Original Article

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

Henrique Tria Bianco,[1] Rui Povoa,[2] Maria Cristina Izar,[2] Braulio Luna Filho,[2] Flavio Tocci Moreira,[1] Edson Stefanini,[1] Henrique Andrade Fonseca,[1] Adriano Henrique Pereira Barbosa,[1] Claudia Maria Rodrigues Alves,[1] Adriano Mendes Caixeta,[1,3] Iran Gonçalves Jr,[2] Pedro Ivo de Marqui Moraes,[2] Renato Delascio Lopes,[1,4] Angelo Amato Vincenzo de Paola,[1] Dirceu Almeida,[2] Valdir Ambrosio Moises,[1] Francisco A. H. Fonseca[2]

Escola Paulista de Medicina da Universidade Federal de São Paulo,[1] São Paulo, SP - Brazil

Universidade Federal de Sao Paulo,[2] São Paulo, SP – Brazil

Hospital Israelita Albert Einstein,[3] São Paulo, SP - Brazil

Duke University Hospital,[4] Durham, North Carolina – USA

Abstract

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

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

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

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

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

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

Introduction

Although primary percutaneous coronary intervention (PCI) is considered the "gold standard" treatment for ST-Segment elevation myocardial infarction (STEMI), it is not always available, especially in developing countries.[1] Considering this scenario, the drug-invasive strategy, with fibrinolysis and referral for coronary angiography, has proved to be a viable option, according to the guidelines and observed in several studies, including STREAM, with unquestionable benefits when applied within the first hours of the event.[2-5] Therefore, a project was started in 2010, by the Municipal Health Department, Universidade Federal de Sao Paulo and the Itinerant Health Care Service, which organized a planned system of thrombolysis in suburban health centers, including transfer to the university center for angiography and treatment of the related artery. Hence, the use of bedside biomarkers is essential for the discrimination of patients who have obtained adequate results and those who should be referred for rescue angioplasty.

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

Mailing Address: Henrique Tria Bianco •
Escola Paulista de Medicina da Universidade Federal de São Paulo -
Rua Loefgren, 1350. Postal Code - 04040-001, São Paulo, SP – Brazil
E-mail: henriquetria@uol.com.br
Manuscript received March 24, 2020, revised manuscript June 19, 2020, accepted July 29, 2020

DOI: https://doi.org/10.36660/abc.20200241

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

Methods

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

Drug-invasive strategy

The drug-invasive strategy was defined as the use of thrombolysis with TNK, using a weight-adjusted dose , followed by cardiac catheterization within 24 hours.[7] After the STREAM [3] study results in 2013, patients aged >75 years received half a dose (1/2-TNK). Only patients with an unquestionable contraindication to fibrinolysis were excluded from this analysis. The patients were premedicated with a loading dose of acetylsalicylic acid and clopidogrel. Rescue angiography was indicated by the local medical staff due to the suspected ineffective thrombolysis for the treatment of the infarct-related artery (IRA).

Assessed electrocardiographic variable

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

Assessed angiographic variables

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

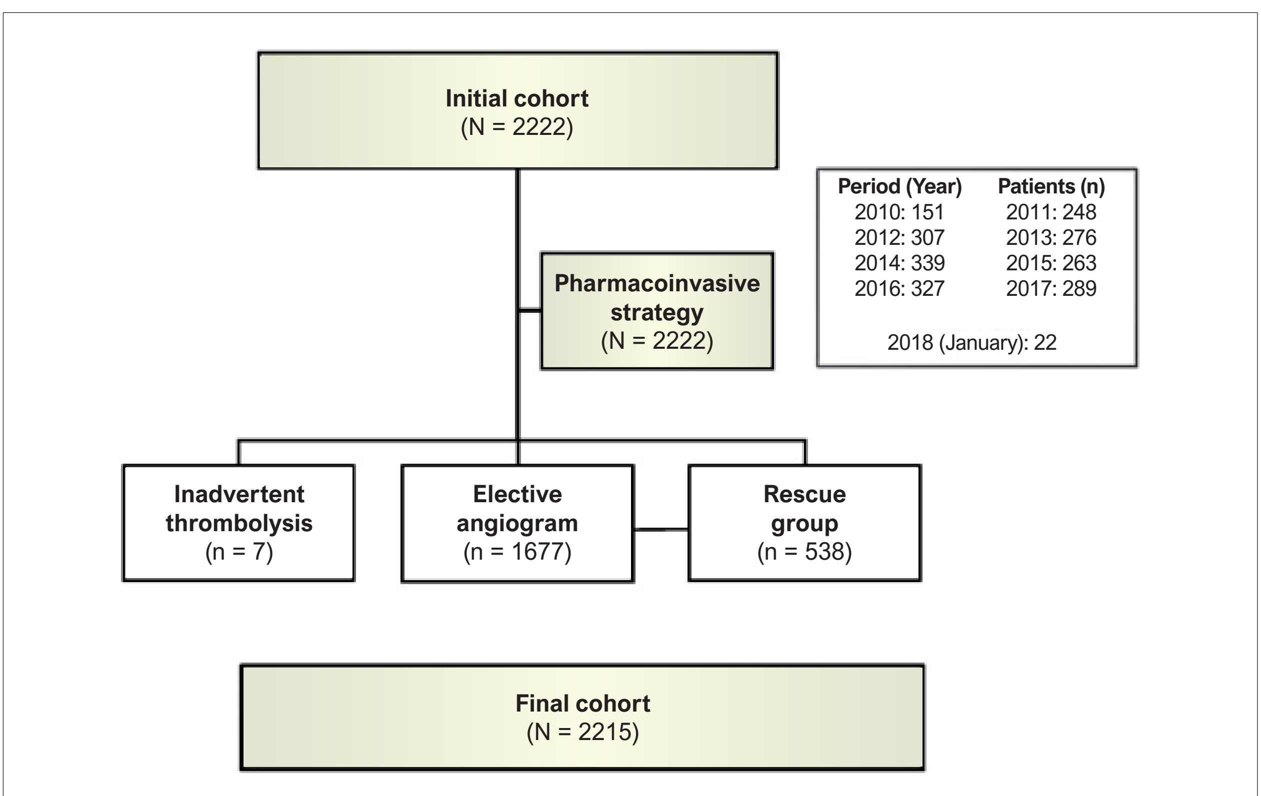

Figure 1 – *Flowchart of the studied cohort.*

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

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

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

Statistical analysis

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

Results

Patients of both genders, 70.2% of which were men were included; the median age was 58 years, IQR (50-66). The time from symptom onset to the primary care center was 220 minutes, IQR (140-345). The prevalence of risk factors and the patients' characteristics in the basal period is reported in Table 1. Briefly, 60.7% were hypertensive; 29.8% had diabetes; 63.1% were smokers. In addition, 11% had a previous myocardial infarction and 4.3% had a previous stroke. The risk predictors used were recorded at the baseline period. Most patients were in low functional class by the Killip-Kimball classification:[8] **I** (73%), **II** (16.3%), **III** (2.2%), **IV** (8.6%); and had a low risk profile according to the prediction scores, TIMI-Risk:[9] 3, IQR(2-5); GRACE[10]: 136, IQR (117-161), meaning a low risk profile.

Distribution of coronary flow according to TIMI / MBG

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

Distribution of the infarct-related arteries

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

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

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

Clinical characteristics of patients referred for rescue therapy

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

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

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

Data on medical history, comorbidities and presentation time were largely derived from medical interviews. Demographic information and risk factors were reported by patients and trained staff reviewed the data during hospital admission. For comparisons between groups, the Mann-Whitney nonparametric test for continuous variables and χ2 test for discrete variables were used. The data are expressed as median (MD) and interquartile range (IQR), or number and percentage. eGFR†: glomerular filtration rate estimated by MDRD (Modification of Diet in Renal Disease); TNK‡: Tenecteplase; Cath-lab: catheterization laboratory.

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

Discussion

A critical aspect of damage reduction associated with myocardial infarction is the guarantee of access to the emergency care, in which the identification of symptoms and the performance of the initial ECG are fundamental. With primary PCI unavailable in basic health units and in many hospitals, the drug-invasive strategy is recommended in STEMI.[2] The best method to obtain reperfusion has been widely debated, essentially skewed by the competitive perception regarding the possibilities of revascularization. It is well established that the best strategy is the one available within well-established deadlines, being indifferent within the first hours of the onset of ischemic symptoms. The trialist group demonstrated that in patients with pain within 6 hours, 30 deaths were prevented/1,000; between 7 and 12 hours, approximately 20 deaths/1,000 would be prevented.[11] Thus, the importance of the fast identification of ischemic symptoms and prompt care are highlighted. Consequently, even the primary PCI, as well as fibrinolysis, are well-established treatments and the benefits are maximized when treatment occurs as soon as possible.[12] A meta-analyses reported an increased risk of recent-onset heart failure, with a relative increase in the incidence per one hour-delay in reperfusion strategies.[13]

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

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

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

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

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

In this context, the "open artery" hypothesis was postulated, indicating the prognostic impact if the artery was recanalized.[17] Within this broad spectrum, Gibson et al.[18] introduced a refined method for the myocardial perfusion value: TIMI-flow and reperfusion therapy were considered angiographically successful when TIMI-3 was reached.[19,20] However, even when this score is reached, some patients have inadequate tissue perfusion and several mechanisms have been suggested, among others, distal embolization and the no-reflow phenomenon.[21-23] Subsequently, Hoffmann et al.[24] disclosed the MBG concept with the angiographic index of the microvascular flow, since patients with TIMI-3 and normal MBG flow had lower mortality rates. The restoration of the coronary patency is not a guarantee of tissue perfusion; therefore, we understand that the presence of adequate MBG is a relevant prognostic characteristic and should be added to the TIMI- flow classification, commonly used to define successful angiographic reperfusion.[25-27] The abnormalities evaluated by MBG correlate with unfavorable ventricular remodeling, even after adjustment for the presence of TIMI-3 flow.[28-31]

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

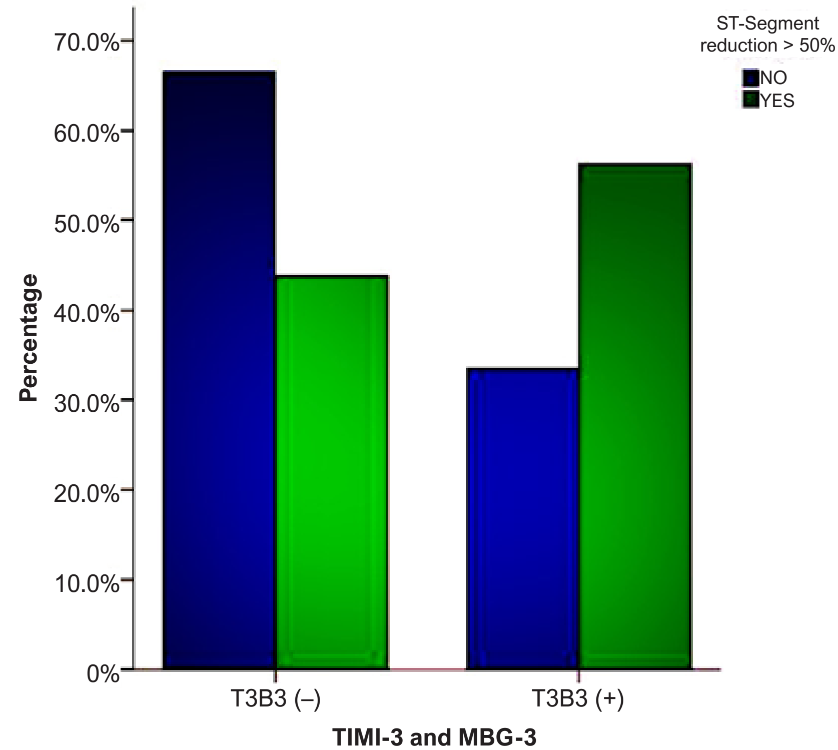

Figure 2 – *Correlation between angiographic patterns (TIMI-3 and MBG-3) and the electrocardiographic criteria for reperfusion.*

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

Correlation Coefficient (Kendall index)					
Sex				**ST Segment Reduction**	**TIMI-3 / Blush-3**
Men	Kendall coefficient	ST-Reduction	Correlation Coefficient	1.0	**0.203***
			N	1537	1506
		TIMI-3 / Blush-3	Correlation Coefficient	**0.203***	1.0
			N	1506	1523
Women	Kendall coefficient	ST-Reduction	Correlation Coefficient	1.0	**0.231***
			N	652	637
		TIMI-3 / Blush-3	Correlation Coefficient	**0.231***	1.0
			N	637	643

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

PCI, not post-thrombolysis, and did not consider the MBG pattern as a defining variable of a better angiographic pattern of reperfusion. The presence of angiographically verified early resolution of the ST-Segment elevation post-primary PCI successfully identifies patients that are more likely to benefit from early restoration of flow in the IRA. It is also noteworthy that the TIMI-flow measures greatly overestimate the success in the primary PCI. In the post-fibrinolysis studies, the definition of angiographic success was characterized by the presence of TIMI 2 and 3. However, patients with TIMI-flow <3 show a worse clinical evolution, especially in the medium and long-term, when compared to the group of patients with TIMI-flow 3.

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

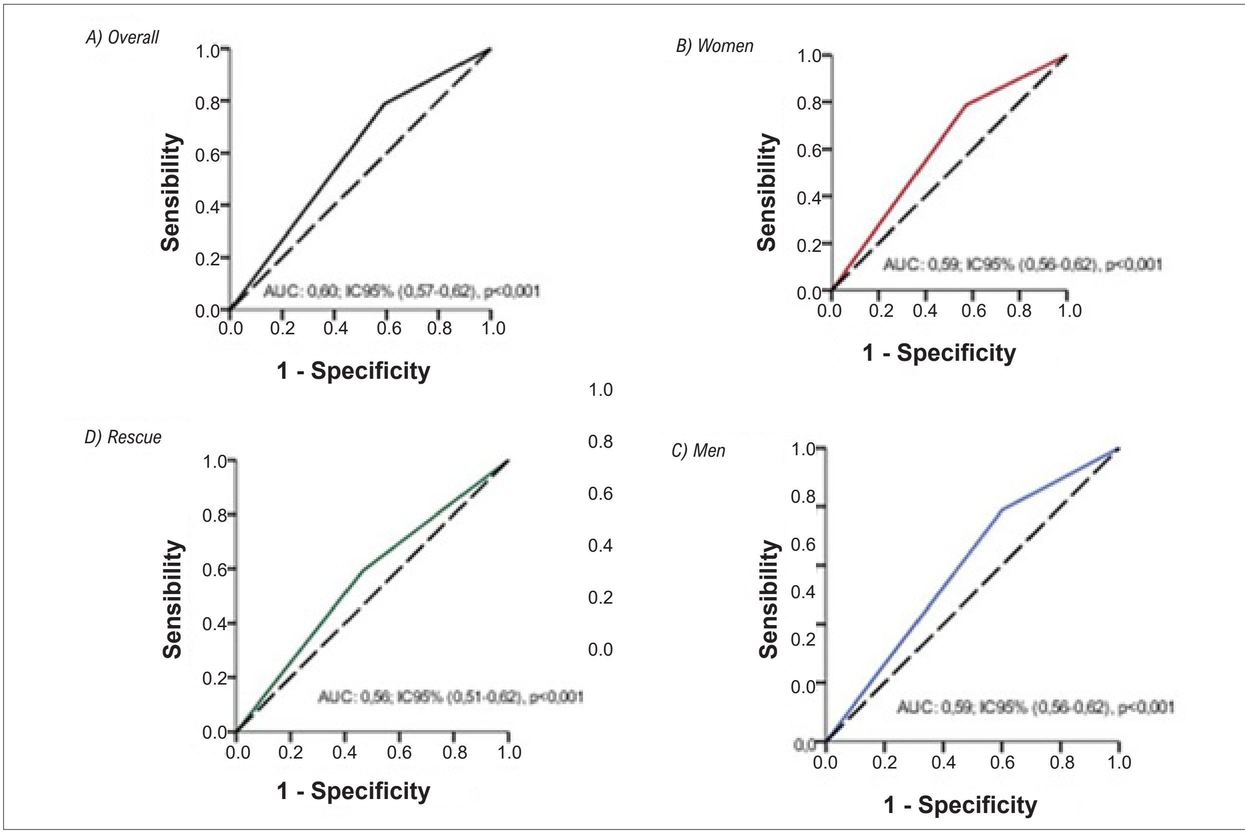

Figure 3 – *Area under the curve of patients with TIMI-flow 3 / Myocardial Blush Grade 3 and ST-Segment reduction for all patients and stratified by gender. A) Overall; B) Women; C) Rescue group; D) Men.*

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

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

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

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

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

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

Ideally, a reperfusion indicator should be readily obtained and applicable mainly at the bedside. In our cohort, referral to the early angiographic study was possibly due to changes in the ST-Segment, because patients who did not have post-thrombolysis reduction were more rapidly referred to rescue therapy. In the group with ST-segment reduction >50%, the mean time between thrombolysis and the catheterization laboratory was 960 minutes *vs*. 410 minutes in the group without ST-segment reduction. However, this may have been a mistaken option, because 24.5% had TIMI-3 / MBG-3, characterizing a diagnosis of false-positive severity. In addition, 38.5% of the group with a reduction >50% showed an angiographic pattern of TIMI-flow <3, underestimating the real risk. In a recent study by our group, which assessed 104 patients, the analysis of the measurement of the QT interval and its dispersion in the 12 leads, and also only in the region with ST-segment elevation (named regional dispersion of the QT interval) pre and 60-minutes post-lysis, showed an increase in the regional dispersion of the QT interval (dQT-Reg) post-lysis in anterior wall infarctions in the cases with TIMI-3 / MBG-3 flow, with sensitivity and specificity of 93% and 71%, respectively. Although the study evaluated a small number of patients, these data suggest dQT-Reg as a promising instrument in the noninvasive identification of reperfusion.[38]

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

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

Limitations of the study

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

Conclusion

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

Acknowledgments

The authors would like to thank the doctors, nurses, and technicians working at the hemodynamics laboratories, coronary units and regional emergency medical services. Also, we would like to express our tribute and reverence to Professor Antonio Carlos de Camargo Carvalho, who designed this thematic project, and who left us too soon (*1947-2019†).

Author Contributions

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

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of post-doctoral submitted by Henrique Tria Bianco, from Universidade Federal de São Paulo (UNIFESP).

References

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

16. Sutton AG, Campbell PG, Graham R, Price DJ, Gray JC, Grech ED, et al. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. J Am Coll Cardiol. 2004;44(2):287-96.

17. Roe MT, Ohman EM, Maas AC, Christenson RH, Mahaffey KW, Granger CB, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. J Am Coll Cardiol. 2001 Jan;37(1):9-18.

18. Gibson CM, Cannon CP, Daley WL, Dodge Jr JT, Alexander Jr B, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996 Mar 1;93(5):879-88.

19. Hof AWJ. Successful reperfusion therapy: from epicardial to myocardial salvage. Rev Esp Cardiol. 2010;63(7):757-9.

20. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for acute myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 study. Circulation. 1993;87(6):1829-39.

21. Fernandes MR, Fish RD, Canales J, Aliota J, Silva GV, Perin EC, et al. Restoration of microcirculatory patency after myocardial infarction. results of current coronary interventional strategies and techniques. Tex Heart Inst J. 2012;39(3):342-50.

22. Stambuk K, Krcmar T,Zeljkovic I. Impact of intracoronary contrast injection pressure on reperfusion during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: A prospective randomized pilot study. Int J Cardiol Heart Vasc. 2019 Aug 20;24:100412.

23. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, et al. Clinical implications of the "no reflow" phenomenon: a predictor of complications and left ventricular remodelling in reperfused anterior wall myocardial infarction. Circulation. 1996;93(2):223-8.

24. Hoffmann R, Haager P, Lepper W, Franke A, Hanrath P. Relation of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction. Heart. 2003;89(10):1147-51.

25. Henriques JPS, Zijlstra F, Hof AWJ, Boer MJ, Dambrink JHE, Gosselink M, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation. 2003;107(16):2115-9.

26. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am Coll Cardiol. 2002;39(4):591-7.

27. Kampinga MA, Nijsten MW, Gu YL, Dijk WA, de Smet BJ, Heuvel AF, et al. Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in patients with ST-elevation myocardial infarction in routine clinical practice? Circ Cardiovasc Interv. 2010 Jun 1;3(3):216-23.

28. Prado AP, Fernández-Vázqueza F, Cuellas-Ramóna JC, Gibson CM. Coronary angiography: beyond coronary anatomy. Rev Esp Cardiol. 2006;59(6):596-608.

29. Dibra A, Mehilli J, Dirschinger J, Pache J, Neverve J, Schwaiger M, et al. Thrombolysis in myocardial infarction myocardial perfusion grade in angiography correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis. J Am Coll Cardiol. 2003;41(6):925-9.

30. Angeja BG, Gunda M, Murphy SA, Sobel BE, Rundle AC, Syed M, et al. TIMI myocardial perfusion grade and ST segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. Circulation. 2002;105(3):282-5.

31. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. Catheter Cardiovasc Interv. 2008;72(7):950-7.

32. Ndrepepa G, Alger P, Kufner S, Mehilli J, Schömig A, Kastrati A. ST-segment resolution after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Cardiol J. 2012;19(1):61-9.

33. Zwaan HB, Stoel MG, Roos-Hesselink JW, Veen G, Boersma E, Birgelen C. Early versus late ST-segment resolution and clinical outcomes after percutaneous coronary intervention for acute myocardial infarction. Neth Heart J. 2010 Sep;18(9):416-22.

34. Matetzky S, Novikov M, Gruberg L, Freimark D, Feinberg M, Elian D, et al. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. J Am Coll Cardiol. 1999;34(7):1932-8.

35. Kaluzay J, Vandenberghe K, Fontaine D, Ganame J, Anné W, Merwe N, et al. Importance of measurements at or after the j-point for evaluation of ST-segment deviation and resolution during treatment for acute myocardial infarction. Int J Cardiol. 2005 Feb 28;98(3):431-7.

36. McLaughlin MG, Stone GW, Aymong E, Gardner G, Mehran R, Lansky AJ, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. J Am Coll Cardiol. 2004;44(6):1215-23.

37. Yan AT, Yan RT, Tan M, Casanova A, Labinaz M, Sridhar K, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J. 2007;28(9):1072-8.

38. Dotta G, Fonseca FAH, Izar MCO, Souza MT, Moreira FT, Pinheiro LFM, et al. Regional QT interval dispersion as an early predictor of reperfusion in patients with acute myocardial infarction after fibrinolytic therapy. Arq Bras Cardiol. 2019 Jan;112(1):20-9.

39. Califf RM, O'Neil W, Stack RS, Aronson L, Mark DB, Mantell S, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med. 1988 May;108(5):658-62.

40. Khoury NE, Borzak S, Gokli A, Havstad S, Smith ST, Jones M. "Inadvertent" thrombolytic administration in patients without myocardial infarction: clinical features and outcome. Ann Emerg Med. 1996;28(3):289-93.

41. Bär F, Vainer J, Stevenhagen J, Neven K, Aalbregt R, Ophuis TO, et al. Ten-year experience with early angioplasty in 759 patients with acute myocardial infarction. J Am Coll Cardiol. 2000 Jul;36(1):51-8.

42. Bradley EH, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med. 2006;355(22):2308-20.

Original Article