evidence and the cost of technology, generating a debate that ends up consuming time between the consolidation of evidence and the incorporation of technology into health systems around the world. However, this struggle is even longer in developing countries, creating a paradox in which technology is present in medical practice but inaccessible to most of the population for years. Such a mismatch establishes a gap between the realities of developed and developing countries in terms of procedure volume, number of trained centers, operators' expertise, and the availability of different devices.

With an eye on the subject, in this edition of *Arquivos Brasileiros de Cardiologia*, Bernardini et al.[12] sought as a primary objective to compare the TAVI practice between Latin American centers and the rest of the world, based on data from the WRITTEN 2015 survey that covered 250 centers worldwide, being 29 in Latin America, represented here as LATAM 15, and 221 in other countries and continents (WORLD 15). The research consisted of a questionnaire composed of 59 questions covering different TAVI domains sent to several centers worldwide whose decision to participate was spontaneous and voluntary. As a secondary objective, the authors also sought to assess the evolution of TAVI practice in Latin America (LA) after 5 years through a new round of the questionnaire on the continent in 2020 (LATAM 20).

The results are not surprising when compared to the rest of the world, noting that in LA, the cumulative experience and the annual volume of procedures were much lower (median 34 vs. 200; p<0.001), reflecting the gap between developed and developing countries. However, there is a positive side observed in this study, which shows an approximation of the practices of the LATAM 20 centers with the WORLD 15 centers. It is worth mentioning the nearly 2-fold increase in procedure volume comparing the 5-year period between 2015 and 2020 in LA – event though not statistically significant – (median 62 vs 34 procedures; p=0.08); the significant increase in the proportion of patients with intermediate and low surgical risk (15.2% vs 21.2% and 2.2% vs 6.4%, respectively for LATAM 15 and 20, p=0,04) and the significant increase in the number of centers performing transfemoral procedures with conscious sedation/local anesthesia (LATAM 15 4% x LATAM 20 11%; P<0.001). The approximation of practices also appears in the peri- and post-procedure and follow-up procedures, which in the LATAM 20 centers are in step with those observed in the WORLD 15 centers.

The fact that the findings are backed by retrospective information, provided through optional and non-compulsory questionnaires, weakens the extrapolation

Keywords

Aortic Valve Stenosis; Aortic Valve/abnormalities; Transcatheter Aortic Valve Replacement/methods; Percutaneous Coronary Intervention/methods

Mailing Address: Rodrigo Modolo •
Boston Sicentific Corporation – 1 Scimed Place, Maple Grove, MN 55311 – Minnesota, USA.
E-mail: modolo.rodrigo@gmail.com

DOI: https://doi.org/10.36660/abc.20220325

of interpretations. However, they do not weaken the view that the mismatch between LA and the rest of the world exists and needs to be addressed by public health authorities in these countries. The authors also reinforce the importance of continuing education work developed by medical societies in partnership with industry for the consistent growth and improvement of the technique in our LA countries

Conflict of interest

Dr. Modolo is employeed full-time by Boston Scientific Corporation, the manufacturer of the Acurate valve systems.

References

1. Cribier A. Commemorating the 15-year anniversary of TAVI: insights into the early stages of development, from concept to human application, and perspectives. EuroIntervention. 2017;13(1):29-37. doi: 10.4244/EIJV13I1A3.
2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370(19):1790-8. doi: 10.1056/NEJMoa1400590.
3. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607. doi: 10.1056/NEJMoa1008232.
4. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705. doi: 10.1056/NEJMoa1814052
5. Melo P, Modolo R. The Role of Inflammation in Post-TAVI Outcomes. Arq Bras Cardiol 2021;117(5):1028-9. doi: 10.36660/abc.20210809.
6. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380(18):1706-15. doi: 10.1056/NEJMoa1816885.
7. Soeiro AM, Cardozo FA, Guimaraes PO, Pereira MP, Souza PVR, Boros GAB, et al. Patient in Cardiorespiratory Arrest - Is it Possible to Perform Transcatheter Aortic Valve Implantation (TAVI) in this Scenario? Arq Bras Cardiol 2021;117(2):404-6. doi: 10.36660/abc.20201097.
8. Bourantas CV, Modolo R, Baumbach A, Sondergaard L, Prendergast BD, Ozkor M, et al. The evolution of device technology in transcatheter aortic valve implantation. EuroIntervention. 2019;14(18):e1826-e1833. doi: 10.4244/EIJ-D-18-01048.
9. Serruys PW, Kawashima H, Chang CC, Modolo R, Wang R, de Winter RJ, et al. Chronic haemodynamic performance of a biorestorative transcatheter heart valve in an ovine model. EuroIntervention. 2021;17(12):e1009-e1018. doi: 10.4244/EIJ-D-21-00386.
10. Modolo R, Chang CC, Abdelghani M, Kawashima H, Ono M, Tateishi H, et al. Quantitative Assessment of Acute Regurgitation Following TAVR: A Multicenter Pooled Analysis of 2,258 Valves. JACC Cardiovasc Interv 2020;13(11):1303-11. doi: 10.1016/j.jcin.2020.03.002.
11. Thyregod HGH, Ihlemann N, Jorgensen TH, Nissen H, Kjeldsen BJ, Petursson P, et al. Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients. Circulation. 2019 Feb 1. doi: 10.1161/CIRCULATIONAHA.118.036606.
12. Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Maluenda G, Nazif T, et al. Evolução e Estado Atual das Práticas de Implante Transcateter de Válvula Aórtica na América Latina – estudo WRITTEN LATAM. Arq Bras Cardiol. 2022; 118(6):1085-1096.

The Volume-Time Curve by Three-Dimensional Echocardiography in Chagas Cardiomyopathy: Insights into the Mechanism of Hemodynamic Adaptations

AAirandes de Sousa Pinto,[1,2] Maria Carmo Pereira Nunes,[3] Carlos Alberto Rodrigues,[2] Bráulio Muzzi Ribeiro de Oliveira,[4] João da Rocha Medrado Neto,[1] Timothy C. Tan,[5] Manoel Otavio da Costa Rocha[3]

Programa de Pós-Graduação em Ciências da Saúde e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais,[1] Belo Horizonte, MG – Brazil

Universidade Estadual de Feira de Santana,[2] Feira de Santana, BA – Brazil

Universidade Federal de Minas Gerais,[3] Belo Horizonte, MG – Brazil

Instituto de Previdência dos Servidores do Estado de Minas Gerais – IPSEMG,[4] Belo Horizonte, MG – Brazil

University of Western Sydney – Department of Cardiology,[5] Penrith South, New South Wales – Australia

Abstract

Background: Three-dimensional echocardiography (3D ECHO) allows the generation of a volume-time curve representative of changes in the left ventricular (LV) volume throughout the entire cardiac cycle.

Objective: This study aims to demonstrate the hemodynamic adaptations present in Chagas cardiomyopathy (CC) by means of the volume and flow measurements obtained by the volume-time curve by 3D ECHO.

Methods: Twenty patients with CC and 15 healthy subjects were prospectively enrolled in a cross-sectional design study. 3D ECHO was performed in all subjects and the volume over time curves of the LV was generated. The flow was obtained by the first derivative of the volume-time curve using the software MATLAB. Statistical significance was set at $p<0.05$.

Results: Although CC patients had lower LV ejection fraction compared to the control group (29.8±7.5 vs. 57.7±6.1, $p<0.001$), stroke volume (61.5±25.2 vs. 53.8±21.0, $p=0.364$) and maximum ejection flow during systole (-360.3±147.5 vs. -305.6±126.0, $p=0.231$) were similar between the groups. Likewise, the maximum flow in the early diastolic filling phase and during atrial contraction was similar between groups. An increase in preload expressed by LV end diastolic volume (204.8±79.4 vs. 93.0±32.6), $p<0.001$) may maintain the flow and stroke volumes similar to the controls.

Conclusion: Using a non-invasive tool, we demonstrated that an increase in LV end-diastolic volume may be the main adaptation mechanism that maintains the flow and stroke volumes in the setting of severe LV systolic dysfunction.

Keywords: Echocardiography, Three Dimensional Echocardiogram; Atrial Fibrillation; Stroke Volume; Chagas Cardiomyopathy; Frank-Starling Law.

Introduction

Current two-dimensional (2D) echocardiography methods for the assessment of left ventricular (LV) volume are limited by observer variability, and geometric assumptions.[1] The advent of three-dimensional echocardiography (3D ECHO) allowed ventricular volumes assessed without using any geometric assumptions, allowing the generation of a volume-time curve representative of changes in LV volume throughout the entire cardiac cycle, thus much less subject to observer variability due to the semiautomated detection of LV edges.[2] However, currently 3D ECHO has been used for morphological evaluation of cardiac structures, but hemodynamic evaluation is still performed using 2D echocardiographic variables, including dimension and velocity in the continuity equation. Although single plane measurements of LV size are routinely used to evaluate cardiac chamber enlargement, 3D volume measurements best represent overall chamber dilatation.[1] In addition, measurements of instantaneous flow within a cardiac chamber can be obtained using data from the first derivative of volume curves.

This non-invasive approach for characterization of cardiac chamber dilatation has not been studied in patients with Chagas cardiomyopathy. Therefore, this study aims to demonstrate the hemodynamic adaptations present in Chagas cardiomyopathy using the measures of volume and flow obtained by volume-time curve using 3D echocardiography.

Mailing Address: Maria do Carmo P. Nunes •
Departamento de Medicina Interna - Faculdade de Medicina da Universidade Federal de Minas Gerais – Av. Professor Alfredo Balena, 190. Postal Code 30130-100, Santa Efigênia, Belo Horizonte, MG – Brazil
E-mail: mcarmo@waymail.com.br
Manuscript received December 09, 2020, revised manuscript July 05, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20201308

Methods

A total of 44 patients presenting Chagas cardiomyopathy were initially recruited for the study. Patients with arterial hypertension, atrial fibrillation, valvular heart disease, congenital heart disease, pericardiomyopathy, and those who had pacemakers were excluded. Based on these exclusion criteria, 24 patients were excluded and 20 patients were included in the study (study flowchart, Figure 1). The individuals in the control group had no clinical history of cardiovascular disease. Clinical and echocardiographic examinations were normal.

Chagas cardiomyopathy was defined as the presence of LV ejection fraction smaller than or equal to 54% and LV end-diastolic diameter greater than 56 mm.

The echocardiographic study was performed by a single examiner, using a IE 33-Philips echocardiograph according to the protocol of the American Society of Echocardiography.[3] Three-dimensional echocardiography was performed in all subjects using a X3-1 transducer. The volume-time curves of the left ventricle were generated by proprietary software Qlab (Figure 2, A). These curves yielded left ventricular end-diastolic volume, left ventricular end-systolic volume and stroke volume. The volume curve was generated at intervals of around 3 ms. The software MATLAB version R2017a generated a polynomial adjusted to the left ventricular volume curve (Figure 2, B). The correlation between the volume curves generated by Qlab and the polynomial obtained by Mathlab presented $r \geq 0.99$ in all patients.

The flow values during cardiac cycle (Figure 2, C) were obtained by the first derivative of the representative polynomial of the volume curve.

For our analysis, we used the maximum flow during systole, early filling and atrial contraction (Figure 2, C). In addition, we calculated the maximum flow systole divided by left ventricular end-diastolic volume (QS/LVEDV) (Figure 2, D).

Statistical analysis

This study was designed to achieve 95% power to detect a 50% reduction in the ratio between peak instantaneous systolic flow (QS) and LV end-diastolic volume in patients with Chagas cardiomyopathy compared to the control group based on the values obtained by Marshall et al. (n1=12, n2=10, mean x1=3.4 sec^{-1} and x2=1.22 sec^{-1}).[4] Therefore, considering an alpha error of 0.05 and a patient:control ratio of 1, a sample of 3 patients and 3 controls was obtained. For the calculations, the G Power software version 3.1 was used.

Chi-square test was used to compare the categorical variables between the groups. The continuous variables with normal distribution were expressed as mean±standard deviation or as median or interquartile range if they presented

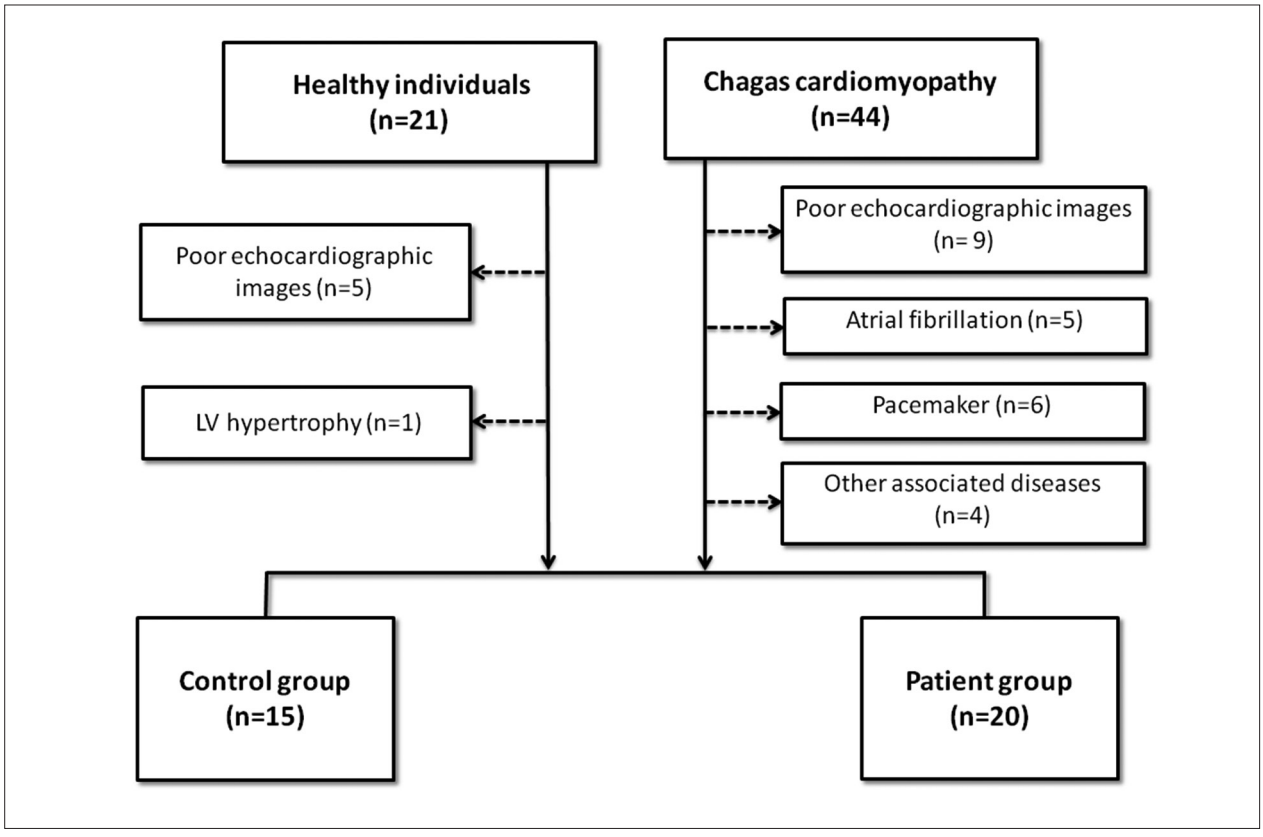


Figure 1 – *Study population flow chart.*

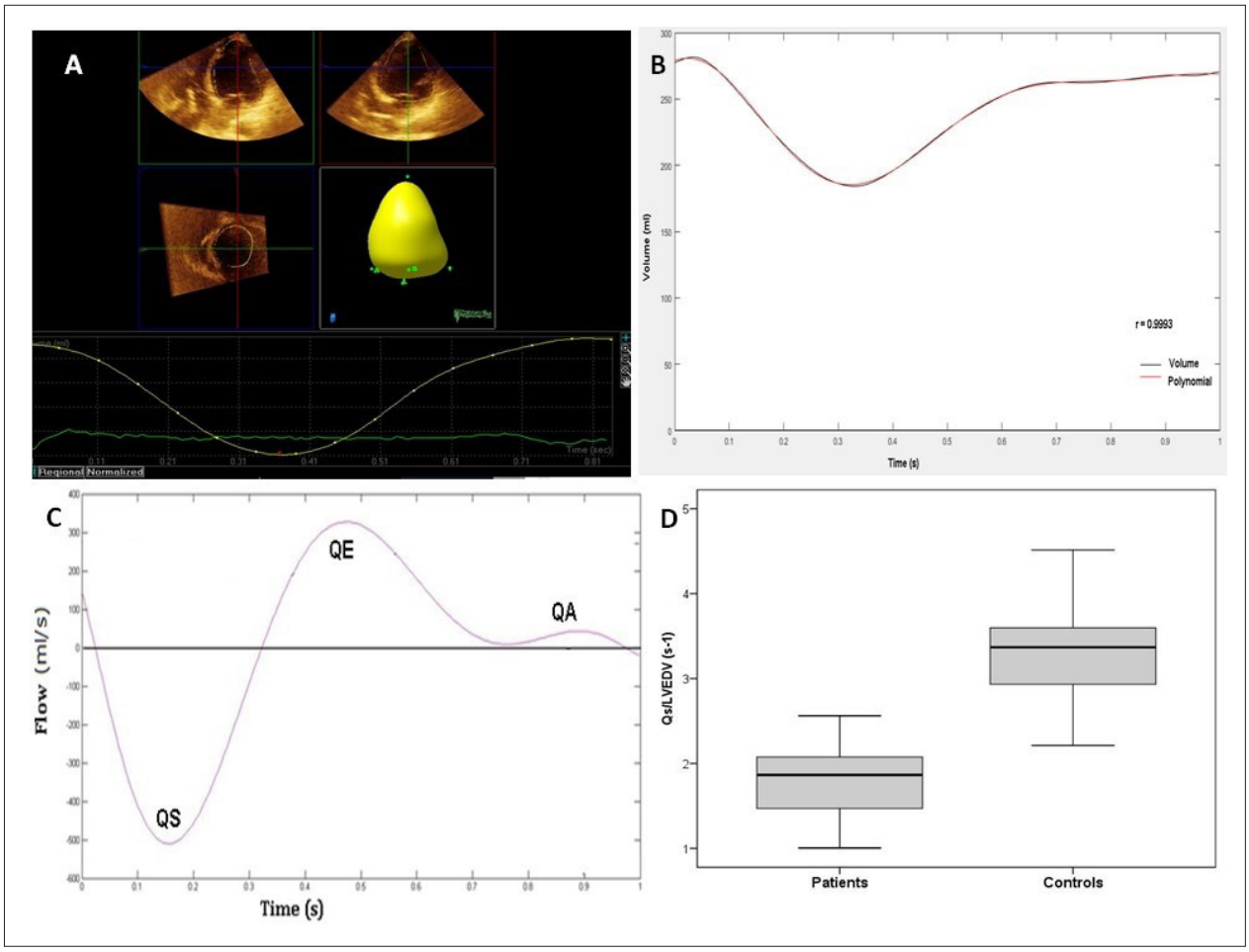


Figure 2 – *A) Left ventricular volume curve generated by Qlab software in a patient with Chagas cardiomyopathy. B) Representation of the left ventricular volume curve, in black, generated by the Qlab Software and the interval of the polynomial generated by the MATLAB software, in red. C) Flow curve obtained in a patient with Chagas cardiomyopathy during the cardiac cycle. Negative values occur during systole and positive values during diastole. QS= Absolute maximum systolic flow, QE= peak flow during early left ventricular filling. QA = peak flow during atrial contraction. D) Boxplot of the absolute value of the QS/LV end-diastolic volume according to the study group.*

a non-normal distribution. We used the Shapiro-Wilk test to assess the normality of the variables.

Unpaired Student's t test was used to compare continuous variables with normal distribution, and the Mann-Whitney test was used to compare variables with non-normal distribution between the groups.

The correlations were performed using the Pearson method. Statistical significance was set at $p<0.05$. All analyzes were performed using the software SPSS version 15.0 (SPSS, Inc., Chicago, IL).

This study was approved by the Research Ethics Committee of Universidade Federal de Minas Gerais (CAAE:48354315.8.3001.5091) and written informed consent was obtained from all patients.

Results

Twenty patients with CC, mean age 45±12, 55% males, were compared with 15 sex- and age-matched healthy controls. There was no sex difference between patients and controls. The echocardiographic characteristics of the study population are shown in Table 1. The majority the patients (70%) had exertional dyspnea, on treatment for heart failure, mainly using angiotensin-converting enzyme inhibitors and beta-blockers (Table 2).

Heart rate (beats per minute) was similar between the Chagas cardiomyopathy and the control group — 62.4±10.2 vs. 66.1± 11.0, $p=0.3$, respectively.

The patients with CC had greater LV end-diastolic and end-systolic volumes, and lower LV ejection fraction, compared to the control group. However, stroke volume and maximum ejection flow during systole (QS) were similar between the groups. There was a strong correlation between QS and stroke volume: $r=0.91$, $p<0.001$.

The CC group had a lower QS/LV end-diastolic volume ratio compared with the controls (Figure 2, D). The QS/LV end-diastolic volume ratio presented a strong correlation with the ejection fraction: $r=0.89$, $p<0.001$.

Doppler evaluation of mitral velocity did not show any difference in E, A, E/A ratio and E wave deceleration time. As expected, the patients with CC showed an increase in preload compared with the control group, as demonstrated by an increased LV end-diastolic volume and E/e' ratio.

The maximum flow in the early and passive filling phase (QE) and during atrial contraction (QA) was similar between patients and controls.

Discussion

In our study, we evaluated the hemodynamic adaptations of the LV in CC using volume and flow curves by 3D echocardiography compared to a control group. Although the patients with CC had severe LV systolic function with ejection fraction of 30%, the stroke volumes were similar to controls. This discrepancy may be explained by the adaptive mechanisms that occur in chronic LV systolic dysfunction.[5,6] The ventricle with low ejection fraction but with increased end-diastolic volume ejects the same amount of blood as a ventricle with normal end-diastolic volume and ejection fraction.[7] This is due to preservation of the Frank-Starling mechanism in CC at rest, which is in agreement with the findings of Holubasch et al.[5]

Three-dimensional echocardiography allows non-invasive preload measurement with high accuracy. End-diastolic LV volume is the best representation of preload, which expresses the degree of myocardial stretch before contraction. Limitations in evaluating accurately ventricular volume by standard echocardiographic methods lead to used ventricular filling pressures as a surrogate measurement of preload. However, the relationship between filling pressures and ventricular volume is not linear, depending on the compliance of left-sided cardiac chamber.[8]

The volume-time curve by 3D echocardiography also provides information for calculating flow at any stage of the cardiac cycle. In our study, the flow was obtained by polynomial interpolation. Polynomial interpolation is an accurate low-complexity method that allows to measure the variation of any derivable curve. We recently used this tool to conduct a Covid-19 growth rate analysis.[9,10]

Maximal ejection flow (QS) was similar between the groups, which did not reflect left ventricular systolic function. The strong correlation between absolute QS and stroke volume suggests that the same mechanism that normalized the Stroke volume competed for the normalization of QS. Therefore, QS/LV end-diastolic volume withdraws the effect of left ventricular dilatation, which is increased preload, and derive a variable that allows assessing LV global systolic function. Indeed, in our study, absolute QS/LV end-diastolic volume was lower in those patients who had CC than in normal controls, which is in agreement with the findings of other authors.[4,11,12]

This artifice is the same used to calculate ejection fraction. By dividing the systolic volume (SV) by end-diastolic left ventricular volume, the result is more than a percentage of the final left ventricular volume that is ejected. The ratio represents the normalization of stroke volume by the representative of preload: LV end volume. Since preload is one of the determinants of systolic function, this may explain the prognostic importance of ejection fraction in cardiomyopathies.

Table 1 – Echocardiographic characteristics of the study population

Variable *	Chagas cardiomyopathy (n=20)	Controls (n=15)	p value
LV end-diastolic diameter (mm)	68.4±9.2	46.6±4.2	<0.001
LV end-systolic diameter (mm)	56.1±10.8	30.1±3.7	<0.001
LV end-diastolic volume (mL)	204.8±79.4	93.0±32.6	<0.001
LV end-systolic volume (mL)	143.3±60.8	39.2±13.6	<0.001
Stroke volume (mL)	61.5±25.2	53.8±21.0	0.364
3D LV ejection fraction (%)	29.8±7.5	57.7±6.1	<0.001
QS (mL/s)	- 360.3±147.5	-305.6±126.0	0.231
QS/LV end-diastolic volume (s-1)	1.80±0.40	3.28±0.64	<0.001
QE (mL/s)	270.4±135.3	201.9±61.5	0.104
QA (mL/s)	134.4±88.1	109.1±37.8	0.623
QE/QA	2.2±1.3	1.8±0.5	0.382
Mitral peak E velocity (m/s)	81.0±30.2	81.9±19.5	0.921
Deceleration time (ms)	166.5 (79)	190.0 (38)	0.290
Mitral peak A velocity (m/s)	51.2±24.5	55.4±15.6	0.583
Mitral E/A ratio	1.9±1.1	1.6±0.6	0.404
E/e' ratio	15.2±9.3	7.6±1.7	0.002

Data are expressed as mean±standard deviation, or median (interquartile range). LV: left ventricular; QS:peak instantaneous systolic flow; QE: peak flow during early left ventricular filling; QA: peak flow during atrial contraction.

Table 2 – Medications used by the 20 patients with chronic dilated Chagas cardiomyopathy

Medications	Number of patients (%)
Diuretics	19 (95)
Spironolactone	5 (25)
Angiotensin-converting enzyme inhibitors	16 (80)
Angiotensin receptor antagonists	3 (15)
Digoxin	13 (65)
Amiodarone	6 (30)
Anticoagulant therapy	8 (40)
Beta-blockers	17 (85)
Aspirin	1 (5)

Similarly, Hammersmeister et al.[11] validated a method for assessing LV volume and flow in 1974, in several cardiovascular diseases, by cardiac catheterization.[11] Ventricular volume was calculated by ventriculography at a frequency of 60 frames/s, using the area-length method. The flow was obtained by the first derivative of the polynomial that approached the volume curve. However, this method is limited due to its invasive nature. On the other hand, in our study, we obtained the LV volume curve during the cardiac cycle with a frequency three times greater than a similar method described by Hammermeister et al.[11] In addition, we found a strong correlation between the polynomial and LV volume curve, allowing the calculation of flow with great accuracy.

The absence of difference between diastolic flow values between groups was also observed by Hammermeister et al.[13] The "U" behavior of these variables considering diastolic function worsening explains these results, as observed by Ohno et al.[6] in an experimental study.[6] Despite this, the E/e'ratio was higher in the group with CC than in the control group, which is in agreement with Oliveira et al.,[14] who observed that this variable was an independent predictor for elevated brain natriuretic peptide (BNP) levels in CC.[14]

Three-dimensional echocardiography allows to revisit experimental studies from the beginning of the last century, when the Frank-Starling mechanism was described and the mechanical factors related to stroke volume, recognized at that time as a measure of cardiac function, were studied.[15]

This study had the following limitations: left ventricular diastolic function was not classified, but the parameters to assess diastolic function were taken. The normal values for QS/LV end-diastolic volume was based on the controls, which may not be the reference values. Finally, the clinical importance and prognostic implications of these findings are not fully known yet. However, our objective was to demonstrate the hemodynamic adaptations present in Chagas cardiomyopathy using the measures of volume and flow obtained by the volume-time curve.

Conclusions

Our study shows that instantaneous systolic flow and stroke volume were similar between patients with severe ventricular dysfunction due to CC and healthy controls. Using a non-invasive tool for the first time in CC, we demonstrated that an increase in LV end-diastolic volume, which is a measure of ventricular preload, is the main adaptation mechanism that maintains the flow and stroke volumes in the setting of severe systolic dysfunction. QS/LV end-diastolic volume, in this study, was shown to be representative of left ventricular global systolic function, whose usefulness and prognostic value should be studied in later studies.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content Pinto AS, Nunes MC, Rodrigues C, Oliveira BM, Medrado Neto JR, Tan TC, Rocha MOC; Acquisition of data: Pinto AS, Nunes MC; Analysis and interpretation of the data: Pinto AS, Nunes MC, Rodrigues C, Oliveira BM, Medrado Neto JR, Rocha MOC; Statistical analysis: Pinto AS, Nunes MC, Medrado Neto JR; Obtaining financing: Nunes MC, Rocha MOC; Writing of the manuscript: Pinto AS, Nunes MC, Rodrigues C.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by FAPEMIG and CNPq.

Study Association

This article is part of the thesis of Doctoral submitted by Airandes de Sousa Pinto, from Programa de Pós-Graduação em Ciências da Saúde e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais.

References

1. Mehrotra R, Alagesan R, Srivastava S. Quantitative assessment of left ventricular systolic function using 3-dimensional echocardiography. Indian Heart J. 2013;65(5):620–8. DOI: 10.1016/j.ihj.2013.08.027
2. Velasco O, Beckett MQ, James AW, Loehr MN, Lewis TG, Hassan T, et al. Real-Time Three-Dimensional Echocardiography: Characterization of Cardiac Anatomy and Function—Current Clinical Applications and Literature Review Update. BioRes Open Access. 2017;6(1):15–8. doi: 10.1089/biores.2016.0033.
3. 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. Eur Heart J Cardiovasc Imaging. 2015;16(3):233–71. doi: 10.1093/ehjci/jev014.
4. Marshall RC, Berger HJ, Costin JC, Freedman GS, Wolberg J, Cohen LS, et al. Assessment of cardiac performance with quantitative radionuclide angiocardiography: sequential left ventricular ejection fraction, normalized left ventricular ejection rate, and regional wall motion. Circulation. 1977;56(5):820 -9. doi: 10.1161/01.cir.56.5.820.
5. Holubarsch C, Ruf T, Goldstein DJ, Ashton RC, Nickl W, Pieske B, et al. Existence of the Frank-Starling Mechanism in the Failing Human Heart: Investigations on the Organ, Tissue, and Sarcomere Levels. Circulation. 1996;94(4):683–9. doi: 10.1161/01.cir.94.4.683.
6. Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation. 1994;89(5):2241–50. DOI: 10.1161/01.cir.89.5.2241
7. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J. 2012;33(14):1787–847. DOI: 10.1161/01.cir.89.5.2241
8. Bers,DM, Borlaug,BA. Mechanisms of Cardiac Contraction and Relaxation. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Eleventh Eleventh Edition. Philadelphia: Elsevier; 2019.
9. Pinto AS, Santos EG, Rodrigues CA, Nunes PC, Cruz LA, Costa MG, Rocha MOC. Covid-19 growth rate analysis: application of a low-complexity tool for understanding and comparing epidemic curves. Rev Soc Bras Med Trop . 2020 Jan 1;53.
10. Pinto AS, Rodrigues CA, Sobrinho CL, Cruz LA, Santos EG, Nunes PC, et al. Covid-19 epidemic curve in Brazil: A sum of multiple epidemics, whose inequality and population density in the states are correlated with growth rate and daily acceleration. An ecological Study. Rev Soc Bras Med Trop. 2022 vol 55. https:// doi.org/10.1590/0037-8682-0118-2021
11. Hammermeister KE, Brooks RC, Warbasse JR. The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and disease. Circulation. 1974;49(4):729–38. DOI: 10.1161/01.cir.49.4.729
12. Magorien DJ, Shaffer P, Bush C, Magorien RD, Kolibash AJ, Unverferth DV, et al. Hemodynamic correlates for timing intervals, ejection rate and filling rate derived from the radionuclide angiographic volume curve. Am J Cardiol. 1984;53(4):567–71. DOI: 10.1161/01.cir.49.4.729
13. Hammermeister KE, Warbasse JR. The rate of change of left ventricular volume in man. II. Diastolic events in health and disease. Circulation. 1974;49(4):729-38. doi: 10.1161/01.cir.49.4.729.
14. Oliveira BMR, Botoni FA, Ribeiro ALP, Pinto AS, Reis AM, Nunes MCP, et al. Correlation between BNP levels and Doppler echocardiographic parameters of left ventricle filling pressure in patients with Chagasic cardiomyopathy. Echocardiogr Mt Kisco N. 2009;26(5):521–7. doi: 10.1111/j.1540-8175.2008.00842.x.
15. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. J Physiol. 1914;48(5):357–79. doi: 10.1113/jphysiol.1914.sp001669.

Is it Possible to Non-Invasively Study the Hemodynamic Adaptations of Chagas Cardiomyopathy by the Volume-Time Curve Using 3D Echocardiography?

José Luiz Barros Pena[1,2]

Faculdade Ciências Médicas de Minas Gerais,[1] *Belo Horizonte, MG – Brazil*

Hospital Felício Rocho,[2] *Belo Horizonte, MG – Brazil*

Short Editorial related to the article: The Volume-Time Curve by Three-Dimensional Echocardiography in Chagas Cardiomyopathy: Insights into the Mechanism of Hemodynamic Adaptations

Three-dimensional echocardiography (3DE) represents a great innovation in cardiovascular ultrasound.[1] Increased computer processing power and advances in the development of transducers have allowed acquiring of cardiac structures from any spatial point of view, without assumptions about their shape. Recent studies have demonstrated that when cardiac chamber sizes are quantified using 3DE, their volumes are similar to those obtained using cardiac magnetic resonance imaging compared to two-dimensional echocardiography (2DE).[2,3] The usefulness of 3DE has particularly been demonstrated primarily in realistic anatomical heart valve images and in guiding and monitoring cardiac procedures.[4]

3DE allows volume calculation of the left ventricle (LV) throughout the cardiac cycle, making it possible to construct a volume-time curve. This method is more accurate than 2DE because the left ventricular volume is constructed by analyzing hundreds of points at the edge of the endocardium. No specific plane or geometric model is necessary to describe the complex LV structure. In this paper, Pinto et al.[5] tested the hypothesis of studying the hemodynamic adaptations of non-invasive Chagas cardiomyopathy using the volume-time curve generated by 3DE.[5] They generated a polynomial adjusted to the LV volume curve using specific software. Their objective was to present a cross-sectional study evaluating LV function, comparing volume curves in 20 patients with Chagas cardiomyopathy (CC) and 15 gender- and age-matched healthy controls.

The CC patients presented greater LV end-diastolic and end-systolic volumes and lowered LV ejection fraction than the control group. However, the stroke volume and maximum ejection flow during systole, QS, were similar between groups. A strong correlation existed between flow and stroke volumes, Rs=0.91, $p<0.001$.

The CC group presented a lower QS / LV end-diastolic volume ratio than the control. The QS/LV end-diastolic volume ratio presented a strong correlation with ejection fraction, Rs=0.89, $p<0.001$.

Keywords

Echocardiography,Three-Dimensional/methods; Heart Failure; Chagas Caddiomyopathy; Stroke Volume; Blood Pressure.

Mailing Address: José Luiz Barros Pena •
Faculdade Ciências Médicas de Minas Gerais – Pós-Graduação – Alameda Ezequiel Dias, 275. Postal Code 30130-110, Belo Horizonte, MG – Brazil
E-mail: jlbpena@cardiol.br

DOI: https://doi.org/10.36660/abc.20220284

The maximum flow in the early and passive filling phases, QE, and during atrial contraction, QA, was similar between patients and controls.

Although the CC patients had severe LV systolic dysfunction with a 30% ejection fraction, the stroke volumes were similar to controls.[5]

Any LV with a low ejection fraction but increased end-diastolic volume ejects the same amount of blood as a LV with normal end-diastolic volume and ejection fraction. This difference occurs due to the preservation of the Frank-Starling mechanism in CC patients at rest.[6]

According to the mechanism, the greater the ventricular diastolic volume, the more the myocardial fibers are stretched during diastole. Within a normal physiologic range, the more the myocardial fibers are stretched, the greater the tension in the muscle fibers and the greater the ventricular contraction force when stimulated.[6]

Holubarsch et al.[7] found that the Frank-Starling mechanism is maintained in the end-stage of failing human hearts, whereas significant alterations of diastolic myocardial distensibility are evident in chronic heart failure.[7]

Three-dimensional echocardiography can accurately measure a non-invasive preload, and the volume-time curve can calculate flow at any stage of the cardiac cycle.[8,9]

Hammermeister et al.[10] invasively validated this measure in 1974. Peak LV systolic ejection rate (S dV/dt) was calculated from a single plane, and cineangiographically measured LV volumes in 113 adult patients and related to other measures of cardiovascular function. Mean S dV/dt for the group of 29 normal patients was not significantly different in patients with coronary artery disease, aortic stenosis, mitral stenosis, or cardiomyopathy. S dV/dt correlated poorly with the ejection fraction and LV end-diastolic pressure.[10]

This study shows that instantaneous systolic flow and stroke volume were similar between patients with severe ventricular dysfunction due to CC and healthy controls. The great merit of the methodology is the first usage of a non-invasive tool in CC.

They demonstrated and confirmed that an increase in LV end-diastolic volume in CC patients is the main adaptation mechanism maintaining flow and stroke volumes in severe systolic dysfunction.

This study showed the QS/LV end-diastolic volume to represent LV global systolic function. Further studies are recommended to confirm the usefulness and prognostic value of these findings in improving the clinical management of CC patients.

References

1. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, Faletra FF, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging.2012;13(1):1-46. doi: 10.1093/ehjci/jer316.
2. Ruddox V, Mathisen M, Bækkevar M, Aune E, Edvardsen T, Otterstad JE. Is 3D echocardiography superior to 2D echocardiography in general practice? A systematic review of studies published between 2007 and 2012. Int J Cardiol.2013;168(2):1306-15. doi: 10.1016/j.ijcard.2012.12.002.
3. Saraiva RM, Scolin EMB, Pacheco NP, Bouret ME, Mediano MFF, Holanda MT, Costa ARD. 3-Dimensional Echocardiography and 2-D Strain Analysis of Left Ventricular, Left Atrial and Right Ventricular Function in Healthy Brazilian Volunteers. Arq Bras Cardiol. 2019 Nov;113(5):935-45. doi: 10.5935/abc.20190155.
4. Velasco O, Beckett MQ, James AW, Loehr MN, Lewis TG, Hassan T, Janardhanan R. Real-Time Three-Dimensional Echocardiography: Characterization of Cardiac Anatomy and Function-Current Clinical Applications and Literature Rev Update. Biores Open Access. 2017;06(1):15-8. doi: 10.1089/biores.2016.0033.
5. Pinto AS, Nunes MC, Rodrigues C, Oliveira BM, Medrado Neto JR, Tan TC, et al. The volume-time curve by three-dimensional Echocardiography in Chagas cardiomyopathy: insights into the mechanism of hemodynamic adaptations. Arq Bras Cardiol. 2022; 118(6):1099-1105.
6. Delicce AV, Makaryus AN. Physiology, Frank Starling Law. 2022 Feb 10. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 29262149.
7. Holubarsch C, Ruf T, Goldstein DJ, Ashton RC, Nickl W, Pieske B, et al. Existence of the Frank-Starling Mechanism in the Failing Human Heart: Investigations on the Organ, Tissue, and Sarcomere Levels. Circulation. 1996;94(4):683–9. doi: 10.1161/01.cir.94.4.683.
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. J Am Soc Echocardiogr. 2015;28(1): 1-39e14. doi: 10.1016/j.echo.2014.10.003.
9. Thavendiranathan P, Rankin K. 3-Dimensional Echocardiography: Moving from Pretty Pictures Toward Patient Outcomes. JACC Cardiovasc Imaging. 2019;12(10):1927-9. doi: 10.1016/j.jcmg.2018.06.020.
10. Hammermeister KE, Brooks RC, Warbasse JR. The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and disease. Circulation. 1974;49(4):729–38. DOI: 10.1161/01.cir.49.4.729.

Albumin-Bilirubin Score to Predict Outcomes in Patients with Idiopathic Dilated Cardiomyopathy

Mei Jiang,[1,2] Xue-biao Wei,[3]* Jie-leng Huang,[2] Ze-da-zhong Su,[2] Ying-wen Lin,[2] Dan-qing Yu[1,2]*

The Second School of Clinical Medicine, Southern Medical University,[1] Guangzhou, Guangdong – China

Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences,[2] Guangzhou, Guangdong – China

Department of Geriatric Intensive Medicine, Guangdong Provincial Geriatrics Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences,[3] Guangzhou, Guangdong – China

**The authors contributed equally to this article*

Abstract

Background: **Liver dysfunction is a postulated variable for poor prognosis in dilated cardiomyopathy (DCM).**

Objective: **This study aimed to investigate the prognostic value of the albumin-bilirubin (ALBI) score, a relatively new model for evaluating liver function, in patients with idiopathic DCM.**

Methods: **A total of 1025 patients with idiopathic DCM were retrospectively included and divided into three groups based on ALBI scores: grade 1 (≤ −2.60, n = 113), grade 2 (−2.60 to −1.39, n = 835), and grade 3 (> −1.39, n = 77). The association of ALBI score with in-hospital major adverse clinical events (MACEs) and long-term mortality was analyzed. P-value less than 0.05 was considered statistically significant.**

Results: **The in-hospital MACEs rate was significantly higher in the grade 3 patients (2.7% versus 7.1% versus 24.7%, p < 0.001). Multivariate analysis showed that ALBI score was an independent predictor for in-hospital MACEs (adjusted odds ratio = 2.80, 95%CI: 1.63 – 4.80, p < 0.001). After a median 27-month follow-up, 146 (14.2%) patients died. The Kaplan–Meier curve indicated that the cumulative rate of long-term survival was significantly lower in patients with higher ALBI grade (log-rank = 45.50, p < 0.001). ALBI score was independently associated with long-term mortality (adjusted hazard ratio = 2.84, 95%CI: 1.95 – 4.13, p < 0.001).**

Conclusion: **ALBI score as a simple risk model could be considered a risk-stratifying tool for patients with idiopathic DCM.**

Keywords: **Dilated Cardiomyopathy; Heart Failure; Prognosis.**

Introduction

Dilated cardiomyopathy (DCM), one of the leading causes of heart failure, is characterized by ventricular dilation and systolic dysfunction.[1] About 50% of the cases have an unknown cause, which is termed as idiopathic DCM.[2] Epidemiological data have indicated that the one-year mortality of DCM is 25% to 30%, which continuously increased at 5 years.[3] Therefore, continued risk assessment is essential to identify patients at high risk of death and establish optimal treatment strategies to improve prognosis.

Liver injury is common in patients with heart failure owing to impaired perfusion and systemic congestion due to hemodynamic changes.[4] Hepatic dysfunction has been identified as one of the risk factors for poor outcomes in patients with DCM.[5] The albumin-bilirubin (ALBI) score is a simple and objective method to assess liver function. In previous studies, ALBI score has been widely used in patients with liver diseases, including hepatocellular carcinoma, liver cirrhosis, and liver failure.[6-8] In addition, Matsue et al indicated that the ALBI score is associated with fluid overload and the prognosis of patients with acute heart failure.[9] However, it is yet unclear whether this score can be considered a risk-stratifying tool in patients with idiopathic DCM. Hence, this study was conducted to investigate the association of the ALBI score and adverse outcomes in idiopathic DCM.

Methods

Study design and patients

This was a retrospective cohort study conducted at Guangdong Provincial People's Hospital. Patients

Mailing Address: Dan-qing Yu •
Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital,Guangdong Academy of Medical Sciences, Guangzhou 510080 – China
E-mail: gdydq100@126.com
Manuscript received January 21, 2021, revised manuscript July 29, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210035

diagnosed with idiopathic DCM were consecutively enrolled between January 2010 and November 2015. The diagnosis of DCM was in agreement with the statement of the European Society of Cardiology working group on myocardial and pericardial diseases.[10] The exclusion criteria were as follows: 1) age < 18 years; 2) presence of malignant tumor; 3) pregnancy; 4) autoimmune disease; 5) previous cardiac synchronization therapy or heart transplantation; and 6) DCM with definite etiology such as hypertensive heart disease, coronary artery disease (> 50% obstructive lesion in one or more epicardial vessels), valvular heart disease, congenital heart disease, myocarditis triggers, alcoholic cardiomyopathy, peripartum cardiomyopathy, cardiomyopathy caused by endocrine disorder, noncompaction of the ventricular myocardium, and arrhythmia-induced cardiomyopathy. Furthermore, we also excluded patients without admission serum albumin or bilirubin records. A total of 1025 idiopathic DCM patients were enrolled. The present study was approved by the ethics committee of Guangdong Provincial People's Hospital, with a waiver of informed consent.

Examination and data collection

Venous blood samples were collected for measurement of albumin and bilirubin concentrations in the morning after an overnight stay. Serum albumin and bilirubin levels were detected on an automated biochemical analyzer (Beckman Coulter AU5821 or AU5831; Beckman Coulter Inc, CA, USA). Transthoracic echocardiography was routinely performed within 24 hours of admission. Left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and other echocardiogram indices were measured according to the recommendations of the American Society of Echocardiography.[11]

Clinical variables were collected from the electronic case report form by one researcher and randomly checked by another. Estimated glomerular filtration rate (eGFR, expressed in mL/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[12] The ALBI score was calculated using the following formula: $0.66 \times \log_{10}$ bilirubin-$0.085 \times$albumin.[6]

Follow-up and outcomes

All in-hospital survival patients were followed up through telephone interviews. We also reviewed hospital readmission records and outpatient clinic interviews for possible events. The primary outcome was long-term mortality, and the secondary outcome was in-hospital major adverse clinical events (MACEs) such as death, stroke, dialysis, and acute heart failure during hospitalization.

Statistical analysis

Included patients were divided into three groups based on ALBI score: grade 1 (≤ −2.60, n = 113); grade 2 (−2.60 to −1.39, n = 835); and grade 3 (> −1.39, n = 77). The distribution of variables was assessed by the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean ± standard deviation, and non-normally distributed continuous variables are presented as median and interquartile range. Categorical variables are presented as numbers and percentage. Continuous variables were compared using one-way ANOVA when normally distributed or the Kruskal-Wallis H test when not normally distributed. The chi-square test was performed for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of ALBI score for predicting adverse events. Logistic regression and Cox survival analysis were used to assess the effect of ALBI score on in-hospital MACEs and long-term mortality, respectively. Significant variables in univariate analysis (except the elements of ALBI) were included into the multivariate analysis. In addition, Kaplan–Meier curves were drawn and compared using the log-rank test among groups. For all analyses, $p < 0.05$ was considered to indicate statistical significance. All analyses were conducted using SPSS software (version 16.0; SPSS Inc, Chicago, IL, USA).

Results

In all, 1025 patients were included in this analysis. Baseline characteristics among the groups are displayed in Table 1. Patients in the grade 3 group were more likely to be male. In addition, patients with higher ALBI grade had worse cardiac function; namely, the rate of patients with New York Heart Association (NYHA) functional class > II was higher. Positive trends were observed for serum creatinine, alanine transaminase (ALT), total bilirubin, and LAD in relation to increasing ALBI score. However, a negative trend was observed for hemoglobin and serum albumin in relation to increasing ALBI score. Diuretics (including furosemide and spironolactone) and digoxin were more frequently used in patients with higher ALBI grade.

During hospitalization, 15 patients (1.5%) died; 48 (4.7%) suffered from acute heart failure; 23 (2.2%) required renal dialysis, and 23 (2.2%) suffered a stroke. The in-hospital MACE rate was significantly higher in patients with grade 3 than in those with grades 1 and 2 (2.7% versus 7.1% versus 24.7%, $p < 0.001$, Table 1). In univariate logistic regression analysis, ALBI score, NYHA functional class > II, anemia, eGFR < 60 mL/min/1.73 m^2, lgALT($\log_{10}$ALT), total bilirubin, LAD, LVEDD, LVEF, and β-blocker usage were associated with in-hospital MACEs (Table 2). After adjusting for potential risk factors, ALBI score was an independent predictor of in-hospital MACEs (adjusted odds ratio = 2.80, 95% confidence interval [CI]: 1.63 – 4.80, $p < 0.001$, Table 2).

After a median 27 months of follow-up, 146 (14.2%) patients died. The Kaplan–Meier curve indicated that the cumulative rate of long-term survival rate was significantly lower in patients with higher ALBI grade (log-rank test = 45.50, $p < 0.001$, Figure 1). The univariate Cox proportional hazard model of long-term mortality is shown in Table 3. ALBI score was associated with increased risk of long-term death (unadjusted hazard ratio = 3.16, 95%

Table 1 – Baseline characteristics classified by tertile of ALBI grade

Clinical variables	Grade 1 (n=113)	Grade 2 (n=835)	Grade 3 (n=77)	p
Age (years)	52.8±12.5	55.9±13.6	52.7±16.2	0.018
Sex				
Male, n (%)	70(61.9)	609(72.9)	65(84.4)	0.003
Female, n (%)	43(38.1)	226(27.1)	12(15.6)	
Hypertension, n (%)	31(27.4)	221(26.5)	18(23.4)	0.809
Diabetes, n (%)	15(13.3)	148(17.7)	9(11.7)	0.228
Smokers, n (%)	29(25.7)	233(27.9)	20(26.0)	0.840
NYHA functional class>II	43(38.1)	445(53.3)	53(68.8)	<0.001
Hemoglobin (g/L)	143.3±17.0	139.4±18.4	134.0±24.6	0.004
Serum creatinine, (μmol/L)	85.0(69.3.102.5)	94.0(78.5.113.0)	113.5(90.0.152.0)	<0.001
Liver function tests				
ALT (U/L)	24.5(16.8.34.0)	29.0(19.0.48.0)	31.5(20.3.106.8)	0.001
Albumin (g/L)	41.9±2.2	34.8±3.5	25.9±3.3	<0.001
Total bilirubin, (μmol/L)	15.6(11.4.20.8)	21.6(15.1.31.2)	45.7(23.7.78.3)	<0.001
Echocardiography data				
LAD, (mm)	41.4±7.0	44.6±7.2	46.8±9.5	<0.001
LVEDD, (mm)	67.1±8.3	67.0±8.7	68.0±8.0	0.604
LVEF, (%)	30.1±7.5	29.2±7.7	27.5±8.7	0.075
Medicine during hospitalization				
ACEI/ARB	95(84.1)	708(84.8)	60(77.9)	0.286
Beta-blockers	90(79.6)	658(78.8)	54(70.1)	0.196
Lasix	90(79.6)	730(87.4)	72(93.5)	0.015
Aldactone	89(78.8)	741(88.7)	72(93.5)	0.003
Digoxin	48(42.5)	509(61.0)	65(84.4)	<0.001
In-hospital MACEs	3(2.7)	59(7.1)	19(24.7)	<0.001

ACEI: angiotensin-converting enzyme inhibitors; ALBI: albumin-bilirubin; ALT: alanine transaminase; ARB: angiotensin receptor blocker; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MACEs: major adverse cardiac events; NYHA: New York Heart Association.

CI: 2.31 – 4.33, p < 0.001). Other significant variables included age, NYHA functional class > II, anemia, eGFR < 60 mL/min/1.73 m^2, lgALT, hypoproteinemia, total bilirubin, LAD, LVEDD, LVEF, and β-blocker and digoxin use. These significant risk factors, except the components of ALBI score, were included in the multivariate Cox survival model, which revealed that ALBI score remained an independent predictor for long-term mortality (adjusted hazard ratio = 2.84, 95% CI: 1.95 – 4.13, p < 0.001, Table 4). In addition, the ALBI score was included in this model as a categorical variable rather than a continuous one. The result showed that, compared with ALBI grade 1, the adjusted hazard ratio was 5.69 (95% CI: 1.40 – 23.18, p = 0.015, Table 4) and 16.79 (95% CI: 3.91 – 72.04, p < 0.001, Table 4) for Grade 2 and 3, respectively.

ROC curve analysis indicated that the area under the curve of ALBI score, serum albumin, and total bilirubin for predicting long-term death were 0.684 (95% CI: 0.654 – 0.714, Figure 2), 0.662 (95% CI: 0.631 – 0.692, Figure 2) and 0.588 (95% CI: 0.556 – 0.619, Figure 2) respectively. ALBI score exhibited relatively superior predictive ability for long-term death than serum albumin (0.684 versus 0.662, p = 0.026, Figure 2) and total bilirubin (0.684 versus 0.588, p = 0.002, Figure 2).

Discussion

To our knowledge, this is the first study to evaluate the prognostic role of ALBI score in patients with idiopathic DCM. The results showed that ALBI score was an independent risk factor for in-hospital MACEs and long-term mortality. In addition, ALBI score exhibited better predictive ability for long-term death than serum albumin and total bilirubin. The ALBI score can be easily measured and would be useful in identifying idiopathic DCM patients who are at a high risk of poor outcomes.

Table 2 – Univariate and multivariable logistic regression analysis for in-hospital MACEs

Clinical variables	Univariate analysis		Multivariate analysis		
	OR	p	OR	95% CI	p
ALBI score	4.07	<0.001	2.80	1.63 – 4.80	<0.001
Age (years)	1.01	0.440			
Female sex	0.92	0.754			
Hypertension	0.85	0.540			
Diabetes	1.24	0.456			
Smokers	0.85	0.554			
NYHA functional class>II	1.88	0.010	1.20	0.70 – 2.05	0.506
Anemia	2.16	0.015	1.75	0.88 – 3.47	0.112
eGFR<60mL/min/1.73 m^2	2.42	<0.001	1.70	1.02 – 2.83	0.040
lgALT	2.73	<0.001	1.77	1.08 – 2.92	0.025
Hypoproteinemia	2.48	<0.001			
Total bilirubin	1.01	0.001			
LAD	1.03	0.049	1.01	0.97 – 1.04	0.680
LVEDD	1.04	0.004	1.03	1.00 – 1.06	0.085
LVEF	0.95	0.001	0.97	0.94 – 1.01	0.152
ACEI/ARB usage	0.74	0.312			
Beta-blocker usage	0.41	<0.001	0.47	0.28 – 0.79	0.004
Lasix usage	1.21	0.603			
Aldactone usage	0.97	0.921			
Digoxin usage	1.59	0.065			

ACEI: angiotensin-converting enzyme inhibitors; ALBI: albumin-bilirubin; ALT: alanine transaminase; ARB: angiotensin receptor blocker; CI: confidence interval; DB: direct bilirubin; eGFR: estimated glomerular filtration rate; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OR: odds ratio; TB: total bilirubin.

DCM is characterized by ventricular remodeling which can gradually develop into left heart failure and even global heart failure.[13,14] In addition, right ventricular dysfunction is prevalent in patients with DCM, [15] and it has been demonstrated to influence the course and prognosis of DCM.[16] Progression of right ventricular dysfunction can lead to systemic congestion, resulting in sinusoidal congestion and peri-sinusoidal edema, which impair delivery of oxygen and nutrients to hepatocytes.[17-19] In addition, decreased cardiac output and inadequate liver perfusion may trigger hypoxic injury. This injury of hepatocytes can manifest as decreased serum albumin and elevated bilirubin.

Albumin, which reflects the synthetic function of the liver, has multiple physiological roles, such as counterbalancing hydrostatic pressure, antioxidant and anti-inflammatory functions, and transporting molecules and drugs.[20] We found that hypoalbuminemia was related to adverse outcome in patients with idiopathic DCM. This could be explained by several theories. First, in addition to being a marker of liver injury, hypoalbuminemia is frequently associated with renal dysfunction.[20,21] Albumin is restricted by the normal glomerular barrier, and filtered albumin can be reabsorbed by proximal tubular cells.[22] However, increased protein urine discharge can be found in renal insufficiency, which results in hypoalbuminemia. Therefore, hypoalbuminemia might reflect the concurrent renal dysfunction and portend poor outcomes. Second, hypoalbuminemia results in lower serum osmotic pressure and can exacerbate pulmonary edema and pleural effusion, precipitating refractory heart failure in patients with DCM.[21] Third, serum albumin and prealbumin levels have been shown to reflect nutritional status.[23,24] Malnutrition at times may progress to cardiac cachexia, which is characterized by protein-calorie malnutrition with muscle wasting and peripheral edema, leading to poor quality of life and increased mortality.[24]

Similarly, in patients with advanced DCM, several metabolic processes of bilirubin in the liver, including uptake, conjugation, and secretion, are attenuated by hepatocellular hypoxia and congestion, leading to greater increase in serum total bilirubin. Although bilirubin has antioxidant and anti-inflammatory properties, extremely elevated bilirubin levels represent impaired hemodynamics caused by right ventricular dysfunction, which has an adverse prognostic effect on patients with DCM.[16] In

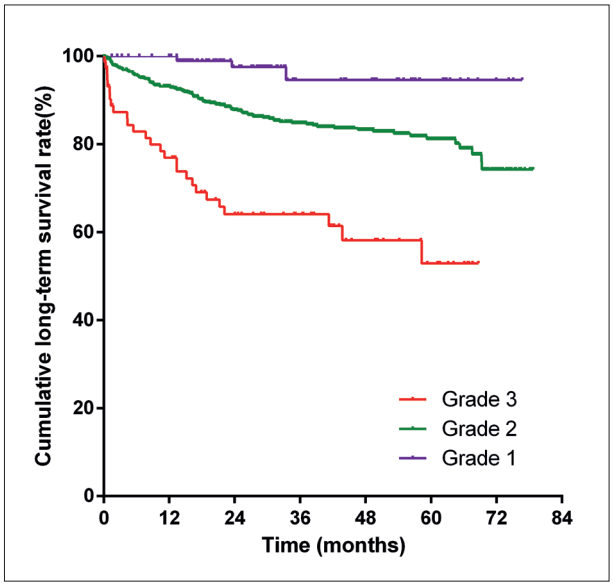


Figure 1 – *Kaplan–Meier curve of overall survival.*

addition, hyperbilirubinemia reflects poor latent cardiac status in chronic heart failure.[25] Lang et al. indicated that bilirubin had adverse effects on erythrocytes, inducing suicidal death of erythrocytes. Excessive damage to erythrocytes leads to severe anemia and further affects the prognosis.[26] These pieces of evidence support our finding that hyperbilirubinemia is a risk factor for patients with idiopathic DCM.

Both hypoalbuminemia and hyperbilirubinemia were risk factors for poor prognosis in patients with idiopathic DCM. The ALBI score, combining these two effects, has been extensively tested as an objective, simple, and distinguishing method for assessing liver function.[27] To the best of our knowledge, no study yet has evaluated the prognostic value of ALBI score in patients with idiopathic DCM. The present study demonstrated that ALBI score was independently associated with in-hospital and long-term adverse outcomes. The ALBI score consists of only two variables, and it is a simple risk-stratifying tool in patients with idiopathic DCM. Based on the current study,

Table 3 – Univariate Cox proportional hazard of long-term mortality

Clinical variables	HR	95% CI	p-value
ALBI score	3.16	2.31 – 4.33	<0.001
Age (years)	1.03	1.02 – 1.04	<0.001
Female sex	0.96	0.67 – 1.39	0.845
Hypertension	0.99	0.69 – 1.44	0.975
Diabetes	0.96	0.62 – 1.49	0.854
Smokers	1.03	0.72 – 1.49	0.859
NYHA functional class>II	1.81	1.28 – 2.54	0.001
Anemia	1.97	1.25 – 3.10	0.003
eGFR<60mL/min/1.73 m^2	2.09	1.51 – 2.91	<0.001
lgALT	1.78	1.21 – 2.62	0.004
Hypoproteinemia	2.46	1.73 – 3.48	<0.001
Total bilirubin	1.01	1.00 – 1.01	<0.001
LAD	1.03	1.01 – 1.05	0.016
LVEDD	1.04	1.03 – 1.06	<0.001
LVEF	0.96	0.94 – 0.98	<0.001
ACEI/ARB usage	0.93	0.60 – 1.44	0.733
Beta-blocker usage	0.53	0.37 – 0.75	<0.001
Lasix usage	1.08	0.67 – 1.76	0.742
Aldactone usage	1.43	0.83 – 2.48	0.202
Digoxin usage	1.55	1.09 – 2.20	0.016

ACEI: angiotensin-converting enzyme inhibitors; ALBI: albumin-bilirubin; ARB: angiotensin receptor blocker; ALT: alanine transaminase; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Table 4 – Multivariate Cox proportional hazard of long-term mortality

Clinical variables	HR	95% CI	p-value
Model 1			
ALBI	2.84	1.95 – 4.13	<0.001
Age (years)	1.03	1.02 – 1.05	<0.001
NYHA functional class>II	1.25	0.86 – 1.82	0.236
Anemia	1.25	0.76 – 2.06	0.382
eGFR<60mL/min/1.73 m^2	1.30	0.91 – 1.85	0.156
lgALT	1.46	1.00 – 2.14	0.050
LAD	1.00	0.98 – 1.03	0.898
LVEDD	1.04	1.02 – 1.06	<0.001
LVEF	0.99	0.97 – 1.01	0.348
Beta-blocker usage	0.65	0.45 – 0.95	0.024
Digoxin usage	1.05	0.72 – 1.54	0.804
Model 2			
ALBI			
Grade 1	-	-	-
Grade 2	5.69	1.40 – 23.18	0.015
Grade 3	16.79	3.91 – 72.04	<0.001
Age (years)	1.03	1.02 – 1.05	<0.001
NYHA functional class>II	1.24	0.85 – 1.81	0.262
Anemia	1.37	0.84 – 2.24	0.205
eGFR<60mL/min/1.73 m^2	1.29	0.90 – 1.84	0.168
lgALT	1.57	1.08 – 2.28	0.019
LAD	1.00	0.98 – 1.03	0.758
LVEDD	1.04	1.02 – 1.07	<0.001
LVEF	0.98	0.96 – 1.01	0.180
Beta-blocker usage	0.59	0.41 – 0.85	0.005
Digoxin usage	1.08	0.74 – 1.58	0.702

ALBI: albumin-bilirubin; ALT: alanine transaminase; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

the clinical application of the ALBI score might be extended from hepatic diseases to idiopathic DCM.

Limitations

Our study has some limitations. First, this was a retrospective cohort study; therefore, some admission bilirubin and albumin levels were missing, which may affect the results. Second, bilirubin and albumin were not dynamically detected. The relationship between prognosis and ALBI score at different time points is unknown. Finally, as our included study population did not represent patients with idiopathic DCM in different settings, such as in western countries, the study results should be validated in different idiopathic DCM cohorts.

Conclusions

This study showed that the ALBI score was independently associated with increased risk of in-hospital MACEs and long-term mortality in patients with idiopathic DCM. Moreover, compared to bilirubin and albumin, the ALBI score exhibited relatively superior predictive ability for long-term mortality, which might identify more patients at high risk of poor outcomes.

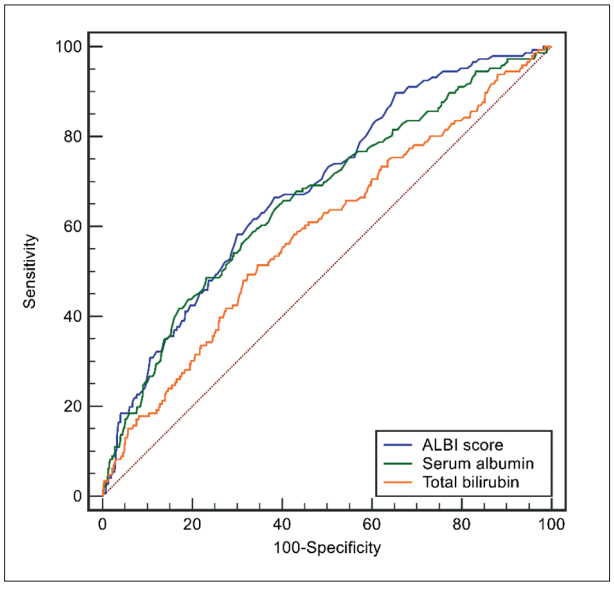


Figure 2 – *ROC analysis of long-term mortality.*

Author Contributions

Conception and design of the research: Mei J, Xue-biao W, Danqing Y; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Mei J, Xue-biao W, Jie-leng H, Zedazhong S, Ying-wen L; Writing of the manuscript: Mei J, Xue-biao W; Critical revision of the manuscript for intellectual content: Danqing Y.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Medical Science and Technology Research Founding of Guangdong (A2019409).

Study Association

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

References

1. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The Diagnosis and Evaluation of Dilated Cardiomyopathy. J Am Coll Cardiol. 2016;67(25):2996-3010. doi: 10.1016/j.jacc.2016.03.590.
2. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying Causes and Long-term Survival in Patients with Initially Unexplained Cardiomyopathy. N Engl J Med. 2000;342(15):1077-84. doi: 10.1056/NEJM200004133421502.
3. Jefferies JL, Towbin JA. Dilated Cardiomyopathy. Lancet. 2010;375(9716):752-62. doi: 10.1016/S0140-6736(09)62023-7.
4. Yılmaz MB, Nikolaou M, Mebazaa A. Cardiohepatic Interactions in Heart Failure. Anadolu Kardiyol Derg. 2013;13(7):731-2. doi: 10.5152/akd.2013.250.
5. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement from the American Heart Association. Circulation. 2016;134(23):e579-e646. doi: 10.1161/CIR.0000000000000455.
6. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of Liver Function in Patients with Hepatocellular Carcinoma: A New Evidence-based Approach-the ALBI Grade. J Clin Oncol. 2015;33(6):550-8. doi: 10.1200/JCO.2014.57.9151.
7. Wang J, Zhang Z, Yan X, Li M, Xia J, Liu Y, et al. Albumin-Bilirubin (ALBI) as an Accurate and Simple Prognostic Score for Chronic Hepatitis B-related Liver Cirrhosis. Dig Liver Dis. 2019;51(8):1172-8. doi: 10.1016/j.dld.2019.01.011.
8. Deng M, Ng SWY, Cheung ST, Chong CCN. Clinical Application of Albumin-Bilirubin (ALBI) Score: The Current Status. Surgeon. 2020;18(3):178-86. doi: 10.1016/j.surge.2019.09.002.
9. Matsue Y, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, et al. Clinical and Prognostic Values of ALBI Score in Patients With Acute Heart Failure. Heart Lung Circ. 2020;29(9):1328-37. doi: 10.1016/j.hlc.2019.12.003.
10. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, et al. Proposal for a Revised Definition of Dilated Cardiomyopathy, Hypokinetic Non-dilated Cardiomyopathy, and its Implications for Clinical Practice: A Position Statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2016;37(23):1850-8. doi: 10.1093/eurheartj/ehv727.
11. 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. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006.
13. Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving Concepts in Dilated Cardiomyopathy. Eur J Heart Fail. 2018;20(2):228-39. doi: 10.1002/ejhf.1103.
14. Ambrosy AP, Vaduganathan M, Huffman MD, Khan S, Kwasny MJ, Fought AJ, et al. Clinical Course and Predictive Value of Liver Function Tests in Patients Hospitalized for Worsening Heart Failure with Reduced Ejection Fraction: An Analysis of the EVEREST Trial. Eur J Heart Fail. 2012;14(3):302-11. doi: 10.1093/eurjhf/hfs007.
15. Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA, et al. The Prevalence and Prognostic Significance of Right Ventricular Systolic Dysfunction in Nonischemic Dilated Cardiomyopathy. Circulation. 2013;128(15):1623-33. doi: 10.1161/CIRCULATIONAHA.113.002518.
16. Merlo M, Gobbo M, Stolfo D, Losurdo P, Ramani F, Barbati G, et al. The Prognostic Impact of the Evolution of RV Function in Idiopathic DCM. JACC Cardiovasc Imaging. 2016;9(9):1034-42. doi: 10.1016/j.jcmg.2016.01.027.
17. Sundaram V, Fang JC. Gastrointestinal and Liver Issues in Heart Failure. Circulation. 2016;133(17):1696-703. doi: 10.1161/CIRCULATIONAHA.115.020894.
18. Giallourakis CC, Rosenberg PM, Friedman LS. The Liver in Heart Failure. Clin Liver Dis. 2002;6(4):947-67. doi: 10.1016/s1089-3261(02)00056-9.
19. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart Failure and Liver Disease: Cardiohepatic Interactions. JACC Heart Fail. 2019;7(2):87-97. doi: 10.1016/j.jchf.2018.10.007.

20. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human Serum Albumin: From Bench to Bedside. Mol Aspects Med. 2012;33(3):209-90. doi: 10.1016/j.mam.2011.12.002.

21. Kempny A, Diller GP, Alonso-Gonzalez R, Uebing A, Rafiq I, Li W, et al. Hypoalbuminaemia Predicts Outcome in Adult Patients with Congenital Heart Disease. Heart. 2015;101(9):699-705. doi: 10.1136/heartjnl-2014-306970.

22. Gorriz JL, Martinez-Castelao A. Proteinuria: Detection and Role in Native Renal Disease Progression. Transplant Rev. 2012;26(1):3-13. doi: 10.1016/j.trre.2011.10.002.

23. Kinugawa S, Fukushima A. Malnutrition in Heart Failure: Important but Undervalued Issue. JACC Heart Fail. 2018;6(6):487-8. doi: 10.1016/j.jchf.2018.03.014.

24. Lourenço P, Silva S, Friões F, Alvelos M, Amorim M, Couto M, et al. Low Prealbumin is Strongly Associated with Adverse Outcome in Heart Failure. Heart. 2014;100(22):1780-5. doi: 10.1136/heartjnl-2014-305747.

25. Shinagawa H, Inomata T, Koitabashi T, Nakano H, Takeuchi I, Naruke T, et al. Prognostic Significance of Increased Serum Bilirubin Levels Coincident with Cardiac Decompensation in Chronic Heart Failure. Circ J. 2008;72(3):364-9. doi: 10.1253/circj.72.364.

26. Lang E, Gatidis S, Freise NF, Bock H, Kubitz R, Lauermann C, et al. Conjugated Bilirubin Triggers Anemia by Inducing Erythrocyte Death. Hepatology. 2015;61(1):275-84. doi: 10.1002/hep.27338.

27. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of Liver Function in Patients with Hepatocellular Carcinoma: A New Evidence-based Approach-the ALBI Grade. J Clin Oncol. 2015;33(6):550-8. doi: 10.1200/JCO.2014.57.9151.

Evaluation of Various Pathophysiological Pathways in the Prognosis of Heart Failure with Reduced Ejection Fraction: Seeing Beyond the Heart

João Marcos Barbosa-Ferreira[1] *and Andreza Araújo de Oliveira*[1]

Universidade Nilton Lins,[1] *Manaus, AM - Brazil*

Short Editorial related to the article: Albumin-Bilirubin Score to Predict Outcomes in Patients with Idiopathic Dilated Cardiomyopathy

The manuscript "Albumin-bilirubin score to predict outcomes in patients with idiopathic dilated cardiomyopathy" provides an important way to assess the prognosis of patients with dilated cardiomyopathy (DCM) by demonstrating a higher rate of major adverse clinical events (MACEs) in patients with a higher score. Furthermore, this score works as an independent predictor of long-term mortality.[1]

Heart Failure with reduced ejection fraction (HFrEF), often characterized as DCM, has its pathophysiological aspects closely related to its therapy and prognosis. The study of the pathophysiology of HFrEF is based on cardiovascular hemodynamic alterations and intense neurohumoral activation (mainly of the autonomic nervous system, renin-angiotensin-aldosterone system and natriuretic peptides system). These pathophysiological aspects are widely used in the therapy and prognostic assessment of patients with HFrEF.[2]

Regarding prognosis, the most studied variables are related to aspects of this pathophysiology or its clinical aspects, such as ejection fraction, cardiac remodeling, catecholamine dosage, functional capacity, maximum oxygen consumption, natriuretic peptide dosage, functional class, pulmonary ultrasound, among other markers.[3-5]

More recently, other pathophysiological pathways have been increasingly studied and incorporated into the treatment of patients with HFrEF. An example of this is the study of changes in glucose metabolism and its treatment in this group of patients. Therefore, the evaluation of other metabolic pathways or the involvement of other organs and systems in patients with HFrEF is an important aspect to be studied regarding the prognosis of these patients.[6]

Rahimi et al. published a systematic review in which the main prognostic variables were related to clinical-epidemiological aspects or the most traditionally studied aspects of pathophysiology, such as age, sex, renal function, blood pressure, and ejection fraction, functional class, functional capacity and levels of natriuretic peptides. However, other parameters such as diabetes, weight or body mass index were also associated with a worse prognosis.[3]

Other parameters not directly related to the heart have also been associated with a worse prognosis in HFrEF. Alatas et al. demonstrated in a multivariate analysis that microalbuminuria predicted in-hospital mortality in patients with HFrEF and mid-range ejection fraction (HFmrEF) but not in preserved ejection fraction (HFpEF).[7] Anemia and iron metabolism have been extensively studied to improve symptoms and quality of life and the prognostic assessment of patients with HF.[8] In addition, Tavares et al. observed an association between cachexia and malnutrition with mortality in patients with chronic Chagas' heart disease, findings also found in other etiologies.[9]

Therefore, greater knowledge of the importance of the involvement of other organs in patients with HF may improve the general assessment of these patients. In this context, liver dysfunction assessed by the Albumin-bilirubin score is useful for a more complete prognostic assessment. Other studies demonstrated the importance of the liver dysfunction also in patients with acute heart failure.[10,11]

We know that HFrEF has shown a substantial improvement in mortality curves over the years, but it remains with high mortality rates, especially between 5 and 10 years.[12,13] New forms of evaluation, including the involvement of other organs and systems and/or even genetic evaluation, may contribute to an even greater improvement in these mortality curves through improved therapy and prognostic assessment.[14]

Keywords

Heart Failure; Prognosis; Biomarkers.

Mailing Address: João Marcos Barbosa-Ferreira •
Rua Ramos Ferreira, 199, Ap 1303. Postal Code 69010-120, Aparecida, Manaus, AM - Brazil
E-mail: jmbemfica@hotmail.com

DOI: https://doi.org/10.36660/abc.20220314

References

1. Jiang M, Xue-biao W, Jie-leng H, Ze-da-zhong S, Ying-wen L, Dan-qing Y. Albumin-Bilirubin Score to Predict Outcomes in Patients with Idiopathic Dilated Cardiomyopathy. Arq Bras Cardiol. 2022; 118(6):1108-1115.
2. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, 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;396(10244):121-8. doi: 10.1016/S0140-6736(20)30748-0.
3. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, et al. Risk Prediction in Patients with Heart Failure: A Systematic Review and Analysis. JACC Heart Fail. 2014;2(5):440-6. doi: 10.1016/j.jchf.2014.04.008.
4. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL Jr. Imaging, Biomarker, and Clinical Predictors of Cardiac Remodeling in Heart Failure With Reduced Ejection Fraction. JACC Heart Fail. 2019;7(9):782-94. doi: 10.1016/j.jchf.2019.06.004.
5. Avila MS, Belfort DSP. Is There a Role for Lung Ultrasonography in the Prognosis of Heart Failure Patients? Arq Bras Cardiol. 2021;116(3):393-4. doi: 10.36660/abc.20201283.
6. McMurray JJV, 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(21):1995-2008. doi: 10.1056/NEJMoa1911303.
7. Alataş ÖD, Biteker M, Demir A, Yıldırım B, Acar E, Gökçek K, et al. Microalbuminuria and its Prognostic Significance in Patients with Acute Heart Failure with Preserved, Mid-Range, and Reduced Ejection Fraction. Arq Bras Cardiol. 2022;118(4):703-9. doi: 10.36660/abc.20201144.
8. Tavares LCA, Lage SHG, Bocchi EA, Issa VS. Undernutrition and Cachexia in Patients with Decompensated Heart Failure and Chagas Cardiomyopathy: Occurrence and Association with Hospital Outcomes. Arq Bras Cardiol. 2022;118(1):3-11. doi: 10.36660/abc.20200644.
9. Chopra VK, Anker SD. Anaemia, Iron Deficiency and Heart Failure in 2020: Facts and Numbers. ESC Heart Fail. 2020;7(5):2007-11. doi: 10.1002/ehf2.12797.
10. Kawata T, Ikeda A, Masuda H, Komatsu S. Association Between Albumin-Bilirubin Score at Admission and In-Hospital Mortality in Patients with Acute Heart Failure. Int Heart J. 2021;62(4):829-36. doi: 10.1536/ihj.21-080.
11. Matsue Y, Kagiyama N, Yamaguchi T, Kuroda S, Okumura T, Kida K, et al. Clinical and Prognostic Values of ALBI Score in Patients With Acute Heart Failure. Heart Lung Circ. 2020;29(9):1328-37. doi: 10.1016/j.hlc.2019.12.003.
12. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of Patients with Chronic Heart Failure in the Community: A Systematic Review and Meta-analysis. Eur J Heart Fail. 2019;21(11):1306-25. doi: 10.1002/ejhf.1594.
13. Santos SC, Villela PB, Oliveira GMM. Mortality Due to Heart Failure and Socioeconomic Development in Brazil between 1980 and 2018. Arq Bras Cardiol. 2021;117(5):944-51. doi: 10.36660/abc.20200902.
14. Chair SY, Chan JYW, Waye MMY, Liu T, Law BMH, Chien WT. Exploration of Potential Genetic Biomarkers for Heart Failure: A Systematic Review. Int J Environ Res Public Health. 2021;18(11):5904. doi: 10.3390/ijerph18115904.

Low Concordance between NYHA Classification and Cardiopulmonary Exercise Test Variables in Patients with Heart Failure and Reduced Ejection Fraction

Luiz Eduardo Fonteles Ritt,[1,2] Rebeca Sadigursky Ribeiro,[2] Isabela Pilar Moraes Alves de Souza,[1,2] João Victor Santos Pereira Ramos,[2] Daniel Sadigursky Ribeiro,[2] Gustavo Freitas Feitosa,[1] Queila Borges de Oliveira,[1] Ricardo Stein,[3] Eduardo Sahade Darzé[1,2]

Instituto D'or de Pesquisa e Ensino (IDOR), Hospital Cárdio Pulmonar,[1] Salvador, BA - Brazil

Escola Bahiana de Medicina e Saúde Pública,[2] Salvador, BA - Brazil

Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul,[3] Porto Alegre, RS - Brazil

Abstract

Background: **The New York Heart Association (NYHA) functional classification is the most commonly used classification system for heart failure (HF), whereas cardiopulmonary exercise testing (CPET) is the gold standard for functional status evaluation in HF.**

Objective: **This study aimed to analyze correlation and concordance between NYHA classes and CPET variables.**

Methods: **HF patients with clinical indication for CPET and ejection fraction (EF) < 50% were selected. Correlation (Spearman coefficient) and concordance (kappa) between NYHA classification and CPET-based classifications were analyzed. A $p < 0.05$ was accepted as significant.**

Results: **In total, 244 patients were included. Mean age was 56 ± 14 years, and mean EF was 35.5% ± 10%. Distribution of patients according to NYHA classification was 31.2%% class I, 48.3% class II, 19.2% class III, and 1.3% class IV. Correlation (r) between NYHA and Weber classes was 0.489 ($p < 0.001$), and concordance was 0.231 ($p < 0.001$). Correlation (r) between NYHA and ventilatory classes (minute ventilation/carbon dioxide production [VE/VCO_2] slope) was 0.218 ($p < 0.001$), and concordance was 0.002 ($p = 0.959$). Spearman correlation between NYHA and CPET score classes was 0.223 ($p = 0.004$), and kappa concordance was 0.027 ($p = 0.606$).**

Conclusion: **There was a moderate association between NYHA and Weber classes, although concordance was low. Ventilatory (VE/VCO_2 slope) and CPET score classes had a weak association and a low concordance with NYHA classes.**

Keywords: **Heart Failure; Prognosis; Exercise Test.**

Introduction

Despite being a progressive disease, heart failure (HF) does not have a linear course. Hospitalizations due to HF decompensations are independent factors for prognosis. Risk prediction models and prognostic scores will determine the need to escalate specific therapeutic strategies, such as medication change, cardiac resynchronization therapy, implantable cardioverter-defibrillator, ventricular assist device, and cardiac transplantation.[1]

The New York Heart Association (NYHA) classification is a well-known, low-cost, simple functional stratification tool for HF with prognostic value.[2,3] It divides patients into 4 different groups according to self-reported dyspnea severity and limitations to physical activities.[2,3] However, the NYHA functional class depends on self-reported symptoms and, therefore, is influenced by the subjectivity of each patient.[4,5]

Conversely, functional status is assessed objectively by cardiopulmonary exercise testing (CPET), which is a prognostic tool considered to be the gold standard for HF assessment.[6,7] Important guidelines define CPET as a class I recommendation for cardiac transplantation and a class IIa recommendation for exercise prescription in this context.[6,7]

Classically, CPET prognostic evaluation is based on peak oxygen uptake (VO_{2peak}) measures.[8,9] However, other variables such as minute ventilation/carbon dioxide production (VE/VCO_2) slope, heart rate recovery in 1 minute (HRR_1), oxygen uptake efficiency slope (OUES), end-tidal carbon dioxide partial pressure ($PetCO_2$), and periodic ventilation have demonstrated an independent and incremental prognostic value to VO_{2peak} in HF.[10] Based on those variables, specific prognostic classifications have been validated, namely Weber classes (VO_{2peak}), ventilatory classes (VE/VCO_2 slope), and CPET score (combining VO_{2peak}, VE/VCO_2 slope, HRR_1, OUES, and $PetCO_2$).[11-13]

Even though the NYHA classification system is widely used, there are few studies correlating NYHA classes with HF

Mailing Address: Luiz Eduardo Fonteles Ritt •
Av. Anita Garibaldi, 2199, Ondina - Hospital Cárdio Pulmonar - Centro de Estudos Clínicos. Postal Code 40170130, Salvador, BA – Brazil
E-mail: luizritt@hotmail.com, lefr@cardiol.br
Manuscript received March 12, 2021, revised manuscript August 08, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210222

prognosis or CPET variables.[14,15] Recently, a systematic review compared NYHA classification and CPET variables, and the variable that was common to all analyzed studies was VO_{2peak}, yet with much heterogeneity.[14] This study aimed to evaluate correlation and concordance between NYHA classification for HF and CPET-based functional classifications, namely Weber classes, ventilatory classes, and CPET score.[11–13]

Methods

This cross-sectional study consecutively recruited patients who underwent CPET for HF evaluation. Inclusion criteria were the following: 1) age ≥ 18 years; 2) confirmed HF diagnosis with ejection fraction (EF) < 50%; and 3) clinical indication for CPET between 2009 and 2019. Exclusion criteria were moderate-to-severe chronic obstructive pulmonary disease, pulmonary hypertension, and/or fibrosis or symptomatic anemia.

CPET variables and demographic data were collected together with clinical information and relevant complementary tests (12-lead resting electrocardiogram and Doppler echocardiogram from the past 3 months). CPET was symptom-limited and was performed at maximal effort with a ramp protocol in a treadmill (Micromed Centurion 300, São Paulo, Brazil) using a Cortex 3b breath-by-breath analyzer (Cortex Inc., Leipzig, Germany). Two-point gas calibration was done before the tests. All techniques followed current guidelines, and a nationally certified physician was responsible for each test.[10]

All CPET tests were conducted by the same physician, a cardiologist who specializes in CPET. Before CPET, the same physician in charge of the test determined each patient's NYHA class according to self-reported limitation to physical activity: (I) no limitation to physical activity; (II) slight limitation to physical activity; (III) marked limitation to physical activity; or (IV) unable to perform any physical activity without discomfort.[16] Then, based on CPET variables, patients were classified into Weber classes, ventilatory classes, and CPET score classes according to their CPET results.[11–13]

Weber classification categorizes patients according to their VO_{2peak} as follows: (A) VO_2 > 20 mL.kg^{-1}.min^{-1}; (B) VO_2 16-20 mL.kg^{-1}.min^{-1}; (C) VO_2 10-15 mL.kg^{-1}.min^{-1}; or (D) VO_2 < 10 mL.kg^{-1}.min^{-1}.[12] Ventilatory classes use VE/VCO_2 slope: (I) $VE/VCO_2 \leq 29.9$; (II) VE/VCO_2 30-35.9; (III) VE/VCO_2 36-44.9; or (IV) $VE/VCO_2 \geq 45$.[13] CPET score was calculated for each patient based on the summation of abnormal responses as follows: $VE/VCO_2 \geq 34$ (7 points); $HRR_1 \leq 6$ bpm (5 points); OUES ≤ 1.4 (3 points); $PetCO_2$ < 33 mm Hg (3 points); and $VO_{2peak} \leq 14$ mL.kg^{-1}.min^{-1} (2 points).[11,15] The score is then divided into quartiles: (I) 0-5; (II) 6-10; (III) 10-15; and (IV) > 15.[11]

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables were reported as mean and standard deviation for parametric distribution or as median and interquartile range for nonparametric distribution. Kolmogorov-Smirnov normality test and histogram analysis were used for determination of distribution. Categorical variables were reported as absolute numbers and proportions. Correlation between variables was assessed using Spearman (*s*) or Pearson (*p*) correlation coefficient, and concordance was assessed using kappa (k) coefficient. For all analyses, a $p < 0.05$ was accepted as statistically significant.

An institutional research ethics committee approved the study protocol. Also, the study respects all national and international regulations for human research.

Results

Patients' characteristics are described in Table 1. The sample included 244 patients, mainly men (77.9%), and mean age was 56 ± 14 years. Ischemia was the most frequent etiology (44.4%). Mean EF was 35.5% ± 10%. Patients were on optimized medical therapy as follows: 86.4% angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 91.4% beta-blockers, 57.0% aldosterone antagonists, and 53.5% diuretics. Mean VO_{2peak} was 19.2 ± 6.7 mL.kg^{-1}.min^{-1}, whereas mean VE/VCO_2 slope was 39 ± 10. Mean respiratory exchange ratio (RER) was 1.041 ± 0.12 (25% had a RER > 1.10). All tests were interrupted by the effort criteria, and none was interrupted prematurely or due to hemodynamic, arrhythmic, or ischemic criteria. Patients were distributed according to NYHA classification as follows: 31.3% class I, 48.3% class II, 19.2% class III, and 1.3% class IV (Table 2).

Figure 1 shows NYHA class distribution according to Weber classes (Figure 1A), ventilatory classes (Figure 1B), and CPET score classes (Figure 1C). Correlation (r) between NYHA and Weber classes was 0.489 ($p < 0.001$), and concordance was 0.231 ($p < 0.001$). Correlation (r) between NYHA and ventilatory classes was 0.218 ($p < 0.001$), and concordance was 0.002 ($p = 0.959$). Finally, correlation (r) between NYHA and CPET score classes was 0.223 ($p = 0.004$), and concordance was 0.027 ($p = 0.606$).

Discussion

In patients with HF with reduced ejection fraction who underwent CPET after clinical indication, we found only a moderate association between NYHA and Weber classes, with a low concordance. However, there was an even lower association or concordance rate between NYHA classification and ventilatory or CPET score classes.

All those functional status classifications have their prognostic value validated for HF.[3,11–13] Thus, functional status is the best parameter for risk prediction in those patients.[3,11–13] However, as we showed, there was a low concordance between NYHA classification and the 3 classifications based on CPET (which is an objective clinical test). Even though we found a moderate correlation between NYHA and Weber classes, it seems reasonable to hypothesize that subjectivity interferes in NYHA classification risk prediction for HF and has a subsequent impact on therapeutic decisions.

Table 1 – General patient demographic, clinical, and cardiopulmonary exercise test characteristics (n = 244)

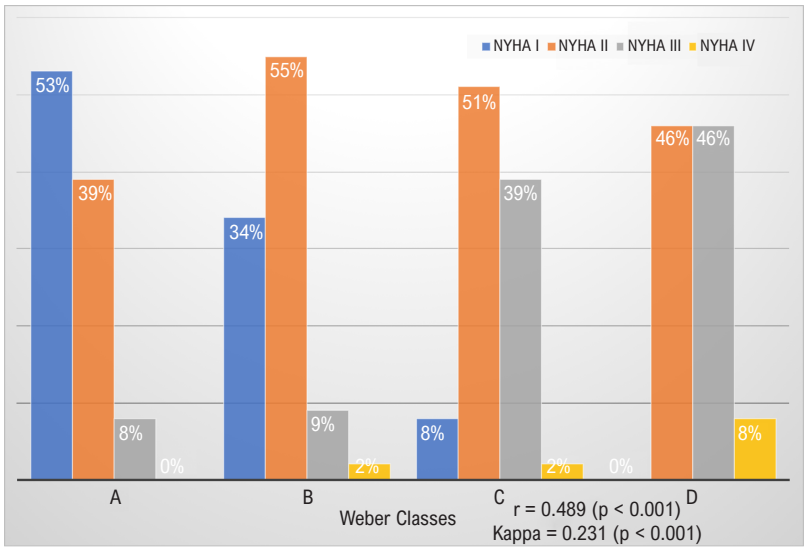
Variables	
Age (mean ± SD)	56±14 years
Gender	
Male, n (%)	190 (77.9)
Etiology	
Ischemic, n (%)	107 (44.4)
Idiopathic, n (%)	56 (23.2)
Viral, n (%)	30 (12.4)
Chagasic, n (%)	18 (7.5)
Other, n (%)	30 (12.5)
Comorbidities	
Hypertension, n (%)	70 (34.7)
Diabetes mellitus, n (%)	43 (21.2)
Coronary artery disease, n (%)	94 (46.3)
Smoking, n (%)	4 (2.0)
Medications used	
ACEI or ARB, n (%)	209 (86.4)
Beta-blocker, n (%)	222 (91.4)
MCRA, n (%)	138 (57.0)
Diuretics, n (%)	129 (53.5)
Implantable devices	
Pacemaker, n (%)	17 (7.0)
CRT and/or ICD, n (%)	28 (11.5)
VO_{2peak} ($mL.kg^{-1}.min^{-1}$), mean ± SD	19.2±6.7
Percent of predicted VO_{2peak} (%), mean ± SD	63±20
EF (%), mean ± SD	35.5±10
RER, mean ± SD	1.041±0.12
VE/VCO_2 slope, mean ± SD	39.0±10.8
$PetCO_2$ (mm Hg), mean ± SD	29.8±4.66
HRR_1, median (IQR)	18.0 (15)
SBP at rest, median (IQR)	120 (10)
HR at rest, median (IQR)	74 (22)

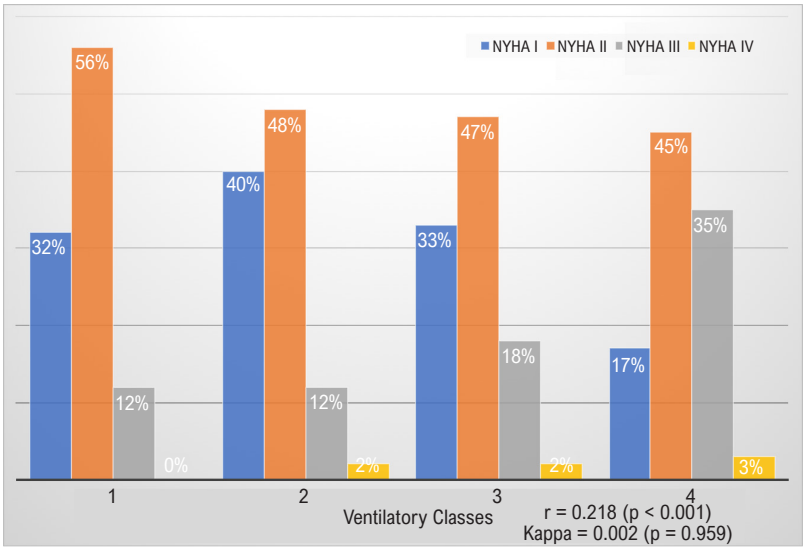
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; MCRA: mineralocorticoid-receptor antagonists; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; VO_{2peak}: peak oxygen uptake; SD: standard deviation; EF: ejection fraction; RER: respiratory exchange ratio; VE/VCO_2: minute ventilation/carbon dioxide production; $PetCO_2$: end-tidal carbon dioxide partial pressure; HRR_1: heart rate recovery in 1 minute; SBP: systolic blood pressure; HR: heart rate; NYHA: New York Heart Association; CPET: cardiopulmonary exercise test; IQR; interquartile range

Table 2 – Sample distribution according to subjective and objective classifications, n (%)

	I	II	III	IV
NYHA class	75 (31.2)	116 (48.3)	46 (19.2)	3 (1.3)
VE/VCO_2 slope	42 (17.2)	70 (28.7)	74 (30.3)	58 (23.8)
CPET score	57 (34.7)	61 (37.2)	36 (22.0)	10 (6.1)
	A	B	C	D
Weber class	95 (39)	55 (22.5)	81 (33.2)	13 (5.3)

NYHA: New York Heart Association; VE/VCO_2: minute ventilation/carbon dioxide production; CPET: cardiopulmonary exercise test.





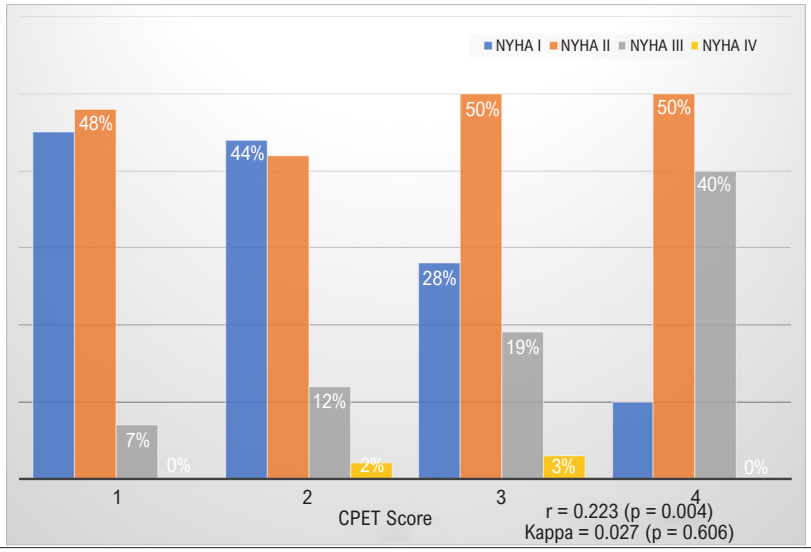


Figure 1 – *NYHA class distribution, correlation, and concordance according to (A) Weber classes, (B) ventilatory classes (VE/VCO_2 slope), and (C) CPET score classes. NYHA: New York Heart Association; VE/VCO_2: minute ventilation/carbon dioxide production; CPET: cardiopulmonary exercise test; r: correlation coefficient.*

A recent systematic review addressed the correlation between NYHA classification for HF and VO_{2peak} measures (determined by CPET).[14] It found a great heterogeneity in NYHA classes among the included studies.[14] Our findings support those of Lim et al. and reflect a further correlation analysis, as we described the correlation between the subjective NYHA classification and some objective classifications that are based on CPET results, either through a validated score or through ventilatory classes. For example, patients subjectively considered to be in NYHA class I by their attending physicians may have ventilatory class IV VE/VCO_2 slope values (poorest prognosis) or be in the poorest prognostic quartile of the CPET score (Figure 1).[11,13]

NYHA classification may lead to different interpretations of the same patient from different attending physicians,[3] especially when symptoms from intermediate classes (II and III) are reported. In a publication from our group, Ritt et al. demonstrated that patients in Weber class B could be divided into two different prognostic groups when the CPET score was calculated.[15] The groups were then divided into one of higher risk and another of lower risk. However, patients in intermediate NYHA classes are generally those whose functional status is of great importance for decision-making. These decisions include increasing or changing medications, providing surgical indications, or implanting devices (such as cardiac resynchronization therapy or ventricular assist device).[16] In such groups, NYHA classification may not be sensitive enough to address minor but important clinical features. Therefore, an objective, easily reproducible, reliable classification is urgently needed. In patients with NYHA class I or II, CPET may reclassify them to higher risk, and patients with NYHA class III may be reclassified to lower risk, especially those who are candidates to medication changes and/or devices. The use of CPET for this purpose is a matter for future studies.

Our study has some limitations, such as lack of clinical follow-up of our patient sample. We excluded symptomatic anemia, as we focused on clinical diagnostic criteria, but one may argue that asymptomatic anemia may also impact functional capacity. Also, the prevalence of depression was not assessed in our patients, although it may contribute to the lack of effort. Our sample had a mean RER of 1.04; one may argue that a RER > 1.10 is the pattern for achieving acidosis, although in HF some use RER > 1.00 as an acceptable criterion.[17] Although this may impact VO_{2peak}, it does not impact VE/VCO_2 slope, OUES, or HRR_1. New studies addressing a wider population and analyzing clinical outcomes are necessary to a better understanding of the actual prognostic value of each HF classification (NYHA, VE/VCO_2 slope, Weber classes, and CPET score). We focused on Weber classes, VE/VCO_2 slope classes, and CPET score because all these parameters may be presented as 4-level scale classifications as NYHA; also, VO_{2peak} and VE/VCO_2 slope are the most studied variables in CPET, and other variables from CPET are inserted in the CPET score. However, future studies focusing on specific CPET variables are valuable. Importantly, it remains to be determined whether there is, in fact, an objective CPET-based strategy that is more accurate than the others.

Conclusion

There was a moderate association between the subjective NYHA classification and the objectively measured Weber classes, although concordance was low. The objectively measured ventilatory classes and CPET score classes had a weak association and a low concordance with the NYHA classification.

Author Contributions

Conception and design of the research: Ritt LEF, Ribeiro RS, Souza IPMA, Ramos JVSP, Stein R; Acquisition of data: Ritt LEF, Ribeiro RS, Souza IPMA, Ramos JVSP, Ribeiro DS, Feitosa GF, Oliveira QB; Analysis and interpretation of the data: Ritt LEF, Ribeiro RS, Souza IPMA, Ramos JVSP, Ribeiro DS, Feitosa GF, Oliveira QB, Stein R, Darzé ES; Statistical analysis: Ritt LEF, Ribeiro RS, Ramos JVSP, Ribeiro DS, Stein R, Darzé ES; Obtaining financing: Ritt LEF; Writing of the manuscript: Ritt LEF, Ribeiro RS, Souza IPMA, Ramos JVSP, Ribeiro DS, Feitosa GF, Oliveira QB, Stein R; Critical revision of the manuscript for intellectual content: Ritt LEF, Stein R, Darzé ES.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

References

1. Chaudhry SP, Stewart GC. Advanced Heart Failure: Prevalence, Natural History, and Prognosis. Heart Fail Clin. 2016;12(3):323-33. doi: 10.1016/j.hfc.2016.03.001.
2. Holland R, Rechel B, Stepien K, Harvey I, Brooksby I. Patients' self-assessed functional status in heart failure by New York Heart Association class: a prognostic predictor of hospitalizations, quality of life and death. J Card Fail. 2010;16(2):150-6. doi: 10.1016/j.cardfail.2009.08.010.
3. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, et al. Clinical Implications of the New York Heart Association Classification. J Am Heart Assoc. 2019;8(23):e014240. doi: 10.1161/JAHA.119.014240.
4. Yap J, Lim FY, Gao F, Teo LL, Lam CS, Yeo KK. Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance: A Systematic Review. Clin Cardiol. 2015;38(10):621-8. doi: 10.1002/clc.22468.

5. Raphael C, Briscoe C, Davies J, Whinnett ZI, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476-82. doi: 10.1136/hrt.2006.089656.

6. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant. 2006;25(9):1024-42. doi: 10.1016/j.healun.2006.06.008.

7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128.

8. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778-86. doi: 10.1161/01.cir.83.3.778.

9. Guimarães GV, Silva MS, d'Avila VM, Ferreira SM, Silva CP, Bocchi EA. Peak VO2 and VE/VCO2 slope in betablockers era in patients with heart failure: a Brazilian experience. Arq Bras Cardiol. 2008;91(1):39-48. doi: 10.1590/s0066-782x2008001300007.

10. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225. doi: 10.1161/CIR.0b013e3181e52e69.

11. Myers J, Oliveira R, Dewey F, Arena R, Guazzi M, Chase P, et al. Validation of a cardiopulmonary exercise test score in heart failure. Circ Heart Fail. 2013;6(2):211-8. doi: 10.1161/CIRCHEARTFAILURE.112.000073.

12. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 1982;65(6):1213-23. doi: 10.1161/01.cir.65.6.1213.

13. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007;115(18):2410-7. doi: 10.1161/CIRCULATIONAHA.107.686576.

14. Lim FY, Yap J, Gao F, Teo LL, Lam CSP, Yeo KK. Correlation of the New York Heart Association classification and the cardiopulmonary exercise test: A systematic review. Int J Cardiol. 2018;263:88-93. doi: 10.1016/j.ijcard.2018.04.021.

15. Ritt LE, Myers J, Stein R, Arena R, Guazzi M, Chase P, et al. Additive prognostic value of a cardiopulmonary exercise test score in patients with heart failure and intermediate risk. Int J Cardiol. 2015;178:262-4. doi: 10.1016/j.ijcard.2014.10.025.

16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, Rev. Esp. Cardiol. 2016;69(12):1167. https://doi.org/10.1016/j.recesp.2016.10.014.

17. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail. 2016;4(8):607-16. doi: 10.1016/j.jchf.2016.03.022.

NYHA Classification and Cardiopulmonary Exercise Test Variables in Patients with Heart Failure

Ricardo Vivacqua Cardoso Costa[1]

Hospital Pró-cardíaco,[1] *Rio de Janeiro, RJ – Brazil*

Short Editorial related to the article: Low Concordance between NYHA Classification and Cardiopulmonary Exercise Test Variables in Patients with Heart Failure and Reduced Ejection Fraction

Heart failure (HF) is considered a prevalent disease, limiting survival and constituting one of the leading causes of hospitalization or death in several countries, including Brazil.[1] Therefore, clinical classification in patients with HF can be considered important as an initial reference, as it informs the functional condition of these patients. Classically, the subjective classification of the New York Heart Association (NYHA) and the objective classification of Weber[2] are the most used. The NYHA functional classification and oxygen consumption at peak exertion were decisive in determining the functional condition of patients with Chagas disease.[3] However, certain patients with minor symptoms are at high risk of hospitalization or death.[4]

In patients with HF, the 6-minute walk test is also considered in assessing functional and prognostic capacity. This test has a predictive value for mortality in patients with HF functional class II and III (NYHA).[5]

Studies of cardiopulmonary assessment have expanded, simultaneously, to studies of exercise physiology, with better precision in the functional evaluation and, through the parameters obtained in the Cardiopulmonary Exercise Test (CPET), we have prognostic inference variables, which define conducts and guide the prescription of exercises.[6]

The well-designed study by Ritt et al.[7] analyzed the correlation and agreement between NYHA classes and CPET variables. The most studied variables today were highlighted.[1] We suggest, as a continuation of the study, to include correlations with Circulatory Power (Maximum Systolic Blood Pressure x V'O2 peak)[8] and V'O2 at the threshold I,[9] parameters that determine prognostic perspectives and, as a future study, the risk score to predict post-discharge mortality in patients with HF.[10]

We reiterate our congratulations to the authors[7] for the study and the suggestion for future research aiming at a classification based on the parameters obtained in the CPET, with accuracy for indication of heart transplantation or placement of artificial ventricle.

References

1 Sociedade Brasileira de Cardiologia. Comitê Coordenador da Diretriz de Insuficiência Cardíaca. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol.2018; 111(3):436-539. doi: 10.5935/abc.20180190.

2. Weber KT, Kinasewitz GT, Janick JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation.1982;65(6):1213-23. doi:10.1161/01.circ.65.6.1213.

3. Silva WT, Costa HS, Figueiredo PHS, Lima MMO, Lima VP, Costa FSM, et al.Determinantes da Capacidade Funcional em Pacientes com Doença de Chagas. Arq Bras Cardiol.2021;117(5): 934-41. doi:https://doi.org/10.36660/abc.20200462.

4. 2021 Esc Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J.2021;42(36):3599-726. doi:10.1093/eurheartj/ehab368.

5. Morais ER, Rassi S. Determinants of the distance covered during a six-minute walk test in patients with chronic heart failure. Int J Cardiovasc Sci. 2019;32(2):2019;32(2):134-42. doi: 10.5935/2359-4802.20180088

6. Ávila DX, Vivacqua RC, Serra S, Montera MW, Tinoco E, Siciliano A. The unsurpassed value of cardiopulmonary exercise testing in assessing the prognosis of heart failure. Eur Heart J.2020;41(Suppl 2):ehaa946.988. https://doi.org/10.1093/ehjci/ehaa946.0988

7. Ritt LEF, Ribeiro RS, Souza IPMA, Ramos JVSP, Ribeiro DS, Feitosa GF, et al. Baixa concordância entre a classificação da NYHA e as variáveis do teste de exercício cardiopulmonar em pacientes com insuficiência cardíaca e fração de ejeção reduzida. Arq Bras Cardiol. 2022; 118(6):1118-1123.

Keywords

Heart Failure; Hospitalization; Mortality; Oxygen Consumption; Exercise Test; Walk Test; Physical Activity; Life Style.

Mailing Address: Ricardo Vivacqua Cardoso Costa •
Hospital Pró-cardíaco – Ergometria – Av. Afrânio Melo Franco, 365 AP 101. Postal Code 22430-060, Rio de Janeiro, RJ - Brazil
E-mail: vivacqua@cardiol.br

DOI: https://doi.org/10.36660/abc.20220196

8. Tabet JY, Metra M, Thabut G, Logeart D, Cohen-Solal A. Prognostic value of cardiopulmonary exercise variables in chronic heart failure patients with or without beta-blocker therapy. Am J Cardiol.2006;98(4):500-3. doi: 10.1016/j.amjcard.2006.03.027.

9. Lala A, Shah KB, Lanfear E, Thibodeau JT, Palardy M, et al. Predictive value of cardiopulmonary exercise testing parameters in ambulatory advanced heart failure.J Am Coll Cardiol HF 2021;9:226-236-36. doi:https://doi.org/10.1016/j.chf.2020.11.008.

10. Lei Wang, Li-Oin Wang, Mo-Li Gu,Liang Li, Chen Wang, Yun-Feng Xia. Escore de risco clínico simples para prever a mortalidade pós-alta hospitalar em pacientes chineses hospitalizados por insuficiência cardíaca. Arq Bras Cardiol.2021;117(4):615-23. doi:10.36660/abc.20200435.

Cost-Effectiveness of Using the Coronary Artery Calcium Score in Guiding Therapeutic Decisions in Primary Prevention in the Brazilian Population

Raul Serra Valério,[1] Giuliano Generoso,[2] Juliano Lara Fernandes,[3,4] Khurram Nasir,[5] Jonathan C. Hong,[6] Marcio Sommer Bittencourt[7]

Diagnósticos da América SA,[1] São Paulo, SP – Brazil
Hospital Sírio-Libanês - Centro de Cardiologia,[2] São Paulo, SP – Brazil
Radiologia Clínica de Campinas,[3] Campinas, SP – Brazil
Instituto de Ensino e Pesquisa Jose Michel Kalaf,[4] Campinas, SP – Brazil
Houston Methodist Debakey Heart & Vascular Center - Center for Outcomes Research,[5] Houston, Texas – USA
Texas Heart Institute - Division of Cardiovascular Surgery,[6] Texas – USA
Universidade de São Paulo - Hospital Universitário de São Paulo,[7] São Paulo, SP – Brazil

Abstract

Background: The use of the coronary artery calcium score to aid cardiovascular risk stratification may be a more cost-effective tool than the conventional strategy.

Objectives: Evaluation of the cost-effectiveness of the use of the calcium score in therapeutic guidance for primary cardiovascular prevention.

Methods: A microsimulation model to assess the clinical and economic consequences of atherosclerotic cardiovascular disease, comparing the prevention strategy using the calcium score and the conventional strategy.

Results: The results obtained demonstrated a better cost-effectiveness of the therapeutic strategy guided by the calcium score, by reducing incremental costs and increasing quality-adjusted life years (QALY), which corresponds, in number, to improving the quality of life of the individual.

Conclusions: The use of the coronary artery calcium score proved to be more cost-effective than the conventional strategy, both in terms of cost and QALY, in most of the scenarios studied.

Keywords: Cost-Benefit Analysis; Primary Prevention; Cardiac Imaging Techniques; Coronary Artery Calcium.

Thanks to new ways of classifying the risk of cardiovascular events in primary prevention, which are recommended by the guidelines of the main cardiology societies in the world, there is a significant increase in the population eligible for the use of statins.[1,2] As an example of these changes, the 2018 dyslipidemia management and 2019 cardiovascular prevention guidelines of the American Heart Association (AHA) and American College of Cardiology (ACC) suggest the use of a cardiovascular risk score (Pooled Cohort Equations, ASCVD) to estimate the risk of cardiovascular events related to atherosclerosis over a period of ten years.[3,4] This score classifies the individual, according to modifiable and non-modifiable variables, as being at high risk (>20% of events in ten years); moderate risk (7.5–20% of events in ten years); borderline (5–7.5% of events in ten years) and low risk (<5% of events in ten years).[3,4]

However, it is possible to note that this classification unites a heterogeneous cardiovascular risk population, since a portion of individuals who are candidates for statin use do not show symptoms or signs of overt atherosclerotic disease. Consequently, many individuals eligible for pharmacological therapy could marginally benefit from this therapy in the long term, since the accumulated benefit of the treatment is directly proportional to the baseline risk.[2,5]

In this scenario, the coronary artery calcium score (CAC), performed by means of computed tomography to quantify the atherosclerotic burden of individuals, may be useful to reclassify the intermediate patient to low or high risk of events, avoiding or eventually even intensifying the need for lipid-lowering therapy in this population.[3,4,6,7]

Thus, it is important to evaluate the therapeutic effectiveness and cost-effectiveness of this tool in comparison to other mechanisms of risk stratification of the population, with the objective of guiding clinical practice, as well as strategically directing health efforts and resources.

Mailing Address: Marcio Sommer Bittencourt •
Centro de Pesquisa Clínica e Epidemiológica - Hospital Universitário/USP – Av. Prof Lineu Prestes, 2565. Postal Code 05508-000, Butantã, São Paulo, SP – Brazil
E-mail: msbittencourt@mail.harvard.edu
Manuscript received April 27, 2021, revised manuscript July 09, 2021, accepted September 01, 2021

DOI: https://doi.org/10.36660/abc.20210347

Several cost-effectiveness studies have compared the use of CAC to therapy guided by risk scores or other classification methods.[5,8–11] Among them, Nasir et al. studied the cost-effectiveness of using CAC and compared it with stratification guided only by the risk score for cardiovascular events. This analysis used data and expected costs in the United States and was based on population data from the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort composed of 6,814 participants from different study centers in the country.[12]

Here, we used the aforementioned study as a reference, with the same population base mentioned, adapting the costs to the Brazilian reality, to determine the reproducibility of the method in Brazil.

Methods

In this analysis, the methods were replicated from the article published by Nasir et al., using a microsimulation model (TreeAge Pro version 2016 — Williamstown, MA, USA). The model simulates the clinical and economic consequences on the basis of atherosclerotic cardiovascular disease, in the context of primary prevention in patients with moderate cardiovascular risk. The strategies compared in this analysis are (Figure 1) explained below.

Strategy 1 (conventional): patients did not undergo CAC and were submitted to pharmacological therapy with moderate-intensity statin.

Strategy 2 (CAC: The CAC was determined in patients, and treatment was guided by the outcome. Subjects with CAC 1–100 underwent moderate-intensity statin treatment.

With a CAC value greater than 100, treatment with high-intensity statin was started. However, with CAC 0, drug treatment was not started.

The intensity of treatment with statins, classified as low-, moderate- and high-intensity, follows the criteria contained in the guidelines of the AHA and the Brazilian Society of Cardiology (SBC).[4,13] The other medications for continuous use, if indicated, were not modified after the risk reclassification.

The comparative analysis of the cost-effectiveness study was based on quality-adjusted life years (QALY) as a measure of benefit. QALY is a health outcome measure, which combines the population's quantity (mortality) and quality (morbidity) of life in a numerical index, being useful to compare and analyze the comparative result between strategies 1 and 2.

The population of this analysis, as mentioned, is based on the MESA study, and the population characteristics and distribution of the calcium score according to cardiovascular risk, based on the ACC/AHA scores, are shown in Tables 1 and 2.

In this investigation, patients were run through the model until they had a cardiovascular event or death from other causes, and the number of years of statin use or cardiovascular event was searched for each patient. The time horizon was updated with one-year cycles. All costs and results were discounted at 3% per year.

As a limitation of our study, we emphasize that the analysis of the assumptions was not performed, since in this case, the results are extensions of studies carried out previously.

Costs

As previously mentioned, the costs were adapted to the Brazilian reality. The values are shown in Table 3, in reais (R$) and, due to the high variability, they are represented in the table in three scales: median, minimum and maximum. Thus, our analysis was conducted with a wide range of assumptions.

It is important to note that the cost of CAC was added to the model only once, as the test is not repeated frequently. In the literature, the warrant time, that is, CAC guarantee time for individuals with CAC=0, is relatively long in addition to

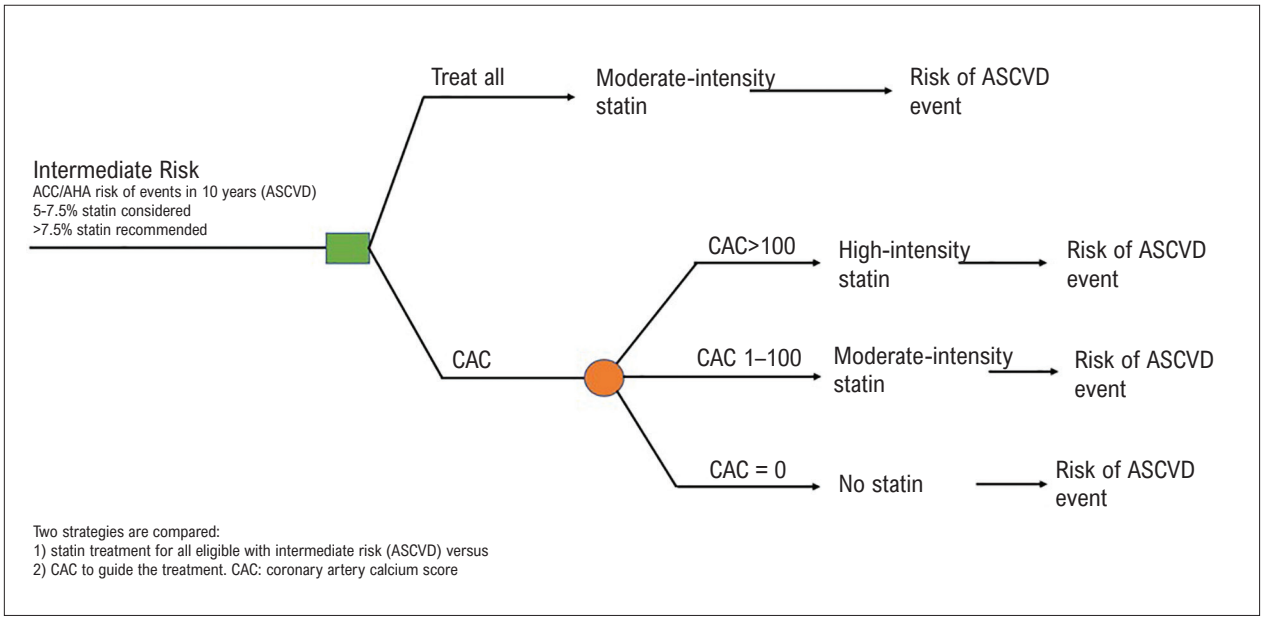


Figure 1 – *Strategies for risk stratification in intermediate-risk patients.*

Table 1 – Characteristics and distribution of coronary artery calcium score in the Multi-Ethnic Study of Atherosclerosis population based on cardiovascular risk categories

	Statin recommended (n=2,377)	Statin considered (n=538)
Age (years)	64.7 ± 3	58.4 ± 6.5
Male	1,434 (60)	299 (51)
Ethnicity		
While	795 (33)	220 (37)
Black	791 (33)	180 (31)
Hispanic	534 (23)	124 (21)
Asian	527 (11)	65 (11)
Diabetes	472 (20)	0 (0)
Hypertension	1.439 (61)	193 (33)
Smoker		
Never	1,023 (43)	280 (47)
Former	918 (39)	211 (36)
Current	436 (18)	98 (17)
Family history of CAD	948 (43)	237 (43)
BMI (kg/m2)	28.7± 5.3	38.5 ± 5.4
Total cholesterol (mg/dl)	201.5 ± 34.8	199.8 ± 30.6
LDL-C (mg/dl)	126.4 ± 31.2	124.6 ± 26.4
HDL-C (mg/dl)	48.5 ± 13.8	49.9 ± 13.9
Triglycerides	132.8 ± 67	126.4 ± 64.4

Values given as mean ± SD or n(%). BMI: body mass index; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

Table 2 – Distribution of coronary artery calcium scores according to American College of Cardiology and American Heart Association guidelines

Statin recommended	**2,377**
CAC 0	878 (33.0)
CAC 1–100	714 (24/1)
CAC >100	685 (23.1)
Statin considered	**598**
CAC 0	338 (11.4)
CAC 1–100	184 (6.2)
CAC >100	67 (2.3)
Total	2,966 (100)

Values are n or n (%). CAC: coronary artery calcium score.

being individualized, taking into account several aspects such as age, sex and the presence of risk factors, including diabetes. Therefore, in case of a zero calcium score, the indication of its repetition is variable and may be indicated at intervals of three to seven years.[14]

The rest of the clinical parameters, including probabilistic multiparameter sensitivity analyses, were used as described in the previous publication.

Results

When comparing the cost-effectiveness of using CAC in the cardiovascular stratification of primary prevention of individuals with moderate cardiovascular risk between strategies 1 and 2, we observed that when considering the median cost of all statins and the CAC, there was a statistically significant reduction of R$ 672.00 in accumulated costs in favor of the group in which CAC was determined (Table 4 – base case). In the same way, when

Table 3 – Brazilian costs

Variable (TreeAge Pro version 2016 – Williamstown, MA, USA)	Median (R$)	Min (R$)	Max (R$)	Source
CAC examination	418	300	713	1
Statin (moderate-intensity), annual cost	276.96	210.96	804	2
Statin (high-intensity), annual cost	435.84	324.60	725.64	3
Statin (all intensities, median), annual cost	356.40	267.78	764.82	4
Fatal infarction	9,816.80	7,853.44	11,780.16	5
Nonfatal myocardial infarction, first year	28,048	22,438.40	33,657.60	6
Nonfatal infarction, other years	4,207.20	3,365.76	5,048.64	7
Cardiac arrest resuscitated	42,072	33,657.60	50,486.40	8
Fatal CVA	12,761.84	10,209.47	15,314.20	9
Nonfatal CVA, first year	56,096	44,876.80	67,315.20	10
Nonfatal CVA, other years	5,890.08	4,712.06	7,068.09	11
Mild complications of statins	650	520	780	12
Major complications of statins	19,500	15,600	23,400	13
Follow-up investigation for non-cardiac findings (repeat imaging)	240	200	340	14
Clinical follow-up and laboratory tests (CAC review, lipid panel, liver panel)	80	65	130	15

CAC: coronary artery calcium score.

Table 4 – Parameters for the microsimulation model that compared strategies for statin therapy in individuals at intermediate risk for an ASCVD event

	CAC	Statin cost	Total cost per guidelines	CAC — Total cost	Cost difference	Guidelines — QALY	CAC — QALY	QALY Difference	Conclusion
Base case	R$ 418.00	R$ 356.00	R$ 6.160,00 (95%CI: 5,587–6,757)	R$ 5.488,00 (95%CI: 4,900–6,113)	-R$ 672	11,849 (95%CI: 10,834–12,829)	11,859 (95%CI: 10,859–12,838)	0.01	CAC dominates
Case with moderate-intensity statins	R$ 418.00	R$ 276.00	R$ 5.492,00 (95%CI: 2,035–10,651)	R$ 5.069,00 (95%CI: 743–10,730)	-R$ 423	11,849 (95%CI: 10,834–12,829)	11,859 (95%CI: 10,859–12,838)	0.01	CAC dominates

CAC: coronary artery calcium score; CI: confidence interval.

the cost of the statin was reduced to the median of moderate-intensity statins, the accumulated cost difference of R$ 423.00 remained, also favorable to the performance of the CAC. In another analysis, we observed that in addition to the financial benefit, there was a greater QALY survival, which confirmed the cost-effectiveness of the method in relation to the conventional strategy based on the guidelines.

Considering the multiple variables presented, 10,000 Monte Carlo simulations were also performed to illustrate the probabilistic sensitivity analysis of the multiple parameters included in the model (Figure 2). The graph in question analyzed the use of the conventional strategy, that is, the non-use of CAC in stratification, through an incremental gain of QALY on the X axis and the incremental cost ($ — in local currency of reais) on the Y axis. Each point on the graph represents a cross between the 10,000 possible simulations. Therefore, it is possible to infer that using the conventional strategy of stratification in these individuals, more than 95% of the combinations were associated with an incremental gain in cost without an incremental gain in QALY; that is, they were favorable to the use of CAC. Thus, there was a financial benefit when comparing the conventional strategy to the strategy that used CAC. However, when analyzing QALY, there was a greater dispersion of the simulations, which did not show a clear difference between the strategies used in the sensitivity analysis, despite a slight tendency to favor the group that involved CAC.

Discussion

Therefore, based on the results of this analysis, adjusted for Brazilian costs, we have data that are favorable to the use of strategy 2, that is, the use of CAC to support cardiovascular stratification and statin indication, with better cost-effectiveness. compared to strategy 1 (conservative).

When comparing the cost-effectiveness of using the CAC as a tool to aid in risk stratification in patients undergoing primary prevention and moderate risk of cardiovascular events, we

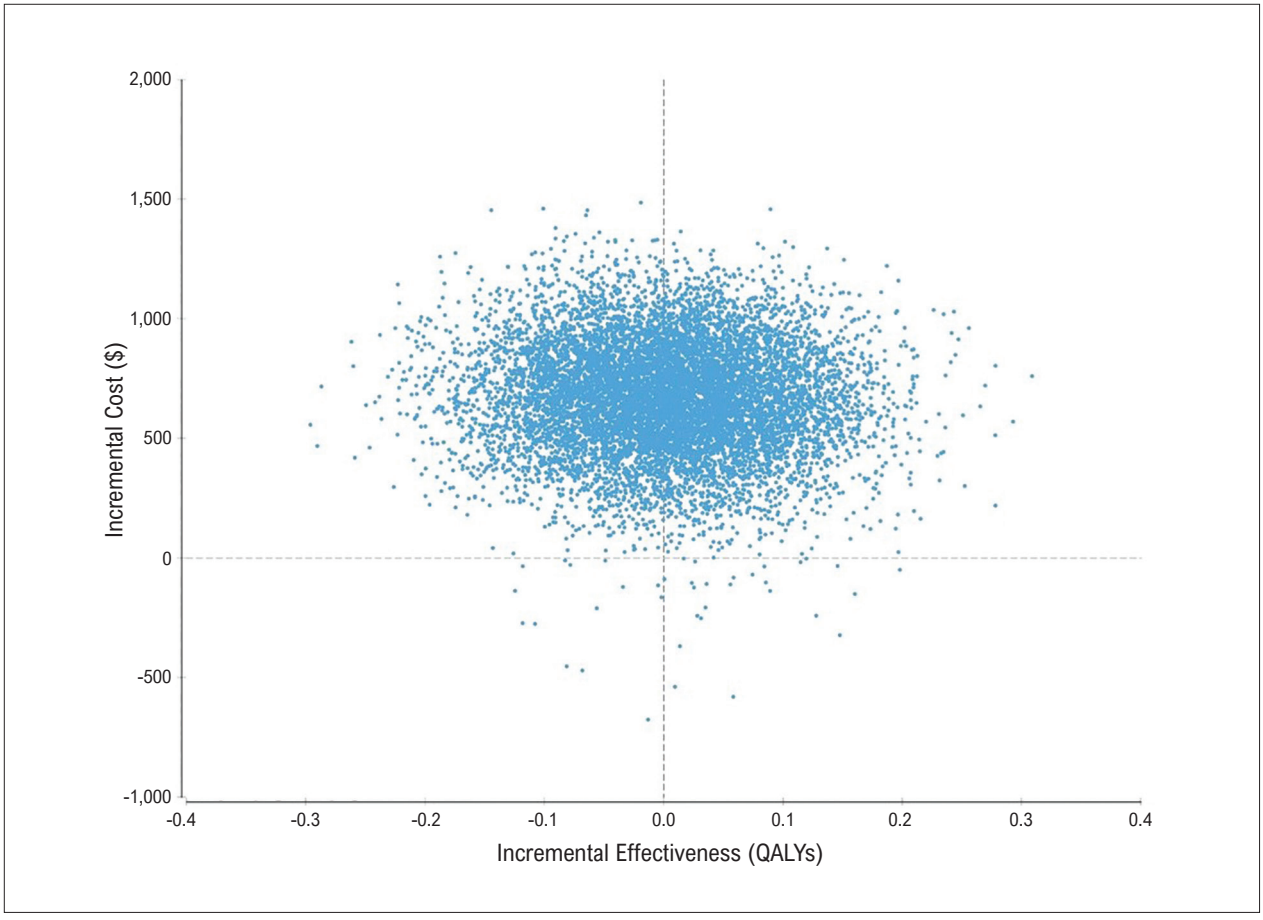


Figure 2 – *Monte Carlo simulations with 10,000 multivariate analyses.*

understand its real benefits and its applicability in clinical practice. The factors that support this analysis are: 1) the reduction of the incremental cost of each strategy; and 2) the increase in QALY, which corresponds, in number, to the benefit incorporated into the individual's quality of life.

The results obtained in this study are in agreement with the literature, even after adjusting the costs to the Brazilian reality. Thus, stratifying individuals at moderate risk for cardiovascular events with CAC and on the basis of the results obtained, deciding whether or not to use a statin proves to be advantageous compared to the conservative strategy.

Thus, the number of individuals eligible for drug treatment is limited and consequently the possibility of adverse drug-related effects. At the same time, treatment of the individual is initiated with real benefit from its use, and therefore, cardiovascular events associated with atherosclerosis can be prevented. Therefore, the cost-effectiveness of the strategy that includes the use of CAC in the stratification of these individuals is evident, as an extremely important tool when implemented on a large scale.

Author Contributions

Conception and design of the research: Valério RS, Generoso G, Bittencourt MS; Acquisition of data: Nasir K, Hong JC, Bittencourt MS; Analysis and interpretation of the data: Valério RS, Generoso G, Fernandes JL, Nasir K, Hong JC, Bittencourt MS; Statistical analysis: Valério RS, Generoso G, Nasir K, Hong JC; Writing of the manuscript: Valério RS, Generoso G, Bittencourt MS; Critical revision of the manuscript for intellectual contente: Generoso G, Fernandes JL, Bittencourt MS.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

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. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, Williams K, Neely B, Sniderman AD, et al. Application of New Cholesterol Guidelines to a Population-Based Sample. N Engl J Med. 2014;370(15):1422-31. doi: 10.1056/NEJMoa1315665.
2. Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934. doi: 10.1016/j.jacc.2013.11.002.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177-232. doi: 10.1016/j.jacc.2019.03.010.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-143. doi: 10.1161/CIR.0000000000000625.
5. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66(15):1657-68. doi: 10.1016/j.jacc.2015.07.066.
6. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis: The Heinz Nixdorf Recall Study. J Am Coll Cardiol. 2010;56(17):1397-406. doi: 10.1016/j.jacc.2010.06.030.
7. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. N Engl J Med. 2008;358(13):1336-45. doi: 10.1056/NEJMoa072100.
8. Ribeiro RA, Duncan BB, Ziegelmann PK, Stella SF, Vieira JL, Restelatto LM, et al. Cost-effectiveness of High, Moderate and Low-dose Statins in the Prevention of Vascular Events in the Brazilian Public Health System. Arq Bras Cardiol. 2015;104(1):32-44. doi: 10.5935/abc.20140173.
9. van Kempen BJ, Ferket BS, Steyerberg EW, Max W, Hunink MGM, Fleischmann KE. Comparing the Cost-effectiveness of Four Novel Risk Markers for Screening Asymptomatic Individuals to Prevent Cardiovascular Disease (CVD) in the US Population. Int J Cardiol. 2016;203:422-31. doi: 10.1016/j.ijcard.2015.10.171.
10. van Kempen BJ, Spronk S, Koller MT, Elias-Smale SE, Fleischmann KE, Ikram MA, et al. Comparative Effectiveness and Cost-effectiveness of Computed Tomography Screening for Coronary Artery Calcium in Asymptomatic Individuals. J Am Coll Cardiol. 2011;58(16):1690-701. doi: 10.1016/j.jacc.2011.05.056.
11. Hong JC, Blankstein R, Shaw LJ, Padula WV, Arrieta A, Fialkow JA, et al. Implications of Coronary Artery Calcium Testing for Treatment Decisions Among Statin Candidates According to the ACC/AHA Cholesterol Management Guidelines: A Cost-Effectiveness Analysis. JACC Cardiovasc Imaging. 2017;10(8):938-52. doi: 10.1016/j.jcmg.2017.04.014.
12. Bild DE, Bluemke DA, Burke GL, Detrano R, Roux AVD, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. Am J Epidemiol. 2002;156(9):871-81. doi: 10.1093/aje/kwf113.
13. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune A Neto, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl 1):1-76. doi: 10.5935/abc.20170121.
14. Dzaye O, Dardari ZA, Cainzos-Achirica M, Blankstein R, Agatston AS, Duebgen M, et al. Warranty Period of a Calcium Score of Zero: Comprehensive Analysis From MESA. JACC Cardiovasc Imaging. 2021;14(5):990-1002. doi: 10.1016/j.jcmg.2020.06.048.

Cost-Effectiveness of Using the Coronary Calcium Score to Guide Therapeutic Decisions in Primary Prevention in the Brazilian Population

Ilan Gottlieb[1]

Casa de Saúde São José,[1] *Rio de Janeiro, RJ – Brazil*

Short Editorial related to the article: Cost-Effectiveness of Using the Coronary Calcium Score in Guiding Therapeutic Decisions in Primary Prevention in the Brazilian Population

Cardiovascular diseases (CVD) statistics never fail to impress even the most hardened and experienced physician. One-third of deaths worldwide are still due to cardiovascular causes (85% of those are myocardial infarction and stroke), and 75% occur in mid-to-low income countries.[1,2] Half the people who died of myocardial infarction never had symptoms before the tragic event, and most never had the diagnosis of coronary artery disease.[3] Despite our best efforts, the prevalence of ischemic heart disease (IHD) has been steadily rising for the last 30 years worldwide due to population aging, but even if we standardize by age, the prevalence has been stable, and notwithstanding fallen. This fact highlights the importance of lifestyle changes that allow for a healthier heart and the need to focus on implementing existing cost-effective policies and interventions.[4]

Coronary calcification is almost always a marker of atherosclerosis. The coronary calcium score (CCS) is a number that quantifies coronary calcification as a surrogate for total coronary atherosclerotic burden. Even though calcification results from plaque healing, higher-risk plaques tend to have proportionately greater non-calcified components;[5] CCS has been proven to be a strong predictor of CVD and IHD events in multiple large, solid, population-based studies.[6]

Primary prevention is guided and titrated by CVD risk, i.e., patients with higher risk should have higher intensity treatment, and low-risk patients may require no treatment besides general healthcare counseling. CCS determines cardiovascular risk better than clinical assessment and clinical risk calculators because CVD has such diverse and complex pathophysiology, with so many different risk factors, that compiling all risk factors in a calculator is ineffective and inaccurate. Additionally, risk factors are so common that they fail to differentiate who will have an event and who will not. For instance, the prevalence of 1 major risk factor (aside from age) is very high among persons aged 40 years who develop IHD,[7] but it is also very high among those who do not develop IHD.[8] Instead of focusing on how to guess who has CVD, we should focus on the early diagnosis of preclinical CVD, and coronary calcium score is probably the best tool available, for it is accurate, relatively cheap, widely available, and cost-effective in multiple clinical scenarios and populations.[9]

This month's ABC brings a very important article that investigates the cost-effectiveness of CCS in Brazil.[10] Since scanning, medications and other healthcare costs vary worldwide, it is important to perform cost-effectiveness analysis locally to guide national healthcare policies better. The authors demonstrated that, among patients clinically classified as intermediate risk, who would be recommended or considered for moderate intensity statin treatment by current clinical guidelines, the introduction of CCS is cost-effective in all analyzed scenarios. Not only an increase in statin intensity would be recommended for the patient population with CCS>100 (25% of the cohort) who would otherwise be taking only moderate-intensity treatment, but perhaps more important is the fact that approximately 45% of the patient population would be withdrawn from medical therapy since they have CCS=0. The cost of the CCS scan is compensated by lowering event rates in CCS>100 and the savings from long-term statin suspension among those with CCS=0.

Some important features are missing from the analysis, since they did not show how they collected cost data and did not provide sensitivity analysis. Nevertheless, despite these shortcomings, their paper is valuable for population healthcare planning in Brazil. Together with other cost-effectiveness data that analyzed similar technologies,[11] their paper reinforces calcium score as a valuable tool to guide and titrate medical therapy and improve patient adherence to necessary behavioral changes.

Keywords

Cardiovascular Diseases/prevention and control; Myocardial Infarction; Stroke; Coronary Artery Disease; Atherosclerosis; Risk Factors; Plaque Atherosclerotic; Statins; Cost-Benefit Analysis.

Mailing Address: Ilan Gottlieb •
Departamento de Radiologia - Casa de Saúde São José - Rua Macedo Sobrinho, 21. Postal Code 22271-080, Humaitá, RJ - Brazil
E-mail: ilangottlieb@gmail.com

DOI: https://doi.org/10.36660/abc.20220293

References

1. World Health Organization (WHO). Home News.Fact Sheets.Detail. Cardiovascular Diseases(CVDs). [Internet]. [Acessado em 15 abril 2022] Disponível em: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Malta DC, Teixeira R, Oliveira GMM, Ribeiro ALP. Cardiovascular disease mortality according to the Brazilian Information System on Mortality and the the Global Burden of Disease Study estimates in Brazil,2000-2017. Arq Bras Cardiol.115(2):152-60. doi: 10.36660/abc.20190867.
3. Zipes DP, Wellens HJJ. Risk factors of Sudden Cardiac Death. Circulation.1998;98:2334-51.doi.org/10.1161/01.CIR.98.21.2334Circulation. 1998;98:2334–2351.
4. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors,1990-2019:update rom the GBD 2019 Study. J Am Coll Cardiol.2020;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
5. Abizaid A, Saad M, Addoumieh A, Ha LD, Elbadawi A,Mahmoud AN, et al.Coronary rtery calcium score and risk of cardiovascular events without established coronary artery disease:a systemic review and meta-analysis. Coron Artery Dis.2021;32(4):317-28. doi: 10.1097/MCA.000000000000097.
6. Hwang D, Kim HJ, Lee SP, Lim S, Koo BK, Kim YJ, et al.Topological data analysis of coronary plaques demonstrates the natural history of coronary atherosclerosis. JACC cardiovasc Imaging. 2021;14(7):1410-21. doi: 10.1016/j.jcmg.2020.11.009.
7. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR,Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003;290(7):891-7. doi: 10.1001/jama.290.7.891.
8. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. BMJ. 2002;324(7353:1570-6. doi: 10.1136/bmj.324.7353.1570.
9. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS,Blankstein R, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association Cholesterol Management Guidellines: MESA(Multi-Ethnic Study of Atherosclerosis) J Am Coll Cardiol.2015;66(15):1657-68. doi: 10.1016/j.jacc.2015.07.066.
10. 2021-0347
11. Bastos do Carmo P, Magliano CA, Rey HCV, Camargo GC, Trocado LFL, Gottlieb I. Cost-effectiveness analysis of CCTA in SUS, as compared to other non-invasive imaging modalities in suspected obstructive CAD. Arq Bras Cardiol. 2022;118(3):578-85. doi: 10.36660/abc.20201050.

LncRNAs are Involved in the Process of Atherosclerosis at Diverse Levels

Shiyi Liang,[1] Weicheng Xv,[1] Chijian Li,[1] Yuxiang Huang,[1] Ge Qian,[1] Yuxiang Yan,[2] Hequn Zou,[3] Yongqiang Li[4]

The Third Affiliated Hospital of Southern Medical University – Department of Nephrology,[1] Guangzhou – China
Capital Medical University – Department of Epidemiology and Biostatistics,[2] Beijing – China
South China Hospital of Shenzhen University, Department of Nephrology,[3] Beijing – China
The Third Affiliated Hospital of Southern Medical University – General Practice Department,[4] Guangzhou – Chin

Abstract

Atherosclerosis is the most common cause of cardiovascular disease globally, associated with a high incidence of clinical events. Accumulating evidence has elucidated that long non-coding RNAs (lncRNAs) as a novel class of transcripts with critical roles in the pathophysiological processes of atherosclerosis. In this review, we summarize the recent progress of lncRNAs in the development of atherosclerosis. We mainly describe the diverse regulatory mechanisms of lncRNAs at the transcriptional and post-transcriptional levels. This study may provide helpful insights about lncRNAs as therapeutic targets or biomarkers for atherosclerosis treatment.

Introduction

Cardiovascular diseases (CVDs) are regarded as a global health problem that accounts for 17.9 million deaths every year.[1] Atherosclerosis (AS), the principal driver of CVDs worldwide, is a lipid-driven chronic inflammatory process with endothelial dysfunction, foam cells formation and final plaque buildup.[2] This process is accompanied by cells proliferation, apoptosis, and the release of pro-inflammatory factors[3] (Figure 1). These can trigger plaque rupture and thrombosis formation, leading to acute clinical events, such as stroke and acute coronary syndrome.[4]

In the mammalian genome, the encoded protein RNAs are only < 3%.[5] That fraction of the coding gene makes, therefore, hard to explain the complex regulatory mechanism of the organism. In recent years, accumulating studies have revealed the important role of non-coding protein RNAs in the pathophysiological processes of various diseases.[6,7] According to the length, the non-coding RNAs (ncRNAs) can be divided into long non-coding RNA (lncRNA, >200 nucleotides) and small non-coding RNA (<200 nucleotides, such as miRNAs, piRNAs and siRNAs).[8] In many researches, some small ncRNAs' regulatory functions and biological effects have been demonstrated.[9-11] The function of many lncRNAs is unknown, but an increasing number of lncRNAs have been characterized.

The biosynthesis of lncRNA is similar to that of mRNA. LncRNAs are transcribed by RNA polymerase II but lack open reading frames, and they are in a lower expression than protein-coding genes.[8] LncRNAs are mainly located within the nucleus and cytoplasm.[12] In the cytoplasm, lncRNAs can bind with ribosomes[13] or originate from the mitochondrial genome.[14] Early reports show that many lncRNAs can't encode proteins because they lack open reading frames (ORFs) or contain few ORFs. But emerging evidence suggests that some lncRNAs contain small ORFs encoding small proteins or micropeptides, which are regarded as key regulators in various biological processes.[8,15,16] Studies demonstrate that lncRNAs play critical roles in the function of endothelial and vascular smooth muscle cells (VSMC), macrophage activation, lipid metabolism and inflammatory response.[17,18] In this review, we mainly discuss the regulation of lncRNAs are involved in the pathophysiologic process of atherosclerosis at transcriptional and post-transcriptional levels.

The pathogenesis of atherosclerosis is accompanied by cell dysfunction, such as proliferation, apoptosis, and migration. The result is foam cells formation and plaque buildup.

The classifications and regulatory mechanism of LncRNAs

According to the correlation between the genomic location and protein-coding genes, lncRNAs can be divided into (1) intergenic lncRNAs (lincRNAs) that express protein-coding genes as an independent unit. (2) intronic lncRNAs that derive from the introns of protein-coding genes. (3) antisense lncRNAs transcribed from the opposite direction of protein-coding genes. (4) sense lncRNAs that overlap with exons of protein-coding genes on the same strand. (5) enhancers that originate in the enhancer of protein-coding genes. (6) bidirectional lncRNAs that are transcribed from the divergent bidirectional promoters.[19,20] The criteria of classification also include the various functions in local gene regulation: cis- (regulating proximal genes expression) and trans- (regulating distant genes expression).[21] Besides, lncRNAs transcripts can also be categorized into linear or circular.[22]

The mechanism of lncRNAs functioning has not been completely elucidated, but it can be classified roughly into several groups: 1. transcriptional regulation is embodied in transcriptional interference, chromatin remodeling and

Keywords

LnRNAs; Emzymes; Enzyme Inhibitors; Endothelial Cells; Lipoproteins, VLDL; RNA Interference

Mailing Address: Yongqiang Li •
The Third Affiliated Hospital of Southern Medical University – GuangDong GuangZhou 510000 – China
E-mail: liyongqiang851@163.com
Manuscrpt received August 15, 2020, revised manuscript April 14, 2021, accepted June 09, 2021

DOI: https://doi.org/10.36660/abc.20201383

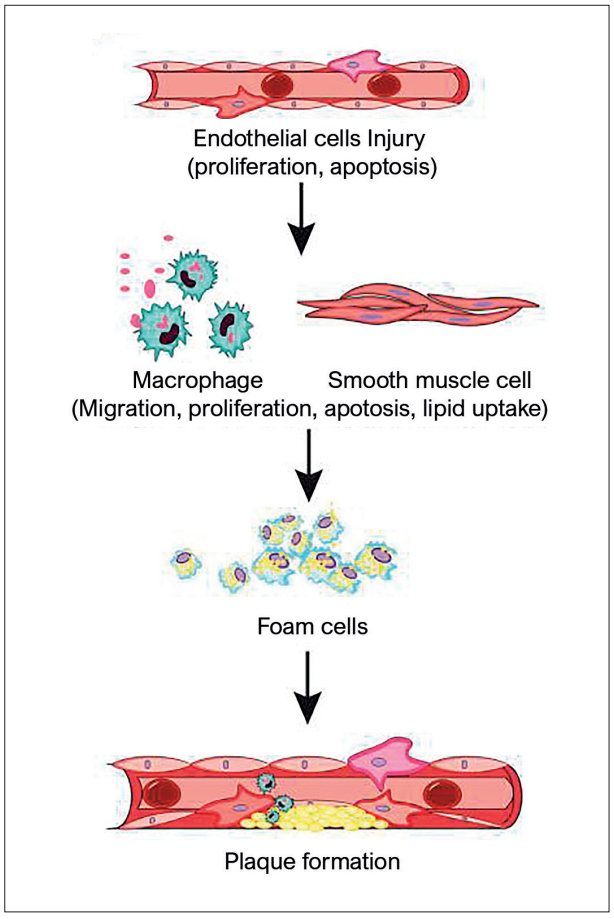


Figure 1 – *The pathogenesis of atherosclerosis.*

promotion of transcription; 2. post-transcriptional levels manifest in mRNAs splicing regulation translational control and even as sponges for miRNAs; 3. Others contain protein localization, telomere replication, and RNA interference, etc. Furthermore, their targeting mechanisms for regulating gene expression are summarized as the following: signals, decoys, guides and scaffolds.[22,23]

Transcriptional regulation

LncRNAs can exert their transcriptional regulation through cis-acting and trans-acting mechanisms. (Table 1) LncRNAs regulate neighboring genes expression in cis via transcriptional interference or chromatin remodeling.[24] Trans-acting lncRNAs can interact with RNA polymerases and transcription elongation factors or serve as a scaffold for chromatin modification complexes to regulate the distant genes.[24,25]

The Wellcome Trust Case Control Consortium (WTCCC) study and the genome-wide association studies found that a region on chromosome 9p21 (Chr9p21) was strongly associated with coronary artery disease strongly.[26] The region is adjacent to a lincRNA named antisense non-coding RNA in the INK4 locus (ANRIL, also known as CDKN2BAS).[27] Holdt LM et al.[28] had revealed that ANRIL expression was correlated with atherosclerosis severity by affecting mRNAs' transcription, and the ANRIL was also detected in atherosclerotic plaques in their study.[28]

Two protein-coding genes, cyclin-dependent kinase inhibitors(CDKN2A, CDKN2B) and the alternative reading frame (ARF) on chromosome 9p21, are tied to ANRIL inextricably, which are tumor suppressors.[27] The polycomb repressive complex-1 (PRC-1) and polycomb repressive complex-2 (PRC-2) are two kinds of polycomb group proteins involved in maintaining chromatin state.[29] Their subunits CBX7 and SUZ12 bind ANRIL separately to silence CDKN2A/B locus through H3 lysine27 (K27H3) trimethylation.[30,31] Yet, the repression of CDKN2A/B may be related to cell proliferation and apoptosis in the atherosclerosis process.[32]

Holdt et al.[28] found that ANRIL was in a position to exert a regulatory function in distant gene expression in trans. Alu element, marking the promoter of the ANRIL trans-regulated genes, is decisive for linear ANRIL trans-regulation. PcG proteins, triggered by binding with ANRIL, were highly abundant downstream of the Alu motifs.[33] The recruitment of PcG proteins could regulate the expression of the target genes (TSC22D3、COL3A1) and attenuate ANRIL-mediated pro-atherogenic functions, such as cell adhesion, proliferation, and apoptosis.[3,33] Furthermore, ANRIL plays a pivotal role in the inflammatory processes through TNF-α/NF-kB-ANRIL/YY1-IL6/8 pathway. PRC-associated proteins Yin Yang 1 (YY1), a transcriptional factor, form a functional complex with ANRIL.[33] ANRIL-YYI complex binds to IL6/8 promoter loci and stimulates their recruitment in the TNF-α/NF-κB signaling, leading to vascular inflammation.[34]

MALAT1, located on chromosome 11q13, is first described as lncRNA associated with metastasis of lung tumors.[35] MALAT1 expression is downregulated in atherosclerotic plaques in comparison to non-atherosclerotic arteries.[36] Michalik et al.[37] found that silencing of MALAT1 inhibited a switch from a promigratory to a proliferative state of the endothelial cells, resulting in the reduction of vessel growth.[37] And MALAT1 also acts as a molecular scaffold to interact with unmethylated Polycomb 2 (Pc2); the expression of Pc2 promotes E2F1 SUMOylation and regulates histone modifications to increase cell proliferation.[38]

In a control experiment, Gast et al.[39] observed that the serum levels of TNF, IL-6, and IFN-γ were increased in the MALAT1-deficient ApoE-/- mice, causing immune dysfunction and aggravated atherosclerosis.[39] MALAT1 may be involved in the LPS-induced inflammatory response via LPS/TLR4/NF-κB signaling. MALAT1 interacts with NF-κB subunits p65/p50, inhibiting p65/p50 binding to target promoters such as TNF-α and IL-6, then attenuating an excessive inflammation.[40]

In lipid metabolism, MALAT1 may be upregulated in macrophages during ox-LDL stimulation.[41] CD36, a class B scavenger receptor, is required for lipid uptake of ox-LDL.[42] MALAT1 overexpression induces the recruitment of β-catenin on the CD36 promoter to enhance CD36

Table 1 – The role of lncRNAs in the pathologic process of atherosclerosis

	lncRNAs	Mechanism	Effect		References
Cells function			**Proliferation**	**Apoptosis**	
Endothelial cells (ECs)	MALAT1	MALAT1-Pc2 (CBX4)-E2F1	+		38
	GAS5	GAS5 - ceRNA (miR-21)	-	+	75
	HOTTIP	TNF-α/PDGFBB-HOTTIP-β-catenin	+		47
	MALAT1	ceRNA (miR-22-3p)		-	60
	TUG1	ceRNA (miR-26a)		+	71
Macrophages、Smooth muscular cells	ANRIL	Bind with CBX7 and SUZ12	+	-	32
	NEAT1	NEAT1-WDR5-SM-specific genes	+		44
	LincRNA-p21	lincRNA-p21-MDM2/ p300-p53	+	-	45
	HAS2	remodeling chromatin structure	+		49,50
	RP11-714G18.1	upregulate LRP2BP expression		-	53
	H19	ceRNA (miR-148b)	+	-	66
	MIAT	ceRNA (miR-181b)	+	-	69
	lncRNAs	**Mechanism**	**Effect**		**References**
Lipid accumulation	MALAT1	MALAT1-CD36-lipid uptake	+		45
	NEAT1	NEAT1-CD36-lipid uptake	-		41
	MeXis	LXR-MeXis-Abca1	-		46
	H19	ceRNA (miR-130b)	-		65
	TUG1	ceRNA (miR-133a)	+		72
	lncRNAs	**Mechanism**	**Effect**		**References**
Inflammatory response	ANRIL	TNF-α/NF-kB-ANRIL/YY1-IL6/8	+		34
	MALAT1	MALAT1-p65/p50-TNF-α and IL-6	-		40
	MALAT1	ceRNA (miR-503 or miR-155)	-		61,62
	H19	ceRNA (miR-130b)	-		
	NEAT1	ceRNA (miR-342-3p)	+		70
	TUG1	ceRNA (miR-133a)	+		72

(+) represents prompt or increase, and (-) represents prevent or decrease.

transcription, promoting lipid uptake in macrophages and accelerating the foam cell formation in atherosclerotic plaques.[41]

NEAT1, an adjacent transcript of MALAT1, can enhance the paraspeckles formation in oxLDL-induced macrophage, which suppresses lipid uptake by binding CD36 mRNA to inhibit CD36 expression and stimulates inflammatory response via phosphorylating p65 to promote TNF-α secretion.[43] Besides, Ahmed ASI et al.[44] found that NEAT1 expression was upregulated in vascular smooth muscle cells (VSMCs) after vascular injury in vivo and in vitro, leading to an inactive chromatin state in SM-specific genes through binding with the chromatin modifier WDR5. The repression of SM-specific genes expression switched VSMCs to proliferative phenotype, promoting VSMCs proliferation and migration and thereby neointima formation.[44]

The expression of lincRNA-p21 was downregulated in the atherosclerotic plaques. LincRNA-p21 decreased MDM2/p53 interaction and increased p300/p53 interaction to facilitate the transcriptional activity of p53, leading to the repression of neointimal formation, the inhibition of cell proliferation and the enhancement of apoptosis in VSMCs and mononuclear macrophage cells in vitro and vivo.[45]

Also, some other lncRNAs are involved in the AS process at the transcriptional level, but the descriptions are limited. The overexpression of lncRNA-MeXis in macrophages may facilitate macrophage reversing cholesterol transport via the LXR-MeXis-Abca1 axis, suggesting that lncRNA-MeXis plays a protective role in the development of atherosclerosis.[46] Ectopic expression of lncRNA-HOTTIP, induced by TNF-α or platelet-derived growth factor (PDGFBB), increases proliferative markers cyclin D1 and PCNA expression through the Wnt/β-catenin pathway, subsequently

prompting the endothelial cell proliferation and migration.[47] The O-GlcNAcylation modulates HAS2-AS1 promoter activation, HAS2-AS1 natural antisense transcript can regulate HAS2 transcription in cis through remodeling chromatin structure,[48] HAS2 may be related to VSMCs proliferation,[49,50] macrophages recruitment,[50] VSMCs migration and neointima formation,[51,52] inflammatory response.[50,52] The expression of lncRNA RP11-714G18.1 in atherosclerotic plaque is low. Still, it can upregulate nearby gene LRP2BP expression to impair cell migration, suppress the adhesion of ECs to monocytes, reduce the neoangiogenesis, decrease VSMCs apoptosis and promote nitric oxide production. Furthermore, the serum LRP2BP was positively related to high-density lipoprotein cholesterol.[53]

HOXC-AS1 may suppress the cholesterol accumulation in macrophages via promoting HOXC6 expression at mRNA levels.[54] LEENE can improve endothelial function by enhancing eNOS initial RNA transcription.[55] Lethe Lin et al.56 acts as a decoy lncRNA to interact with the NF-κB subunit RelA and inhibits RelA binding to target genes DNA, such as IL6, SOD2, IL8, attenuating the inflammatory response.[56] LncRNA-TSLP induces HOTAIR transcription through PI3K/AKT-IRF1 pathway, promoting endothelial cell proliferation and migration in atherosclerosis.[57] Besides, ox-LDL induced TSLP may bind to dendritic cells (DCs) to activate the Th17 inflammation,[58] which is related to the severity and progression of AS.[59]

Post-transcriptional regulation

LncRNAs mainly act as competing endogenous RNAs (ceRNAs) or miRNAs "sponge" interacting with miRNAs in the process of atherosclerosis at the post-transcriptional regulation level. (Table 1) Furthermore, they are also involved in translational control, splicing regulation and small interfering RNA (siRNA) mechanism.[24]

MALAT1 acts as ceRNA in ox-LDL-induced cells injury and plays a protective role in atherosclerosis disease. MALAT1 could compete with miR-22-3p for endogenous RNA and upregulate the target genes CXCR2 and AKT of miR-22-3p to inhibit endothelial cells apoptosis and promote the ECs migration and angiogenesis.[60] Cremer S et al.[61] found that MALAT1 "sponged" miR-503 to reduce the release of pro-inflammatory cytokines, attenuating plaque inflammation.[61] Besides, the suppressor of cytokine signaling 1 (SOCS1) is the target protein of miR-155 that negatively regulates Janus activated kinase (JAK)-signal transducer and activator of transcription (STAT) signaling. MALAT1 could downregulate miR-155 and increase the expression of SOCS1 to alleviate the inflammation and apoptosis in atherosclerosis.[62] Thus, MALAT1 may play a protective role via interacting with miRNAs in the pathogenesis of atherosclerosis.

The expression of lncRNA H19 was up-regulated in ox-LDL treated macrophages. MiR-130b regulates the inflammatory response by decreasing the translational levels of TNF-α, Sp1, NF-κB with lipid stimulation[63] and inhibits adipogenesis by targeting PPAR-g.[64] Silencing of H19 significantly increases the expression of miR-130b, which ameliorates inflammation and lipid synthesis in ox-LDL-treated Raw264.7 cells.[65] H19 can accelerate proliferation and impede apoptosis in ox-LDL-stimulated VSMCs by directly suppressing miR-148b expression and enhancing miR-148b target gene WNT1 expression.[66]

LncRNA-MIAT may be involved in atherosclerotic plaque progression. MIAT is mainly expressed in the macrophages of advanced atherosclerotic plaques. With the ox-LDL treatment, the expression of MIAT is upregulated. Anti-phagocytic molecule CD47, a target gene of miR-149-5p, is related to apoptotic cell clearance and necrotic cores.[67] MIAT interferes with miR-149-5p pathways to increase the CD47 level in macrophages, promoting plaque vulnerability.[68] The formation of the MIAT/miR-181b/STAT3 axis plays a critical role in ox-LDL induced human aorta vascular smooth muscle cells (HA-VSMCs) and human mononuclear cells (U937). MIAT up-regulates signal transducer and activator of transcription 3 (STAT3) protein level through sequestering miR-181b, subsequently promoting proliferation, facilitating cell cycle arrest and inhibiting apoptosis in HA-VSMCs and U937 cells.[69]

NEAT1 was also involved in the atherosclerotic process as ceRNA except for remodeling chromatin at the transcriptional level. Lei Wang et al.[70] found that NEAT1 was significantly upregulated in the presence of ox-LDL and served as a sponge to repress the expression of miR-342-3p, increasing the serum level of IL-6, IL-1β, COX-2, and total cholesterol leading to accelerating inflammation process and the formation of foam cells.[70] LncRNA-TUG1 could down-regulate the expression of miR-26a and increase the mRNA and protein level of TRPC6 to facilitate the endothelial cells apoptosis.[71] Lei Zhang et al.[72] revealed that TUG1 sponged miR-133a and up-regulated fibroblast growth factor 1 (FGF1) expression, resulting in increased hyperlipidemia and excessive inflammatory response aggravated atherosclerotic lesion.[72]

In addition, more and more studies have demonstrated that plenty of atherosclerosis-related lncRNAs plays a crucial role in the pathogenesis of AS by interacting with miRNAs at the post-transcriptional level. LINC00305 acts as an endogenous sponge for miR-136 and inhibits miR-136 expression to suppress the vascular endothelial cells proliferation and enhance apoptosis.[73] LincRNA-p21 functions as ceRNA to promote ECs apoptosis and induces cell cycle progression by targeting the miR-130b.[74] LncRNA-GAS5 negatively regulates miR-21 expression to enhance programmed cell death 4 (PDCD4) expression, suppressing ECs proliferation and triggering ECs apoptosis.[75]

Others

LncRNAs may function through protein localization, telomere replication and RNA interference in some processes,[24] such as localizing RNP particles in legume plants, extending telomere during DNA replication in eukaryote,[76] reducing Dicer-generated siRNA and affecting the expression of Dicer-regulated genes.[77] While their underlying molecular mechanism related to the development of atherosclerosis remains unknown.

Conclusion and Perspective

Taken together, lncRNAs can be involved in several processes associated with atherosclerosis, including inflammatory response, lipid metabolism and cells function. They regulate the pathology of atherosclerosis at epigenetic, transcriptional and post-transcriptional levels, such as chromatin remodeling, promotion of transcription and competing endogenous for miRNAs. Therefore, lncRNAs may serve as promising novel diagnostic markers and therapeutic targets for atherosclerosis and vascular diseases. Moreover, all of these possible roles in physiopathologic processes have opened venues to decipher the function and mechanism of lncRNAs in cardiovascular diseases and other diseases, such as tumors, renal diseases and nervous diseases.

Author Contributions

Conception and design of the research: Liang S, Li U; Acquisition of data: Liang S, Xv W, Li C, Huang Y, Qian G; Obtaining financing: Xv W, Li U; Writing of the manuscript: Liang S; Critical revision of the manuscript for intellectual contente: Yan Y, Zou H, Li U.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by the "Thirteenth Five-Year Plan" of Guangdong Province Educational Science (No. 2020GXJK441), the Project of Traditional Chinese Medicine Bureau of Guangdong Province (CN) (No. 20191228 to ZY), the Science and Technology Planning Project of Tianhe District, Guangzhou City (No.201704KW011), the Young Plants Project, Hospital scientific research fund of the People's Hospital of Huadu District, Guangzhou (NO.2020C03)

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. Skuratovskaia D, Vulf M, Komar A, Kirienkova E, Litvinova L. Promising Directions in Atherosclerosis Treatment Based on Epigenetic Regulation Using MicroRNAs and Long Noncoding RNAs. Biomolecules. 2019;9(6):226. doi: 10.3390/biom9060226.
2. Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. J Cell Biol. 2015;1209(1):13-22. doi: 10.1083/jcb.201412052.
3. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801): 233-41. doi: 10.1038/35025203.
4. Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu, Y et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health. 2020;8(5):e721-9. doi: 10.1038/35025203.
5. Uchida S. Dimmeler Long non-coding RNAs in cardiovascular diseases. Circulat Res. 2015;116(4):737-50. doi: 10.1161/CIRCRESAHA.116.302521.
6. Shigematsu M, Honda S, Kirino Y. Transfer RNA as a source of small functional RNA. J Mol Biol Mol Imaging.2014;1(2):8. PMID: 26389128
7. Guttman J, Rinn L. Modular regulatory principles of large non-coding RNAs. Nature. 2012; 482(7385):339-46. doi: 10.1038/nature10887.
8. Gusic M, Prokisch H. ncRNAs: New Players in Mitochondrial Health and Disease? Front Genet.2020;11:95. doi: 10.3389/fgene.2020.00095
9. Rottiers V, Näär AM. MicroRNAs in metabolism and metabolic disorders. Nat Ver. Mol Cell Biol. 2012;13(4):239-50. doi: 10.1038/nrm3313.
10. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetzsch J, et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. Eur Heart J.2021;42(2):178-88. doi: 10.1093/eurheartj/ehaa898.
11. Alexander-Bryant AA, Zhang H, Attaway CC, Pugh W, Eggart L, Sansevere RM, et al. Dual peptide-mediated targeted delivery of bioactive siRNAs to oral cancer cells in vivo. Oral Oncol. 2017;72: 123-31. doi: 10.1016/j.oraloncology.2017.07.004
12. Carlevaro-Fita J, Johnson R. Global Positioning System: Understanding Long Noncoding RNAs through Subcellular Localization. Mol Cell. 2019;79(5):869-83. doi: 10.1016/j.molcel.2019.02.008.
13. Quinn J J, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nature reviews. Genetics. 2016; 117(1):47-62. doi: 10.1038/nrg.2015.10.
14. Rackham O, Shearwood AM, Mercer TR, Davies SM, Mattick JS, Filipovska A. Long non-coding RNAs are generated from the mitochondrial genome and regulated by nuclear-encoded proteins. RNA (New York NY). 2011;17(12):2085-93. doi: 10.1261/rna.029405.111
15. Hartford CCR, Lal A. When Long Noncoding Becomes Protein Coding. Mol Cell Biol. 2020;40(6):e519-28. doi: 10.1128/MCB.00528-19.
16. van Heesch S, Witte F, Schneider-Lunitz V, Schulz JF, E. Adami E, Faber AB, et al. The Translational Landscape of the Human Heart. Cell. 2019;178(1):242-60. doi: 10.1016/j.cell.2019.05.010.
17. Liu Y, Zheng L, Wang Q, Hu YW. Emerging roles and mechanisms of long non-coding RNAs in atherosclerosis. Int J Cardiol. 2017;228:570-82. 570-82. doi: 10.1016/j.ijcard.2016.11.182.
18. Pierce JB, Feinberg MW. Long Noncoding RNAs in Atherosclerosis and Vascular Injury: Pathobiology, Biomarkers, and Targets for Therapy. Arterioscler Thromb Vasc Biol. 2020;40(9):2002-17. doi: 10.1161/ATVBAHA.120.314222.
19. Yu B, Wang S. Angio-LncRs: LncRNAs that regulate angiogenesis and vascular disease. Theranostics. 2018;8(13):3654-75. PMID: 30026873
20. Lin J, Jiang Z, Liu C, Zhou D, Song J, Liao Y., et al. Emerging Roles of Long Non-Coding RNAs in Renal Fibrosis. Life (Basel, Switzerland). 2020; 10(8):131. doi: 10.3390/life10080131.
21. Kopp F, Mendell JT. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell. 2018;172(3):393-407.
22. Holdt LM, Kohlmaier A, Teupser D. Long Noncoding RNAs of the Arterial Wall as Therapeutic Agents and Targets in Atherosclerosis. Thromb Haemost. 2019;119(8):1222-36. doi: 10.3390/life10080131.

23. Hung J, Miscianinov V, Sluimer JC, Newby DE, Baker AH. Targeting Non-coding RNA in Vascular Biology and Disease. Front Physiol. 2018;9: 1655. doi: 10.3389/fphys.2018.01655

24. Ma L, Bajic VB,Z. Zhang Z. On the classification of long non-coding RNAs. RNA Biol. 2013;10(6):925-33. doi: 10.4161/rna.24604.

25. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, et al. Long non-coding RNA as modular scaffold of histone modification complexes. Science (New York) 2010;329(5992):689-93. doi: 10.1126/science.1192002.

26. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al. Genomewide association analysis of coronary artery disease. The N Engl J Med.2007;357(5):443-53. doi: 10.1056/NEJMoa072366

27. Pasmant E, Sabbagh A, Vidaud M, Bièche I. ANRIL, a long, non-coding RNA, is an unexpected major hotspot in GWAS. FASEB. 2011;25(2):444-8. doi: 10.1096/fj.10-172452.

28. Holdt LM, Beutner F, Scholz M, Gielen S, Gäbel G, Bergert H, et al. ANRIL expression is associated with atherosclerosis risk at chromosome 9p21. Arterioscler Thromb Vasc Biol. 2010;30(3):620-7. doi: 10.1161/ATVBAHA.109.196832.

29. Iwama A. Polycomb repressive complexes in hematological malignancies. Blood. 2017;30(1):23-9. doi: 10.1182/blood-2017-02-739490

30. Yuan W, Wu T, Fu H, Dai C, Wu H, Liu N, et al. Dense chromatin activates Polycomb repressive complex 2 to regulate H3 lysine 27 methylation. Science (New York). 2012;337(6097): 971-5. doi: 10.1126/science.1225237.

31. Yap KL, Li S, Muñoz-Cabello AM, Raguz S, Zeng L, Mujtaba S, et al. Molecular interplay of the non-coding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. Molecular Cell. 2010;38(5):662-74. doi: 10.1016/j.molcel.2010.03.021.

32. Visel A, Zhu Y, May D, Afzal V, Gong E, Attanasio C, et al. Targeted deletion of the 9p21 non-coding coronary artery disease risk interval in mice. Nature. 2010;464(7287):409-12. doi: 10.1038/nature08801

33. Holdt LM, Hoffmann S, Sass K, Langenberger D, Scholz M, Krohn K, et al. Alu elements in ANRIL non-coding RNA at chromosome 9p21 modulate atherogenic cell functions through trans-regulation of gene networks. PLoS Genet. 2013;9(7):e1003588. doi: 10.1371/journal.pgen.1003588.

34. Zhou X, Han X, Wittfeldt A, Sun J, Liu C, Wang X, et al. Long non-coding RNA ANRIL regulates inflammatory responses as a novel component of NF-□B pathway. RNA Biol. 2016;1(1):98-108. doi: 10.3892/mmr.2020.11203

35. Ji P, Diederichs S, Wang W, Böing S, Metzger R, Schneider PM, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene. 2003;22(39):8031-41. doi: 10.1038/sj.onc.1206928.

36. Arslan S, Berkan O, Lalem T, Özbilüm N, Göksel S, Korkmaz O, et al. Long non-coding RNAs in the atherosclerotic plaque. Atherosclerosis. 2017;266:176-81. doi: 10.1016/j.atherosclerosis.2017.10.012.

37. Michalik KM, You X, Manavski Y, Doddaballapur A, Zörnig M, T. Braun T, et al. Long non-coding RNA MALAT1 regulates endothelial cell function and vessel growth. Circ Res.2014;14(9):1389-97. doi: 10.1161/CIRCRESAHA.114.303265.

38. Yang L, Lin C, Liu W, Zhang J, Ohgi KA, Grinstein JD, et al. ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. Cell. 2011;147(4):773-88. doi: 10.1016/j.cell.2011.08.054.

39. Gast M, Rauch BH, Nakagawa S, Haghikia A, Jasina A, Haas J, et al. Immune system-mediated atherosclerosis caused by deficiency of long non-coding RNA MALAT1 in ApoE-/-mice. Cardiovasc Res. 2019;115(12):302-14. doi: 10.1093/cvr/cvy202.

40. Zhao G, Su Z, Song D, Mao Y, Mao X. The long non-coding RNA MALAT1 regulates the lipopolysaccharide-induced inflammatory response through its interaction with NF-κB. FEBS Lett. 2016;590(17): 2884-95. doi: 10.1002/1873-3468.12315

41. Huangfu N, Xu Z, Zheng W, Wang Y, Cheng J, Chen X. LncRNA MALAT1 regulates oxLDL-induced CD36 expression via activating β-catenin. Bioch Biopohys Res Comm. 2018;3:2111-7. (ISSN: 1090-2104)

42. Nicholson AC. Expression of CD36 in macrophages and atherosclerosis: the role of lipid regulation of PPARgamma signaling. Trends Cardiovasc Med. 2004;14(1):8-12. doi: 10.1016/j.tcm.2003.09.004.

43. Huang-Fu N, Cheng JS, Wang Y, Li ZW, Wang SH. Neat1 regulates oxidized low-density lipoprotein-induced inflammation and lipid uptake in macrophages via paraspeckle formation. Mol Med Rep. 2018;17(2):3092-8. doi: 10.3892/mmr.2017.8211

44. ASI Ahmed ASI, Dong K, Liu J, Wen T, Yu L, Xu F, et al. NEAT1Long non-coding RNA (nuclear paraspeckle assembly transcript 1) is critical for phenotypic switching of vascular smooth muscle cells. Proc the Nat Acad Scienc (USA) 2018; 37: E8660-67. doi: 10.3892/mmr.2017.8211

45. Wu G, Cai J, Han Y, Chen J, Huang ZP, Chen C, et al. LincRNA-p21 regulates neointima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhancing p53 activity. Circulation. 2014; 130(17):1452-65. doi: 10.1161/CIRCULATIONAHA.114.011675

46. Sallam T, Jones M, Thomas BJ, Wu X, Gilliland T, Qian K, et al. Transcriptional regulation of macrophage cholesterol efflux and atherogenesis by a long non-coding RNA. Nat Med. 2018;24(3):304-12. doi: 10.1038/nm.4479.

47. Liao B, Chen R, Lin F, Mai A, Chen J, Li H, et al. Long non-coding RNA HOTTIP promotes endothelial cell proliferation and migration via activation of the Wnt/β-catenin pathway.J Cell Biochem. 2018;19(3):2797-805. doi: 10.1002/jcb.26448.

48. Vigetti D, Deleonibus S, Moretto P, Bowen T, Fischer JW, Grandoch M, et al. Natural antisense transcript for hyaluronan synthase 2 (HAS2-AS1) induces transcription of HAS2 via protein O-GlcNAcylation. J Biol Chem. 2014; 289(42):28816-26. doi: 10.1074/jbc.M114.597401.

49. van den Boom M, Sarbia M, von Wnuck Lipinski K, Mann P, Meyer-Kirchrath J, Rauch BH, et al. Differential regulation of hyaluronic acid synthase isoforms in human saphenous vein smooth muscle cells: possible implications for vein graft stenosis. Circ Res.2006;98(1):36-44. doi: 10.1161/01.RES.0000199263.67107.c0.

50. Viola M, Karousou E, D'Angelo ML, Moretto P, Caon I, Luca G, et al. Extracellular Matrix in Atherosclerosis: Hyaluronan and Proteoglycans Insights. Curr Med Chem. 2016;23(26):2958-71. doi: 10.2174/0929867323666160607104602.

51. Sussmann M, Sarbia M, Meyer-Kirchrath J, Nüsing RM, Schrör K, Fischer JW Induction of hyaluronic acid synthase 2 (HAS2) in human vascular smooth muscle cells by vasodilatory prostaglandins. Circ Res. 2004;94(5):592-600. doi: 10.1161/01.RES.0000119169.87429.A0.

52. Kashima Y, Takahashi M, Shiba Y, Itano N, Izawa A, Koyama J, et al. Crucial role of hyaluronan in neointimal formation after vascular injury. PloS One. 2013;8(3):e58760. doi: 10.1371/journal.pone.005876

53. Zhang Y, Zheng L, Xu BM, Tang WH, Ye ZD, Huang C, et al. LncRNA-RP11-714G18.1 suppresses vascular cell migration via directly targeting LRP2BP. Imm cell Biol. 2018; 2:175-89. doi: 10.1016/j.eururo.2018.07.032.

54. Huang C, Hu YW, Zhao JJ, Ma X, Zhang Y, Guo FX. Long Noncoding RNA HOXC-AS1 Suppresses Ox-LDL-Induced Cholesterol Accumulation Through Promoting HOXC6 Expression in THP-1 Macrophages. DNA Cell Biol. 2016; 11:722-9. doi: 10.1089/dna.2016.3422.

55. Miao Y, Ajami NE, Huang TS, Lin FM, Lou CH, Wang YT, et al. Enhancer-associated long non-coding RNA LEENE regulates endothelial nitric oxide synthase and endothelial function. Nat Comm. 2019;1:292-8. doi: 10.1038/s41467-017-02113-y.

56. Rapicavoli NA, Qu K, Zhang J, Mikhail M, Laberge RM, Chang HY. A mammalian pseudogene lncRNA at the interface of inflammation and anti-inflammatory therapeutics. Life. 2013;2:e00762. doi: 10.7554/eLife.00762.

57. Peng Y , Meng K, Jiang L, Zongh Y, Yang Y, Lan Y, et al. Thymic stromal lymphopoietin-induced HOTAIR activation promotes endothelial cell proliferation and migration in atherosclerosis. Biosc Rep.2017;37(4):R20170351. doi: 10.1042/BSR20170351.

58. Lin J, Chang W, Dong J, Zhang F, Mohabeer N, Kushwaha KK, et al. Thymic stromal lymphopoietin over-expressed in human atherosclerosis: potential role in Th17 differentiation. Cellular physiology and biochemistry : Int J Exp Cell Phys Bioch Pharmacol. 2013;31(2-3): 305-18. doi: 10.1159/000343369

59. Smith E K, Prasad M, Butcher M, Dobrian A, Kolls JK, Ley K, et al. Blockade of interleukin-17A results in reduced atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2010;121(15):1746-55. doi: 10.1161/CIRCULATIONAHA.109.924886.

60. Tang Y, Jin X, Xiang Y, Chen Y, Shen CX, Zhang YC, et al. The lncRNA MALAT1 protects the endothelium against ox-LDL-induced dysfunction via upregulating the expression of the miR-22-3p target genes CXCR2 and AKT. FEBS Lett. 2015;589(20Pt8):3189-96. doi: 10.1016/j.febslet.2015.08.046.

61. Cremer S, Michalik KM, Fischer A,Jae N, Winter C. Hematopoietic Deficiency of the Long Non-coding RNA MALAT1 Promotes Atherosclerosis and Plaque Inflammation. Circulation. 2019;139(10):1320-34. doi: 10.1016/j.febslet.2015.08.046.

62. Li S, Sun Y, Zhong L, Xiao Z, Yang M, Chen M, et al. The suppression of ox-LDL-induced inflammatory cytokine release and apoptosis of HCAECs by long non-coding RNA-MALAT1 via regulating microRNA-155/SOCS1 pathway. Nutr Metabol Cardiovasc Dis. 2018; 28(11): 1175-87. . doi: 10.1016/j.numecd.2018.06.017.

63. Zheng H, Dong X, Liu N, Xia W, Zhou L, Chen X, et al. Regulation and mechanism of mouse miR-130a/b in metabolism-related inflammation. Int J Biochem Cell Biol.2016;74:72-83.

64. Pan SD, Yang X, Jia Y, Li R, Zhao R. Microvesicle-shuttled miR-130b reduces fat deposition in recipient primary cultured porcine adipocytes by inhibiting PPAR-g expression. J Cell Physiol. 2014;229(5): 631-9. doi: 10.1002/jcp.24486.

65. Han Y, Ma J, Wang J, Wang L Silencing of H19 inhibits the adipogenesis and inflammation response in ox-LDL-treated Raw264.7 cells by up-regulating miR-130b. Mol Immunol.2018;93:107-14. doi: 10.1016/j.molimm.2017.11.017

66. Zhang L, Cheng H, Yue Y, Li S, Zhang D,He R. H19 knockdown suppresses proliferation and induces apoptosis by regulating miR-148b/WNT/β-catenin in ox-LDL -stimulated vascular smooth muscle cells. J Biomed Sci.2018;25(1):11.. 2018; 1: 11. doi: 10.1186/s12929-018-0418-4.

67. Kojima Y, Volkmer JP, McKenna K, Civelek M, Lusis AJ, Miller CL, et al. CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis. Nature. 2016;536(7614):86-90. doi: 10.1038/nature18935.

68. Ye ZM, Yang S, Xia YP, Hu RT, Chen S, BW, et al. LncRNA MIAT sponges miR-149-5p to inhibit efferocytosis in advanced atherosclerosis through CD47 upregulation. Cell Death Dis. 2019;10(2):138. doi: 10.1038/s41419-019-1409-4.

69. Zhong X, Ma X, Zhang L, Li Y, He R. MIAT promotes proliferation and hinders apoptosis by modulating miR-181b/STAT3 axis in ox-LDL-induced atherosclerosis cell models. Biomed Pharmacother Biomed.2018;97: 1078-85. doi: 10.1016/j.biopha.2017.11.052.

70. Wang L, Xia JW, Ke ZP, Zhang H. Blockade of NEAT1 represses inflammation response and lipid uptake via modulating miR-342-3p in human macrophages THP-1 cells. J Cell Physiol.2019;234(4): 5319-26. doi: 10.1002/jcp.27340.

71. Chen C, Cheng G, Yang X, Li C, Shi R, Zhao N. Tanshinol suppresses endothelial cells apoptosis in mice with atherosclerosis via lncRNA TUG1 up-regulating the expression of miR-26a. Am J TRanslat Res.2016;8(7):2981-91. PMID: 27508018

72. Zhang L, Cheng H, Yue Y, Li S, Zhang D, He R. TUG1 knockdown ameliorates atherosclerosis via up-regulating the expression of miR-133a target gene FGF1. Cardiovasc Pathol. 2018;33: 6-15. doi: 10.1016/j.carpath.2017.11.004.

73. Zhang BY, Jin Z, Zhao Z. Long intergenic non-coding RNA 00305 sponges miR-136 to regulate the hypoxia induced apoptosis of vascular endothelial cells. Biomed Pharmacother. 2017;94:238-43. doi: 10.1016/j.carpath.2017.11.004

74. He C, Ding JW, Li S, Wu H, Jiang YR, Yang W, et al. The Role of Long Intergenic Noncoding RNA p21 in Vascular Endothelial Cells. DNA Cell Biol. 2015;34(11):677-83. doi: 10.1089/dna.2015.2966.

75. Shen Z, She Q. Association Between the Deletion Allele of Ins/Del Polymorphism (Rs145204276) in the Promoter Region of GAS5 with the risk of atherosclerosis. Cell Physiol Biochem. 2018;49(4):1431-43. doi: 10.1159/000493447

76. Campalans A, Kondorosi A, Crespi M. Enod40, a short open reading frame-containing mRNA, induces cytoplasmic localization of a nuclear RNA binding protein in Medicago truncatula. Plant Cell. 2004;16(4): 1047-59. doi: 10.1105/tpc.019406.

77. Hellwig S, Bass BL. A starvation-induced non-coding RNA modulates expression of Dicer-regulated genes. Proc Natl Acad Sci .2008;105(35):1289-902. doi: 10.1073/pnas.0805118105

Mechanical Mitral Valve Thrombosis in a Patient with COVID-19 Infection

Emre Aruğaslan,[1] Yunus Çalapkulu,[1] Ender Örnek,[1] Mustafa Karanfil,[1] Hüseyin Bayram,[2] Seref Alp Küçüker[2]

Departamento de Cardiologia, Hospital da Cidade de Ancara,[1] Ancara – Turkey

Departamento de Cirurgia Cardiovascular, Hospital da Cidade de Ancara,[2] Ancara – Turkey

Introduction

The novel coronavirus disease-2019 (COVID-19) caused by "Severe Acute Respiratory Syndrome Coronavirus-2" (SARS-CoV-2) became a global pandemic. Although respiratory involvement is the predominant presentation, current evidence has shown that COVID-19 is a multisystemic disease with coagulopathy and thromboembolic complications. Increased production of tissue factor and thrombin reduced fibrinolysis due to hyperinflammation are the proposed mechanisms of COVID-19 induced thrombosis.[1]

We present a case of a COVID-19 infected patient with thrombosis of the mechanical mitral valve.

Case Report

A 46-year-old male patient who underwent mitral mechanical valve replacement 3 years ago was admitted with a 1 week history of mild dyspnea and malaise. Physical examination revealed the absence of prosthetic click. There was neither jugular venous distension nor rales on lung auscultation. The patient was hemodynamically stable. Electrocardiography showed sinus rhythm with nonspecific ST-segment changes. Regular medications consisted of only warfarin 5 mg/day. His recent medical history was remarkable due to the COVID-19 infection in his household. It was decided to test the patient for COVID- 19 because of close contact and subfebrile fever (37.5 °C). Real-time polymerase chain reaction nasopharyngeal swab test was positive for SARS-CoV2. Chest computed tomography scan performed in the emergency department revealed bilateral centrilobular infiltrations, which were reported as atypical COVID-19. Transthoracic echocardiography (TTE) detected severely restricted leaflet mobility, with a mean transvalvular gradient of 23 mmHg (Figure 1). Obstructive thrombus with a 2.2 X 0.8 cm diameter extending to the left ventricular outflow tract was seen (Figure 1, Video 1). Fluoroscopy also showed restricted mobility of leaflets. Admission INR was 3.26. Medical records revealed monthly therapeutic INR measurements before hospitalization. There was no other thrombotic episode in the patient's past medical history. There was mild hypoxemia (PaO_2:71 mmHg) on arterial blood gas analysis. Initial laboratory tests showed levels of D dimer 1.0 mg/L (< 0.55), C- reactive protein 0.02708 g/L (0 - 0.005), IL-6 14.7 pg/mL (0 – 3.4), platelets 258 x 10^9/L(150-400), and ferritin 58 μg/L (22 – 322). Blood cultures were obtained to rule out infective endocarditis. Emergent surgery was declined due to hemodynamic stability and active COVID-19 infection.

The patient was admitted to the intensive care unit to monitor symptoms and hemodynamics. Warfarin was stopped, and intravenous unfractionated heparin was administered with aPTT guided dosing. The patient was closely monitored for signs of heart failure and hemodynamic instability. On the third day of treatment, TTE showed decreased mitral valve gradients (mean 12 mmHg). Heparin treatment was continued. However, the patient deteriorated because of supraventricular tachycardia and subsequent pulmonary edema on day 7. Bedside echocardiography was done immediately and demonstrated re-elevation of the mean pressure gradient to 28 mmHg. Emergent thrombolytic was administered 10 mg bolus of tPA and 90 mg infusion in 90 minutes; however, no amelioration was seen in neither clinical nor echocardiographic parameters after lytics. Urgent mitral valve replacement was needed. Adherences from previous cardiac surgery were released after redo median sternotomy. Cardiopulmonary bypass was established with venous cannulation. Thrombosis was observed on the mechanical valve by the left atriotomy approach. The thrombosed mechanical valve was excised, and a new mechanical valve (29 mm, Sorin) was replaced. He was discharged with a target INR of 3.5 after uneventful postoperative care. As COVID-19 infection was supposed to be the trigger of mechanical valve thrombosis, no further hematological investigation was done. The patient has not experienced any adverse event after discharge.

Discussion

We described a case of mechanical mitral valve thrombosis in a COVID-19 patient. Thrombotic complications of the cardiovascular system are evident in the literature. There have been reports of venous thromboembolism and coronary artery thrombosis cases related to COVID-19.[2,3] Bioprosthetic mitral valve thrombosis was successfully treated by the initiation of anticoagulation in an elderly patient with COVID-19.[4] Guidelines recommend at least prophylactic dose of low molecular weight heparin for all hospitalized COVID-19 patients in the absence of absolute contraindications.[1]

Mechanical heart valve thrombosis is a life-threatening complication necessitating prompt diagnosis and treatment.

Keywords

COVID-19/complications; Mitrakl Valvesurgery; Infammation; Thrombosis; Blood Coagulation, Disorders/complications.

Mailing Address: Emre Arugaslan •
Ankara Şehir Hastanesi Kardiyoloji Kliniği, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya/Ankara - Turkey
Email: dremrearugaslan@gmail.com
Manuscript received July 08, 2021, revised manuscript October 08, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210581

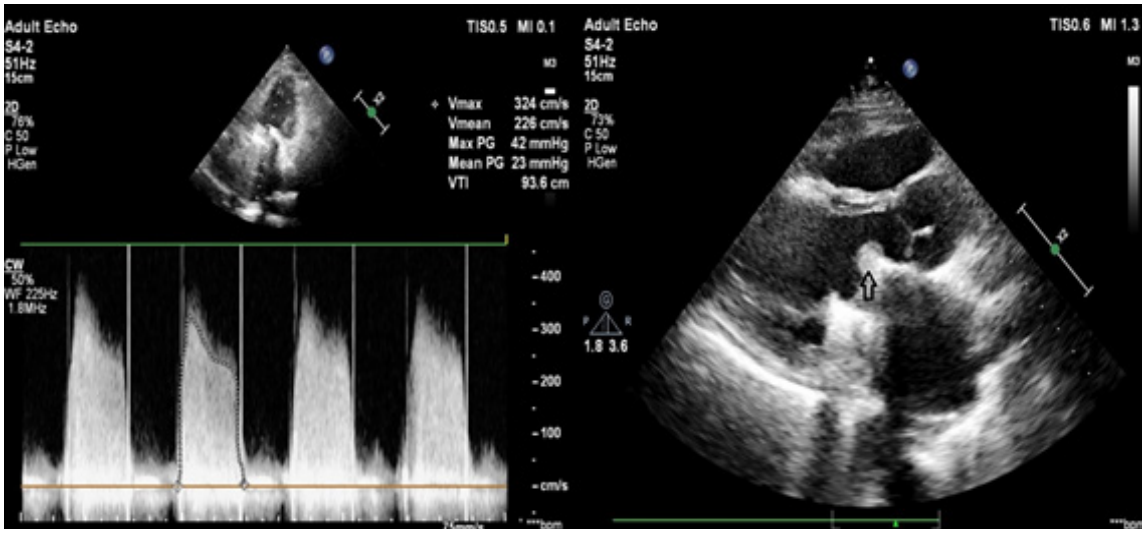


Figure 1 – *Echocardiographic images of obstructed mechanical valve.*

It is usually associated with inadequate anticoagulation. TTE and transesophageal echocardiography (TEE) are essential for diagnosis and determining the degree and cause of valve dysfunction. TEE was not performed in this COVID-19 patient due to the heightened risk for SARS-Cov-2 spread. Cinefluoroscopic provides additional information about leaflet mobility and opening. Emergency valve replacement is recommended for obstructive prosthetic valve thrombosis in critically ill patients, but fibrinolysis should be considered if the surgical risk is high.[5] Low risk of bleeding, involvement of the right valves, first episode of valve thrombosis, and thrombus smaller than 1 cm^2 are other factors that make fibrinolysis more favorable.[6] Heart team decided to administer fibrinolytic due to concerns about perioperative hyper inflammation and hypercoagulability associated with COVID-19 [7] but redo surgery was eventually needed after thrombolytics failed.

COVID-19 infection has been associated with increased mortality in patients undergoing cardiac surgery.[8] Exaggerated inflammatory response to the virus may augment the risk of acute respiratory distress syndrome (ARDS) postoperatively.[9] A case of acute postoperative thrombosis of the aortic valve and subsequent coronary embolism was reported.[10] The risk of perioperative transmission of the virus to health care personnel should also be kept in mind. However, delaying the surgery in a patient with prosthetic valve thrombosis is also risky due to complications such as cardiogenic shock, heart failure and systemic embolism. The decision between surgery and thrombolysis for mechanical valve thrombosis should be individualized. Clinical factors, local experience and surgical expertise are critical factors in the decision pathway.

Conclusions

Literature has consistent data regarding hypercoagulability in COVID-19 infection, so we presumed that Coronavirus disease was the predisposing factor in the development of mechanical valve thrombosis in a patient with therapeutic INR values. However, it should be noted that thrombosis developed although proinflammatory markers were moderately elevated. Similarly, recurrent coronary thrombosis in a moderate case of COVID-19 was reported,[2] so hyper inflammation may not be the sole pathway leading to thrombosis in patients with COVID-19.

Physicians should be aware of thrombotic complications during this outbreak. Preventive and therapeutic use of antithrombotic drugs should be done in parallel to formal recommendations to mitigate the thrombotic burden in COVID-19 patients.[1]

Author Contributions

Conception and design of the research: Bayram H, Küçüker SA; Acquisition of data: Aruğaslan E, Çalapkulu Y; Analysis and interpretation of the data: Karanfil M; Writing of the manuscript: Aruğaslan E, Karanfil M, Örnek E; Critical revision of the manuscript for intellectual contente: Örnek E, Bayram H, Küçüker SA.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

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. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(25):2950–73. doi: 10.1016/j.jacc.2020.04.031.
2. Muguerza J, Loizeau PA. Recurrent coronary thrombotic events in a moderate case of COVID-19. BMJ Case Rep. 2021;14(1):e237624. doi: 10.1016/j.jacc.2020.04.031.
3. Scudiero F, Pitì A, Keim R, Parodi G. Acute pulmonary embolism in COVID-19 patient: a case report of free-floating right heart thrombus successfully treated with fibrinolysis. Eur Heart J Case Rep 2020;5(1):ytaa388. doi: 10.1093/ehjcr/ytaa388.
4. Llopis Gisbert G, Vidal Urrutia V, Moruno Benita MA, Payá Chaume A, Berenguer Jofresa A, Cubillos Arango AM et al. Bioprosthetic Valve Thrombosis and Obstruction Secondary to COVID-19. Can J Cardiol. 2021;37(6):938.e3-938.e6. doi: 10.1016/j.cjca.2020.10.008.
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391.
6. Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa VEE, Accorsi TAD et al. Update of the Brazilian Guidelines for Valvular Heart Disease - 2020. Arq Bras Cardiol. 2020 Oct;115(4):720-75. doi: 10.36660/abc.20201047.
7. Günaydin S, Stammers AH. Perioperative management of COVID-19 patients undergoing cardiac surgery with cardiopulmonary bypass. Perfusion. 2020;3(6):465-73. doi: 10.1177/0267659120941341.
8. Sanders J, Akowuah E, Cooper J, Kirmani BH, Kanani M, Acharya M, et al. Cardiac surgery outcome during the COVID-19 pandemic: a retrospective review of the early experience in nine UK centers. J Cardiothorac Surg. 2021;16(1):43.
9. Mavioğlu HL, Ünal EU, Aşkın G, Küçüker ŞA, Özatik MA. Perioperative planning for cardiovascular operations in the COVID-19 pandemic. Turk Gogus Kalp Damar Cerrahisi Derg. 2020;28(2):236-43. doi: 10.1186/s13019-021-01424-y.
10. Manghat NE, Hamilton MCK, Joshi NV, Vohra HA. Acute postoperative thrombosis of an aortic valve prosthesis and embolic myocardial infarction in a coronavirus disease 2019 (COVID-19)-positive patient-an unrecognised complication. JTCVS Tech 2020: 4:111-3. doi: 10.1016/j.xjtc.2020.09.020.

*Supplemental Materials

See the Supplemental Video, please click here.

Coxiella Burnetii Endocarditis: Can Positron Emission Tomography be an Alternative to Diagnosis?

Marjorie Hayashida Mizuta,[1] Cristhian Espinoza Romero,[1] Santiago Castro Vintimilla,[1] Tatiana de Carvalho Andreucci Torres Leal,[1] Paulo Rogério Soares,[1] Alexandre de Matos Soeiro[1]

Instituto do Coração – Universidade de São Paulo,[1] São Paulo, SP – Brazil

Introduction

Coxiella burnetii infective endocarditis (IE) represents a rarely reported zoonosis in Brazil.[1] It is estimated that *Coxiella burnetii* is responsible for up to 5% of all IE cases worldwide.[2] The disease affects mostly valvulopathy patients and immunocompromised subjects.

Different from the classical acute and sub-acute endocarditis, the clinical picture is frustrating, and, because this is an obligate intracellular microorganism, hemocultures (HMC) are predominantly negative, which makes the clinical suspicion more difficult.[1]

This paper presents a rare endocarditis clinical case that manifested in an atypical manner, and was diagnosed with the help of specific *Coxiella burnetii* serology and of the positron emission tomography (PET).

Case report

A 25-year-old female patient, was born in and is a resident of Monte Santo, Bahia and who is a farming technician, had a history of two mitral valve replacements with biological prosthesis due to rheumatic valve disease, with the most recent occurrence in 2017. She was referred to the emergency unit by the valvulopathy clinic with suspected IE. The patient reported that, in July 2020, she exhibited erythematous lesions in the lower and upper limbs, associated with intermittent low-grade fever, which persisted for 6 months. The picture was fully solved with the use of cephalexin for 5 days, in January 2021. Upon hospital admission, in February 2021, the patient was asymptomatic, exhibited no alterations in the physical examination, and provided a transthoracic echocardiogram (TTE) performed at the clinic 5 days before showing a mitral biological prosthesis whose leaflets exhibited pannus formation, with the possibility of vegetation not excluded (Figure 1A). A transesophageal echocardiogram (TEE) was scheduled to better view the valvular prosthesis. The TEE showed an oval shape, with well-defined borders, which adhered to the posterior leaflet base atrial face, measuring 11x5 mm, and which may correspond to vegetation or suture thread with fibrin, with no mitral prosthesis dysfunction (Figure 1B). Given the IE hypothesis, the patient was admitted to the hospitals and 3 pairs of HMC and laboratory tests were conducted showing 6,720/mm^3 white blood cells, an erythrocyte sedimentation rate at 18 mm, C-reactive protein at 18mg/dl, and normal urine I and liver function tests. Due to the clinical stability, the patient was kept off antibiotics until the hemoculture results were available. As the hemocultures were negative, *Coxiella burnetii* and *Bartonella henselae* serology tests were conducted. Serology was reactive to *Coxiella burnetii* (titer >1:1,600), and treatment was started on the day after hospital admission, combining intravenous 400 mg ciprofloxacin every 12 hours for 7 days, 100 mg oral delivery (OD) doxycycline every 12 hours, and 200 mg OD hydroxychloroquine every 8 hours for 18 months. To complement the investigation, on the third day of hospital stay, a PET was conducted, which, with the use of antibiotic therapy, showed inflammatory activity in the mitral valve area; however, it was deemed possible that the infective process was being resolved (Figure 2). The patient progressed with hemodynamic stability and was discharged after 8 days of hospital stay with the described antibiotic therapy.

Discussion

Coxiella burnetii IE represents a worldwide spread zoonosis. The most common means of transmission in human beings is the inhalation of aerosols derived from cattle organic secretion, during birth or by ingesting contaminated raw milk.[1] In the clinical case, as the patient was under occupational risk, the possibility of *Coxiella burnetii* infection was highly suspected.

Most patients exhibit insidious symptoms of heart failure, and unspecified symptoms, such as low-grade fever and fatigue. The physical examination may detect the presence of hepatosplenomegaly and digital clubbing.[1] Skin manifestations are uncommon and may be represented by purpuric, punctiform, or maculopapular eruptions, and are commonly present in the acute form of the disease.[3] As the patient reported a skin manifestation 7 months prior to admission, during the hospital stay period, the patient was probably in the chronic phase of the disease.

Serology is one of Duke's major criteria for *Coxiella burnetii* IE. It constitutes a diagnostic marker of chronic

Keywords

Endocarditis; Coxiella Burnetti; Q Fever; Heart Valve Prosthesis; Echocardiography,Transesophageal/methods; Positron Emission Tomography Computed Tomography/methods; Antibiotics/therapeutic use

Mailing Address: Marjorie Hayashida Mizuta •
Universidade de São Paulo Instituto do Coração - Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05403-900, Cerqueira César, São Paulo, SP - Brazil
E-mail: marjorie.hm@hotmail.com
Manuscript received May 15, 2021, revised manuscript October 13, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210421

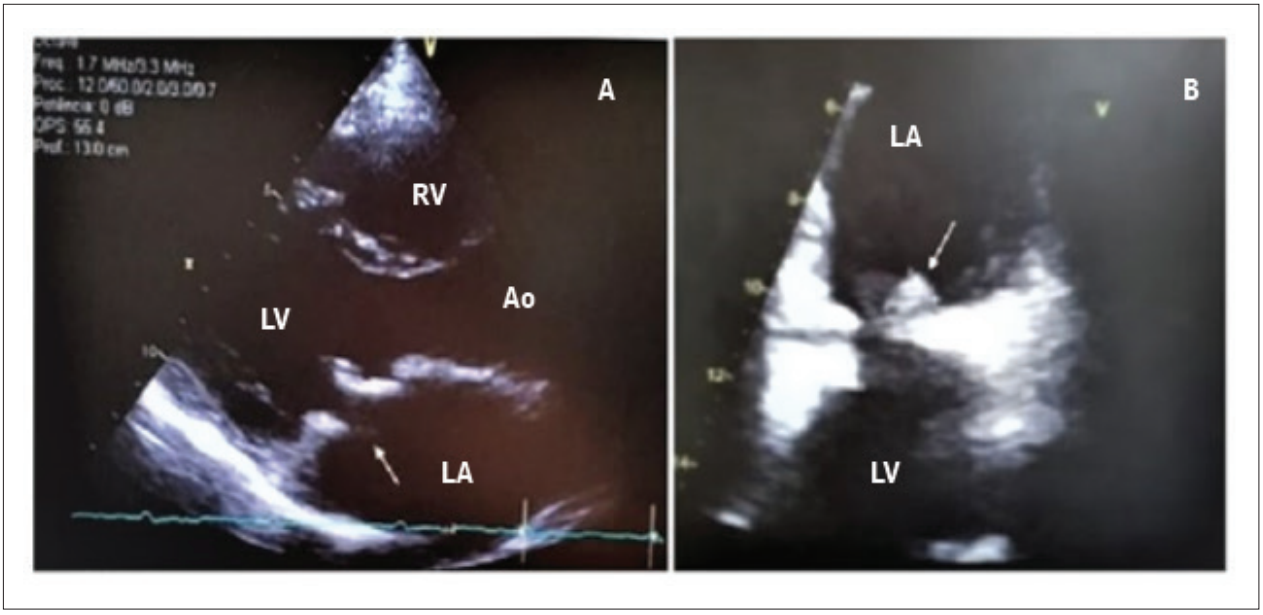


Figure 1 – *A) 2D TTE in longitudinal parasternal position showing mitral prosthesis with thickened leaflets and pannus aspect. B) 2D TEE at 60º showing an oval shape adhered to the posterior leaflet atrial face. RV: right ventricle; LV: left ventricle; AO: aorta; LA: left atrium.*

infection when it exhibits antiphase I IgG antibody titers >1:800, with high sensitivity and specificity.[1]

The TTE is capable of revealing abnormalities in only 12% of the cases, due to the presence of small, nodular, or flat vegetations that go unnoticed even in the TTE.[1]

The PET has demonstrated a diagnostic value in valve prosthesis or intracardiac device IE (87% sensitivity and 92% specificity). It was incorporated in the guideline diagnosis algorithm and is not recommended for native vales or early postoperative stages.[4] There are several reports of PET-CT being used as a diagnostic tool in *Coxiella burnetii* IE, suggesting that this technique may help in locating the infection in patients with serological evidence of persistent infection.[5]

Therefore, this paper presents an IE case with high mortality if not treated early. The diagnosis is difficult due to the chronic behavior of the disease. The vegetation is unspecified to the echocardiogram and hemocultures are negative.[1] The PET and serology stand out in this scenario, considering that a non-conclusive echocardiogram does not exclude the diagnosis in patients with highly suspected IT.[6] In the clinical case, even during antibiotic therapy and in the chronic form of the disease, the PET was able to infer and locate the infection, allowing for a more precise diagnosis and avoiding lethal outcomes.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Mizuta MH, Romero CE, Vintimilla SC, Leal TCAT, Soares PR, Soeiro AM; Acquisition of data: Mizuta MH; Writing of the manuscript: Mizuta MH, Romero CE, Vintimilla SC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

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.

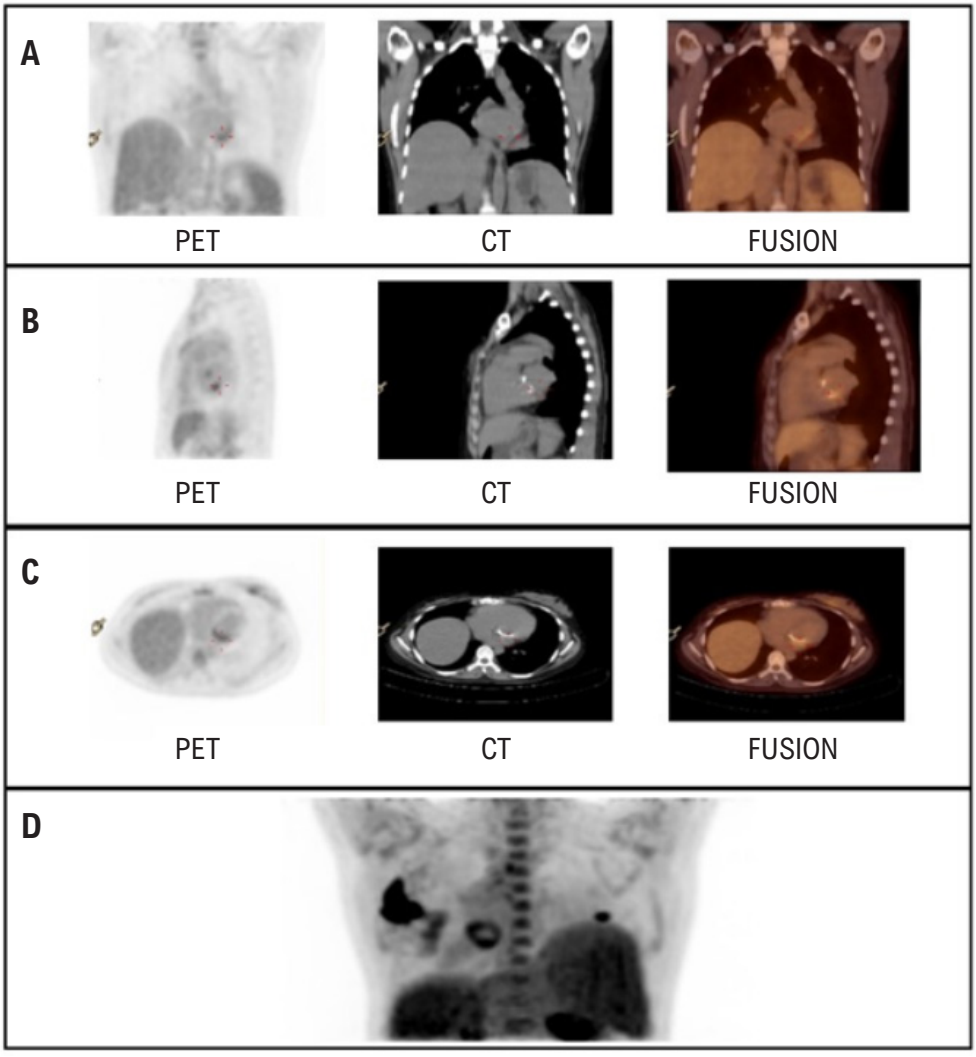


Figure 2 – *PET, computed tomography (CT), and fusion generated images. PET demonstrated diffuse fluorodeoxyglucose uptake in mitral valve topography in the coronal (A), sagittal (B), and axial (C) planes, and in 3D (D).*

References

1. Siciliano RF, Ribeiro HB, Furtado RH, Castelli JB, Sampaio RO, Santos FC, et al. Endocardite por Coxiella burnetii (febre Q): doença rara ou pouco diagnosticada? Relato de caso. Rev Soc Bras Med Trop. 2008 Jul-Aug;41(4):409-12. doi: 10.1590/s0037-86822008000400017.
2. Barbosa MM, Dias C, Araujo E, Costa R. Coxiella Burnetii Infecctive Endocarditis-detection and cure. Int J Cardiovasc Sci.2020;33(6):723-8. doi.org/10.36660/ijcs.20190138
3. Meriglier E, Asquier L, Roblot F, Roblot P, Landron C. A case of Q fever with erythema nodosum. Infection. 2018;46(1):127-9. doi: 10.1007/s15010-017-1058-4.
4. Harding D, Prendergast B. Advanced imaging improves the diagnosis of infective endocarditis. F1000Research.2018;7(Faculty Rev):674. doi: 10.12688/f1000research.13791.1.
5. Ricciardi E, Moscatelli A, Berruti M, Donegani MI, Mikulska MK, Pende A. 18F-Fluorodeoxyglucose positron emission tomography/computed tomography as a diagnostic and follow-up tool in Coxiella burnetii endocarditis of prosthetic valve and aortic valved tube: a case report. Eur Heart J Case Rep.2021;17(5):ytab159. doi: 10.1093/ehicr/ytab159.
6. Grossman GB, Carreira LTF. Papel do PET/CT no diagnóstico da endocardite infecciosa. Artigo de Revisão Arq Bras Cardiol: Imagem Cardiovasc. 2019;32(3):209-13. doi: 10.5935/2318-8219.20190037

Physical Exercise and MicroRNAs: Molecular Mechanisms in Hypertension and Myocardial Infarction

Alex Cleber Improta-Caria[1]

Programa de Pós-Graduação em Medicina e Saúde, Universidade Federal da Bahia,[1] *Salvador, BA – Brazil*

Introduction

Scientific evidence shows that the regular practice of physical exercise (PE) is beneficial for various organs and systems of the human body, mainly for the heart and cardiovascular system.[1] In both systems, aerobic and strength PE promote physiological cardiac hypertrophy, respectively eccentric and concentric, improving myocardial function.[2]

In addition to the benefits for the heart, PE impacts blood vessels through shear stress and alters long-term vascular function, improving endothelial cell and smooth muscle cell function, generating arterial remodeling and a potential antiatherogenic effect.[3] These benefits on the cardiovascular system occur in both healthy individuals and individuals with cardiovascular diseases, such as systemic arterial hypertension (SAH)[4] and myocardial infarction (MI),[5] for example.

However, the molecular mechanisms that govern these PE-induced benefits have not been completely elucidated, especially the mechanisms regulated by microRNAs (miRs), which are small non-coding RNAs that modulate the pattern of gene and protein expression in healthy individuals and those with cardiovascular diseases.[6]

Thus, the present study aims to emphasize the importance of PE in the prevention and treatment of SAH and MI, as well as explaining the role of PE-induced miRs in these pathological conditions.

Systemic arterial hypertension, miRs and PE

SAH is a multifactorial disease and is associated with genetic factors and modifiable risk factors, such as a high-salt and high-calorie diet, smoking, stress, sedentary behavior and physical inactivity, being considered an independent risk factor for MI.[7] PE in turn, is extremely beneficial for individuals with SAH because it reduces pressure levels after training.[8] This decrease in blood pressure is due in part to arterial remodeling, attenuating peripheral vascular resistance and also due to reduced sympathetic nerve activity.[8] However, the role of miRs in reducing blood pressure remains unclear.

Keywords

MicroRNAs/genetic; Hypertension; Myocardial Infarction; Exercise; Physical Exertion.

Mailing Address: Alex Cleber Improta-Caria •
Universidade Federal da Bahia - Medicina e Saúde - Rua Dr. Augusto Viana, s/n. Postal Code 40301-155, Canela, Salvador, BA - Brazil
E-mail: alexcaria.personal@hotmail.com
Manuscript received June 17, 2021, revised manuscript October 21, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210538

Few studies have demonstrated the regulatory role of miRs to reduce blood pressure. In one study, the authors showed that aerobic PE lowered blood pressure in hypertensive rats by reducing the expression of miR-16 that targets the vascular endothelial growth factor (VEGF) gene, with a consequent increase in VEGF expression, improving endothelial function and decrease in miR-21 expression, with a consequent increase in its target, the Bcl-2, attenuating apoptosis, demonstrating that PE promoted an alteration in angiogenic and apoptotic factors, minimizing microvascular abnormalities, and generating peripheral revascularization in SAH.[9]

In this context, it was also shown that aerobic PE increased the expression of miR-27a, decreasing the expression of its target, the ACE gene, increased the expression of miR-155 reducing the expression of the AT1R and decreased the expression of miR-153, increasing the expression of ACE2. These molecular changes induced by PE, generated changes in the phenotype of the aorta artery in hypertensive rats, such as reduced aortic weight and length, decreased wall thickness, attenuation of elastin and hydroxyproline expression, with consequent improvement in the relaxation of the aorta and endothelial function, decreasing blood pressure.[10]

In another study, aerobic PE increased the expression of miR-145 with modulation of the AKT signaling pathway, inducing the phenotype change of vascular smooth muscle cells in hypertensive rats, decreasing the medial layer thickness, promoting arterial remodeling and decreasing systolic and diastolic blood pressure.[11]

Corroborating the abovementioned studies, another study also showed that PE reduced systolic blood pressure in hypertensive rats, but an increase in miR-214 expression was observed in this study, exacerbating the availability of intracellular calcium and the relaxation of isolated cardiomyocytes.[12]

Thus, PE is an excellent tool to modulate the expression of miRs and regulate signaling pathways, inducing long-term cardiac and vascular phenotypic changes in hypertensive rats; however, these experiments still need to be performed in human beings with SAH, to ascertain whether these effects observed in *in vivo* studies occur in humans.

Myocardial infarction, miRs and PE

MI is a condition in which blood flow is reduced in one or more coronary arteries, resulting in a reduction in the supply of oxygen and nutrients to some cardiomyocytes, with consequent death of these cells. MI is considered one of the main causes of morbidity and mortality worldwide.[13] On the other hand, regular PE practice is important to prevent and treat the individuals after an MI, but the molecular mechanisms of these benefits need to be further elucidated.

Regarding the effects of PE on the expression of miRs in post-MI in animal models, aerobic PE increased the expression of miR-29a, miR-29b and miR-29c, decreasing the expression of COL1A1 and COL3A1 genes, reducing the collagen content in the myocardium of post-MI rats quantified by the concentration of hydroxyproline, promoting improvement in cardiac function assessed by echocardiography.[14]

Another study also showed that aerobic PE exacerbated the expression of miR-29a, inhibiting the expression of TGF-β, inactivating its signaling pathway, which is pro-fibrotic. In addition to miR-29a, the authors also showed that PE increased the expression of miR-101a, which targets the FOS gene, decreasing its expression and further attenuating the TGF-β pathway. These PE-induced molecular changes resulted in reduced myocardial interstitial fibrosis in rats after MI[15] (Figure 1).

Therefore, PE has a great potential to reduce the cardiac fibrotic profile in post-MI rats through the modulation of miRs; however, these outcomes also need to be elucidated in humans, both at the molecular and tissue level.

Conclusions

Finally, PE is an excellent strategy to prevent and treat individuals with SAH and post-MI. PE-modulated miRs have been described as regulators of signaling pathways inducing modification of the cardiac and vascular phenotype in hypertensive rats, promoting blood pressure reduction, physiological cardiac hypertrophy and arterial remodeling, with improved endothelial function. Furthermore, PE-modulated miRs also regulated signaling pathways associated with the cardiac fibrosis process in post-MI rats, improving cardiac function. However, these beneficial effects of PE-regulated miRs have been described in animal models, requiring clinical trials to confirm these results obtained *in vivo*, being a promising and challenging new line of research.

Acknowledgements

This study was funded in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*-Brazil (CAPES) - Funding Code 001.

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 contente: Improta-Caria AC.

Potential Conflict of Interest

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

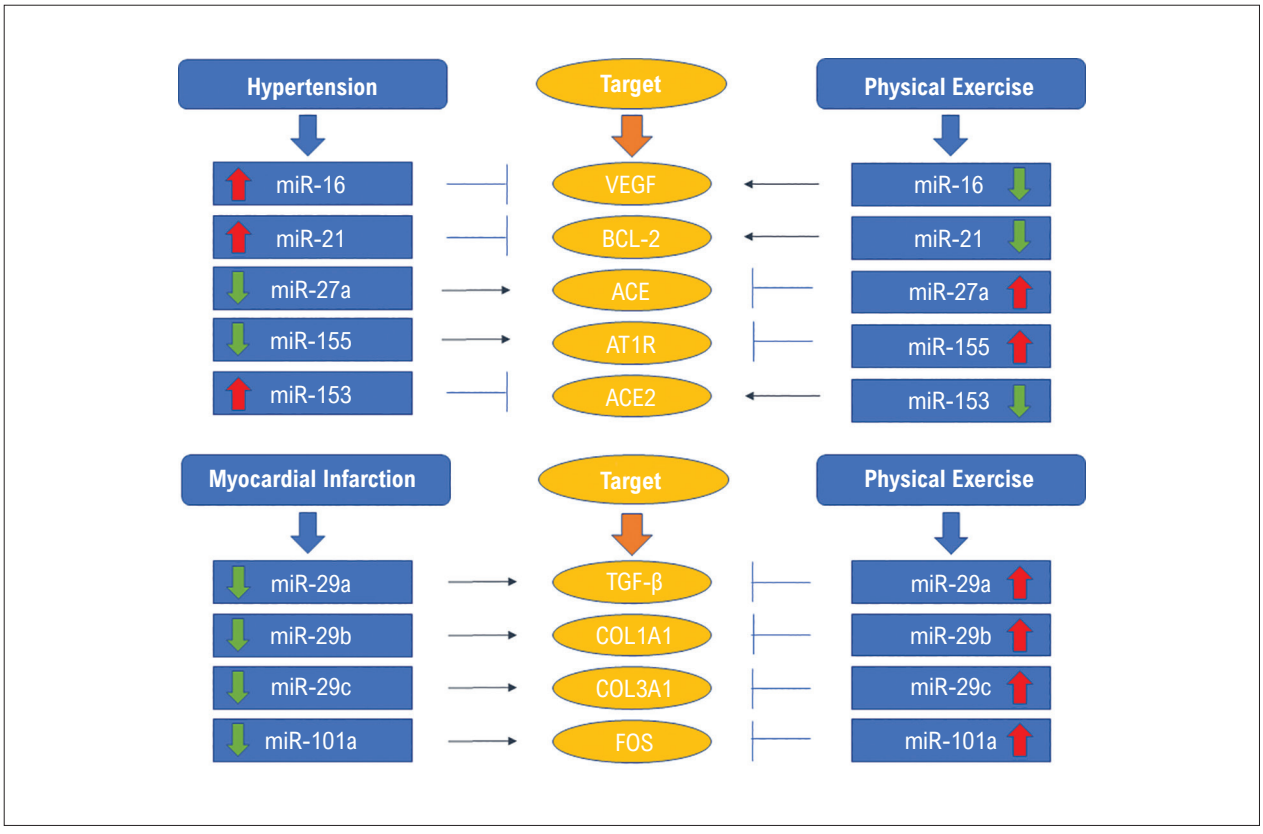


Figure 1 – *PE modulating miRs and targets in SAH and MI.*

Sources of Funding

This study was partially funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

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. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43(7):1334–59. doi: 10.1249/MSS.0b013e318213fefb
2. Fernandes T, Soci UPR, Oliveira EM. Eccentric and concentric cardiac hypertrophy induced by exercise training: microRNAs and molecular determinants. Brazilian J Med Biol Res = Rev Bras Pesqui medicas e Biol. 2011;44(9):836–47. doi: 10.1590/s0100-879x2011007500112
3. Newcomer SC, Thijssen DHJ, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: Role of exercise-induced hemodynamics. J Appl Physiol. 2011;111(1):311-20. doi: 10.1152/japplphysiol.00033.2011
4. Caria ACI, Nonaka CKV, Pereira CS, Soares MBP, Macambira SG, Souza BS de F. Exercise training-induced changes in microRNAs: Beneficial regulatory effects in hypertension, type 2 diabetes, and obesity. Int J Mol Sci. 2018;19(11):1–36. doi: 10.3390/ijms19113608
5. Peixoto TCA, Begot I, Bolzan DW, Machado L, Reis MS, Papa V, et al. Early Exercise-Based Rehabilitation Improves Health-Related Quality of Life and Functional Capacity After Acute Myocardial Infarction: A Randomized Controlled Trial. Can J Cardiol. 2015;31(3):308–13. doi: 10.1016/j.cjca.2014.11.014
6. Baek D, Villén J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. Nature. 2008;455(7209):64–71. doi: 10.1038/nature07242
7. Malachias M, Plavnik FL, Machado CA, Malta D, Scala LCN, Fuchs S. VII Brazilian Guideline of Arterial Hypertension: Chapter 1 - Concept, Epidemiology and Primary Prevention. Arq Bras Cardiol. 2016;107(3 Suppl 3):1–6. doi: 10.5935/abc.20160151.
8. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. J Hum Hypertens. 2002;16(4):225-36.
9. Fernandes T, Magalhães FC, Roque FR, Phillips MI, Oliveira EM. Exercise training prevents the microvascular rarefaction in hypertension balancing angiogenic and apoptotic factors: role of microRNAs-16, -21, and -126. Hypertens. 2012;59(2):513–20. doi: 10.1161/HYPERTENSIONAHA.111.185801
10. 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
11. Liao J, Zhang Y, Wu Y, Zeng F, Shi L. Akt modulation by miR-145 during exercise-induced VSMC phenotypic switching in hypertension. Life Sci. 2018;199:71–9. doi: 10.1016/j.lfs.2018.03.011
12. Rodrigues JA, Prímola-Gomes TN, Soares LL, Leal TF, Nóbrega C, Pedrosa DL, et al. Physical exercise and regulation of intracellular calcium in cardiomyocytes of hypertensive rats. Arq Bras Cardiol. 2018;111(2):172–9. doi: 10.5935/abc.20180113
13. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Vol. 116, Circulation. 2007.116(22):2634-53. doi: 10.1161/CIRCULATIONAHA.107
14. Melo SFS, Fernandes T, Baraúna VG, Matos KC, Santos AAS, Tucci PJF, et al. Expression of microRNA-29 and collagen in cardiac muscle after swimming training in myocardial-infarcted rats. Cell Physiol Biochem. 2014;33(3):657–69. doi: 10.1159/000358642
15. 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

Value of ^{18}F-FDG PET/CT in the Diagnosis and Assessment of Response to Treatment of Lupus Myocarditis

Alvaro M. Perazzo,[1,2,3,4,5] Larissa G. F. Andrade,[3,4] Leonardo G. A. Venancio,[3,4] Pedro Alves da Cruz Gouveia,[2,6] Mariana Feitosa Ramalho Galvão,[2,6] Esdras M. Lins,[3,4,7] Fernando Moraes Neto,[3,4,5] Simone Cristina Soares Brandão[3,4,8]

Divisão de Cirurgia Cardiovascular do Pronto-Socorro Cardiológico de Pernambuco - PROCAPE,[1] Recife, PE – Brazil
Universidade de Pernambuco - UPE,[2] Recife, PE – Brazil
Departamento de Cirurgia - Universidade Federal de Pernambuco - UFPE,[3] Recife, PE – Brazil
Programa de Pós-Graduação em Cirurgia da Universidade Federal de Pernambuco - UFPE,[4] Recife, PE – Brazil
Disciplina de Cirurgia Cardio-Torácica, Universidade Federal de Pernambuco - UFPE,[5] Recife, PE – Brazil
Departamento de Clínica Médica do Hospital Universitário Oswaldo Cruz,[6] Recife, PE - Brazil
Departamento de Cirurgia Vascular, Universidade Federal de Pernambuco - UFPE,[7] Recife, PE – Brazil
Departamento de Medicina Nuclear, Universidade Federal de Pernambuco - UFPE,[8] Recife, PE – Brazil

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with a wide spectrum of clinical manifestations. The cardiovascular system has relevant clinical importance among the affected organs because it is associated with higher mortality in these patients. The heart can be affected in any structure, and lupus myocarditis is a major diagnostic challenge in clinical practice.[1]

Non-invasive tests such as electrocardiograms and echocardiograms are not sensitive or specific enough for this diagnosis. Cardiac magnetic resonance imaging (CMR) is the preferred imaging modality for diagnosing myocarditis, but it has contraindications, such as patients with metallic implants or using gadolinium in chronic kidney disease.

Despite being considered the gold standard, myocardial biopsy has the great disadvantage of being an invasive procedure with inherent risks.[2] Thus, diagnostic alternatives with greater sensitivity, specificity, and less risk to the patient have been studied. The use of positron emission tomography associated with computed tomography with fluorodeoxyglucose (^{18}F-FDG PET/CT) emerges as a new imaging method for evaluating inflammatory processes in rheumatologic diseases, including SLE.[3,4] ^{18}F-FDG PET/CT combines the technique of nuclear medicine with computed tomography imaging.

Although the myocardium can capture glucose as an energy substrate, in the investigation of cardiac inflammatory processes, the preparation with fasting of at least 12 hours, a low-carbohydrate diet, fat and use of heparin 15 minutes before injection of ^{18}F-FDG suppresses physiological glucose uptake by cardiomyocytes. Thus, if we visualize cardiac uptake of ^{18}F-FDG, uptake by inflammatory cells is inferred since they do not suffer interference in glucose uptake with this preparation.[5] Few studies associate ^{18}F-FDG PET/CT with the diagnosis and follow-up of lupus myocarditis.[3,4] The image of this case is of a female patient, 16 years old, hospitalized with persistent fever, significant weight loss, cough, edema, and menstrual delay. She initiated research for several infectious diseases, including tuberculous pericarditis and autoimmune diseases. Among the tests performed, the transthoracic echocardiogram showed a biventricular deficit, pulmonary arterial hypertension, and severe mitral regurgitation. It was decided to perform 18F-FDG PET/CT during the diagnostic investigation due to renal dysfunction. After performing this examination, which showed a marked and diffuse cardiac hyperuptake of FDG (Figure 1), the possibility of lupus myocarditis was raised, which was later confirmed by serological tests, given the entire clinical context. The patient was treated with immunosuppressants (Methylprednisolone and mycophenolate mofetil), and after 2 months, the exam was repeated, showing complete regression of myocardial uptake (Figure 2). Considering the clinical case in question and a literature review, it is suggested that the use of ^{18}F-FDG PET/CT may be useful and promising in the diagnosis and follow-up of patients with lupus myocarditis.

Keywords

Lupus Erythematosus,Systemic/complications; Lupus Myocarditis; Diagnostic, Imaging; Tomography Computed Emission Positrons Tomography/methods; Immunosupressive Agents/therapeutic use.

Author Contributions

Conception and design of the research: Perazzo AM, Andrade LGF, Venancio LGA; Acquisition of data: Perazzo AM, Venancio LGA, Brandão SCS, Gouveia PAC, Galvão MFR; Analysis and interpretation of the data: Perazzo AM, Andrade LGF, Lins EM, Brandão SCS, Neto FM; Writing of the manuscript: Perazzo AM, Andrade LGF, Venancio LGA, Brandão SCS; Critical revision of the manuscript for intellectual contente:Perazzo AM, Andrade LGF, Venancio LGA, Lins EM, Brandão SCS, Neto FM, Gouveia PAC, Galvão MFR.

Simone Cristina Soares Brandão •
Programa de Pós-Graduação em Cirurgia da Universidade Federal de Pernambuco, UFPE - Av. Prof. Moraes Rego, S/N, Cidade Universitaria, Recife, PE- Brazil
E-mail: simone.brandao@ufpe.br
Manuscript received June 13, 2021, revised manuscript October 10, 2021, accepted December 08, 2021

DOI: https://doi.org/10.36660/abc.20210523

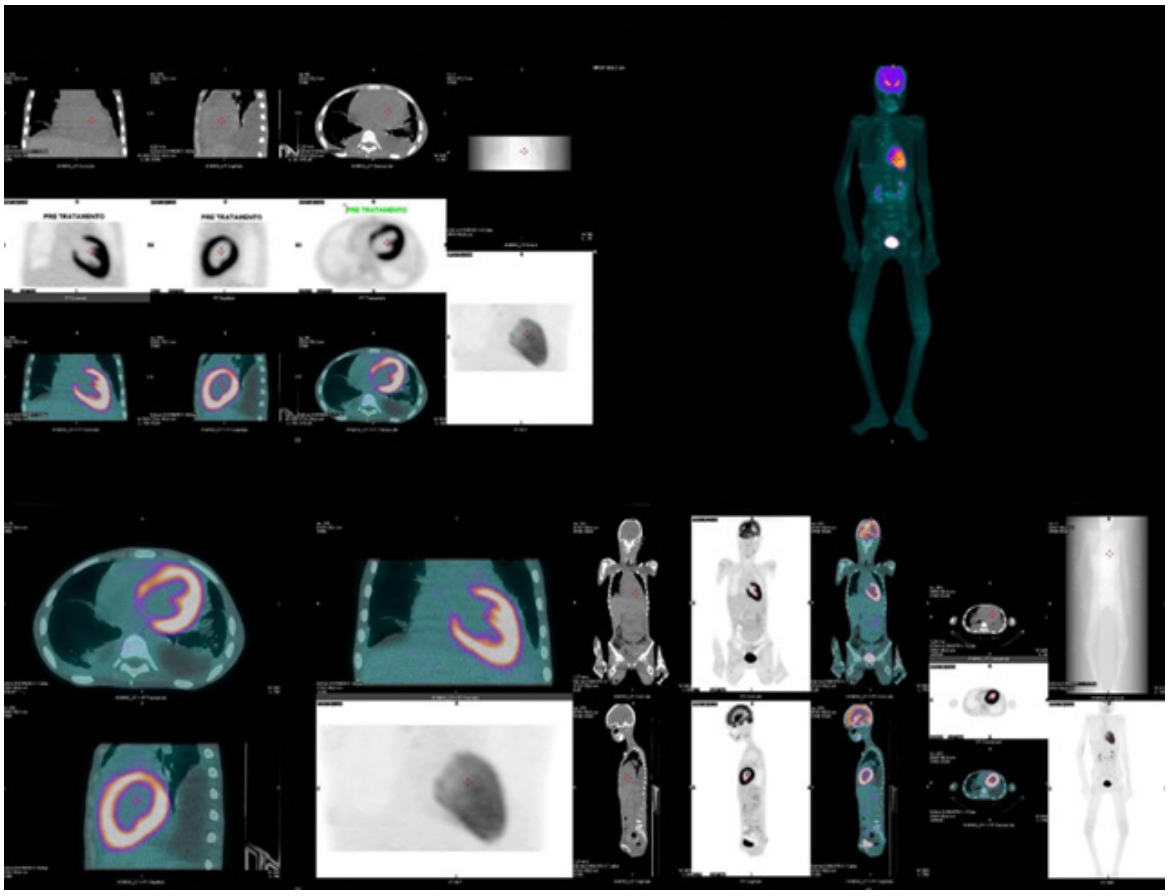


Figure 1 – *^{18}F-FDG PET/CT in pre-treatment lupus myocarditis: There is intense diffuse uptake of ^{18}F-FDG in the left ventricle, suggesting myocarditis.*

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

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.

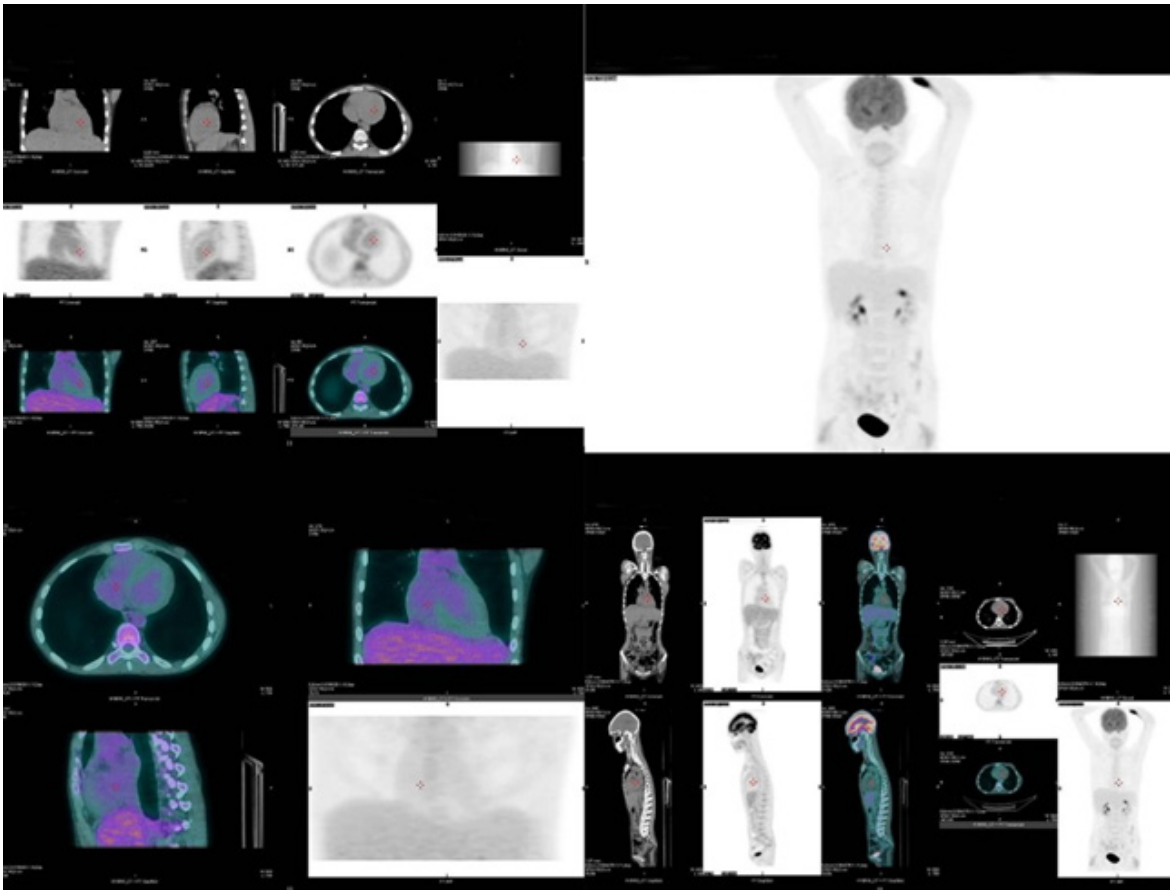


Figure 2 – *^{18}F-FDG PET-CT in post-treatment lupus myocarditis: Complete regression of uptake is observed after 2 months of immunosuppressant treatment.*

References

1. Doria A, Laccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. Lupus. 2005;14(9):683-6. doi: 10.1191/0961203305lu2200oa.
2. Cooper LT. Myocarditis. N Engl J Med. 2009;360(15):1526-38. doi: 10.1056/NEJMra0800028.
3. Alchammas J, Al-Faham Z, Roumayah Y, Wong OCY. The evaluation of lupus myocarditis with 13N-Ammonia and 18F-FDG PET. J Nucl Med Technol. 2016;44(3):210-1. doi: 10.2967/jnmt.115.165639.
4. Perel-Winkler A, Bokhari S, Perez-Recio T, Zartoshti A, Askanase A, Geraldino-Pardilla A. Myocarditis in systemic lupus erythematosus diagnosed by 18 F-fluorodeoxyglucose positron emission tomography. Lupus Sci Med. 2018; 5(1):e000265. doi: 10.1136/lupus-2018-000265.
5. Al-Fahan Z, Jolepalem P, Wong CO. The evaluation of cardiac sarcoidosis with 18F-FDG PET scan. J Nucl Med Technol. 2016; 44(2):92-3. DOI: 10.2967/jnmt.115.158857

Erratum

April 2022 Issue, vol. 118(4), pages 797-857

In the "Joint Guideline on Venous Thromboembolism - 2022", with doi number: https://doi.org/10.36660/abc.20220213, published in the journal Arquivos Brasileiros de Cardiologia, 118(4): 797-857, the following corrections were made:

Included the institution Hospital DF Star, Rede D'Or, Brasília, DF – Brazil, for the author Simone Nascimento dos Santos.

At Angiolab Vitória, Laboratório Vascular, corrected the location "Rio de Janeiro, RJ" for "Vitória, ES".

On page 804, Chart 2, an arrow from "Positive" to "VUS" was inserted.

Only in the Portuguese version, page 806, Chart 5, right column, the position of "Positivo" and "Negativo" was changed.

Only in the Portuguese version, page 822, Chart 9, line 7, corrected the spelling of " Compressibilidade".

DOI: https://doi.org/10.36660/abc.20220372