

# Predictors of in-hospital mortality in patients with ST-segment elevation myocardial infarction undergoing pharmacoinvasive treatment

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**OBJECTIVES:** To identify predictors of in-hospital mortality in patients with acute myocardial infarction undergoing pharmacoinvasive treatment.

**METHODS:** This was an observational, prospective study that included 398 patients admitted to a tertiary center for percutaneous coronary intervention within 3 to 24 hours after thrombolysis with tenecteplase. ClinicalTrials.gov: NCT01791764

**RESULTS:** The overall in-hospital mortality rate was 5.8%. Compared with patients who survived, patients who died were more likely to be older, have higher rates of diabetes and chronic renal failure, have a lower left ventricular ejection fraction, and demonstrate more evidence of heart failure (Killip class III or IV). Patients who died had significantly lower rates of successful thrombolysis (39% vs. 68%;  $p=0.005$ ) and final myocardial blush grade 3 (13.0% vs. 61.9%;  $p<0.0001$ ). Based on the multivariate analysis, the Global Registry of Acute Coronary Events score (odds ratio 1.05, 95% confidence interval (CI) 1.02-1.09;  $p=0.001$ ), left ventricular ejection fraction (odds ratio 0.9, 95% CI 0.89-0.97;  $p=0.001$ ), and final myocardial blush grade of 0-2 (odds ratio 8.85, 95% CI 1.34-58.57;  $p=0.02$ ) were independent predictors of mortality.

**CONCLUSIONS:** In this prospective study that evaluated patients with ST-segment elevation myocardial infarction treated by a pharmacoinvasive strategy, the in-hospital mortality rate was 5.8%. The Global Registry of Acute Coronary Events score, left ventricular ejection fraction, and myocardial blush were independent predictors of mortality in this high-risk group of acute coronary syndrome patients.

**KEYWORDS:** Myocardial Infarction; Mortality; Pharmacoinvasive Therapy.

Falcão FJ, Alves CM, Barbosa AH, Caixeta A, Sousa JM, Souza JA, et al. Predictors of in-hospital mortality in patients with ST-segment elevation myocardial infarction undergoing pharmacoinvasive treatment. *Clinics*. 2013;68(12):1516-1520.

Received for publication on April 18, 2013; First review completed on May 22, 2013; Accepted for publication on June 20, 2013

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## INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the standard of care reperfusion therapy for patients with evolving ST-segment elevation myocardial infarction (STEMI) (1-3). Although individual centers have performed pPCI for many years, a significant number of patients with STEMI either do not receive this optimal treatment or do not receive it in a timely manner due to the small number of

tertiary care centers with an around-the-clock ('24/7') service. Large urban centers and rural areas, where tertiary care hospitals are restricted to specific regions, are less likely to have the capacity to deliver this treatment to the population as a whole (4).

Thus, a pharmacoinvasive treatment strategy has emerged as an alternative for STEMI patients admitted to primary care centers. A pharmacoinvasive strategy consists of the use of intravenous thrombolytic therapy in a primary care center followed by immediate transfer to a tertiary hospital, where early, systematic coronary angiography and percutaneous coronary angioplasty should be performed within 3 to 24 hours, even in cases of successful reperfusion (5).

In Brazil, despite recent social and medical therapeutic advances, the number of acute myocardial infarctions in the population still reaches 300,000 to 400,000 per year, with STEMI representing 30% to 40% of all cases. Furthermore, mortality rates are still high outside major referral centers,

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No potential conflict of interest was reported.

**DOI:** 10.6061/clinics/2013(12)07



with an estimated 1 death for every 5 to 7 cases (6). Therefore, we recently developed a public STEMI network based on a pharmacoinvasive treatment strategy in the metropolitan area of São Paulo as a possible alternative to pPCI. In the present study, we sought to evaluate the rate and predictors of in-hospital mortality in a large population of STEMI patients who underwent pharmacoinvasive treatment.

## ■ METHODS

### Patients and study protocol

Between November 2010 and October 2012, 567 patients with STEMI were transferred to a tertiary hospital (Hospital São Paulo, Escola Paulista de Medicina at Federal University of São Paulo) as part of a municipal primary care program for STEMI. The structured health care network for patients with STEMI has been previously described in detail elsewhere (7). In brief, patients are first admitted to a primary emergency room facility or rescued by the Emergency Mobile Healthcare Service (SAMU) at home and then referred to our tertiary PCI center. Patients were either treated with thrombolysis or underwent pPCI as appropriate and according to current guidelines (1-3). Those patients receiving thrombolysis were referred for an early invasive coronary angiography procedure regardless of successful reperfusion 3 to 24 hours after thrombolysis (i.e., elective or rescue PCI) according to clinical and electrocardiographic criteria. Coronary angiographies were performed by femoral access, and only bare metal stents were used. After excluding patients who did not receive thrombolysis, those who underwent pPCI, and those with no acute myocardial infarction, 398 patients remained for the present analysis.

### Study objective and definitions

The primary objective of this study was to evaluate the rate and predictors of in-hospital mortality in a population of STEMI patients who underwent pharmacoinvasive treatment. Patients were consecutively included and divided into two groups according to mortality (patients who died during the index hospitalization from all causes and patients who survived) and compared according to their clinical, angiographic, and procedural variables as appropriate. Demographic and clinical data were entered into a database prospectively, and all quantitative coronary angiography data were analyzed by one experienced interventional cardiologist. Thrombolysis in myocardial infarction (TIMI) flow and blush grade were assessed as previously reported (8,9). Coronary artery disease (CAD) was defined as single- or multi-vessel disease according to the number of epicardial arteries with at least 1 lesion measuring  $\geq 70\%$  of the diameter of stenosis.

Chronic renal failure was defined as creatinine clearance  $< 60$  mL/min, estimated by the Cockcroft-Gault formula (10). Anemia was defined as plasma hemoglobin measuring less than 13 mg/dL for males or 12 mg/dL for females (11). The Global Registry of Acute Coronary Events (GRACE) score (12) was calculated at admission, and the left ventricular ejection fraction (LVEF) was determined by echocardiography during hospitalization. Successful thrombolysis was defined as a culprit artery with TIMI flow grade 2-3 at the time of coronary angiography. Time intervals between chest pain and the administration of Tenecteplase

(TNK; pain-to-needle time) and between the administration of TNK and coronary angiography (needle-to-balloon time) are expressed in hours. This study was conducted in compliance with the ethical principles of the Helsinki Declaration (2008), as well as local applicable laws and regulations. It was registered in ClinicalTrials.gov with the identifier number NCT01791764.

### Statistical analysis

Continuous variables are expressed as the mean and standard deviation, and categorical variables are expressed as absolute numbers and percentages. Fisher's exact test, Pearson's chi-square test, or Student's t-test were used when appropriate.

A multivariate logistic regression model was used to identify potential independent predictors of mortality. Odds ratios (ORs) and their respective confidence intervals (95% CIs) were used to quantify the effects. The variables included in the model were age, gender, hemoglobin level, diabetes mellitus, hypertension, current smoking status, chronic renal failure, GRACE score, Killip class, baseline and final TIMI flow, and final myocardial blush grade. SPSS® software version 20 (IBM, Armonk, NY, USA) was used for all analyses, and a final *p* value less than 0.05 was considered significant.

## ■ RESULTS

The study flowchart is shown in Figure 1. After excluding pPCI patients, patients without CAD, patients triaged to CABG, and patients treated with thrombolytics other than TNK, a total of 398 patients were selected for the current analysis. The mean pain-to-needle and needle-to-balloon times were  $4.5 \pm 3.8$  and  $16.4 \pm 20.6$  hours, respectively. Overall, the in-hospital mortality rate was 5.8% (compared with 6.5% of the entire population of 567 patients), and the mean GRACE score was  $148.2 \pm 36.9$ . A comparison of demographic and clinical characteristics in non-survivors and survivors is provided in Table 1. Compared with patients who survived, non-survivors were more likely to be older and to have higher rates of diabetes and chronic renal failure, higher GRACE scores, lower LVEFs, and more evidence of heart failure (Killip class III or IV). Additionally, patients who died had a significantly lower incidence of baseline TIMI grade 2 or 3 flow (39% vs. 68%;  $p = 0.005$ ) and a lower final myocardial blush grade (Table 1).

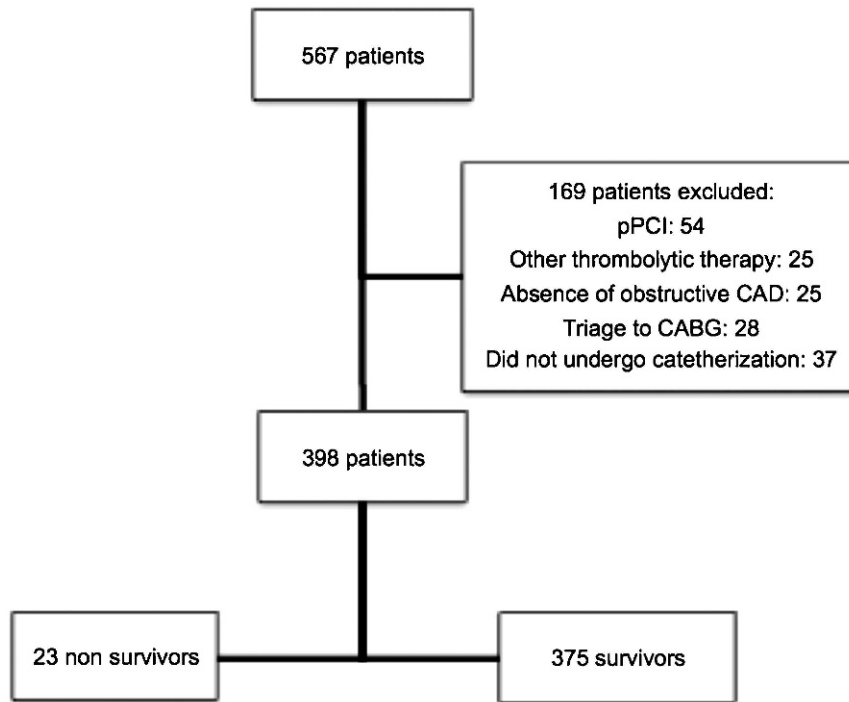
Two patients (0.5%) had a hemorrhagic stroke, 16 (4%) required blood transfusion, and vascular complications related to the access site were observed in 26 (6.5%) patients. A more detailed analysis of the vascular access and bleeding complications in patients undergoing pharmacoinvasive strategy in our institution has been previously reported (13).

### Predictors of in-hospital mortality

Based on the multivariate regression analysis, only GRACE score, LVEF, and final blush grade 0-2 were independent predictors of mortality (Table 2).

## ■ DISCUSSION

Providing optimal care for STEMI patients is challenging in any country, regardless of its wealth and developmental level. This is especially true in large urban centers or rural areas, where a lack of access to tertiary healthcare may make the performance of timely pPCI difficult. The so-called



**Figure 1** - Flowchart of patients included in the study.

pharmacoinvasive treatment strategy, consisting of thrombolysis with TNK and contemporary antithrombotic therapy administered before transport to a PCI-capable hospital, has emerged as an alternative to pPCI. The recommendation of prompt transfer to a referral center with a catheterization laboratory is deemed fundamental to the strategy's success, allowing for (i) immediate reperfusion in cases when thrombolysis fails; (ii) treatment for early reocclusion, which can affect as many as 30% of cases (14); and, ultimately, (iii) early PCI (<24 hours) for patients with successful thrombolytic reperfusion but with severe residual stenosis. Compared with pPCI, this strategy has shown similar clinical outcomes (15-17). Accordingly, this strategy is strongly recommended by the European Society of Cardiology and ACC/AHA guidelines (class I and IIa, respectively) (1,3).

The present study represents one of the largest real-world studies relevant to this subject thus far and shows an in-hospital all-cause mortality rate of 5.8%. Other national, multicenter studies have reported mortality rates of 3.3% in patients who underwent elective PCI after thrombolysis, 7.6% in patients who underwent rescue PCI, and 5.6% in pPCI patients (18,19). In previous randomized multicenter studies comparing a pharmacoinvasive strategy with ischemia-driven PCI, in-hospital mortality rates ranged from 3.0% to 4.5%. These studies, however, also demonstrated shorter pain-to-needle and needle-to-balloon times (2 and 4 hours, respectively), which may explain, at least in part, their lower mortality rates (14,20). A remarkably low mortality rate was also observed in a recently published STREAM trial (21), which compared pPCI with a pharmacoinvasive approach. This study randomized STEMI patients who had a clinical presentation for less than 3 hours and who were at least 60 minutes away from pPCI centers and found an overall mortality rate of 4.7% for both groups. Similar to previous results, such as those

obtained in the TRANSFER AMI study (14), and our own results, one-third of the STREAM patients required rescue catheterization.

In the present analysis, LVEF and the GRACE score emerged as significant predictors of mortality. Successful thrombolysis was achieved in over 65% of patients, similar to the rate reported in the STREAM trial, with a mortality rate of only 3.4% in this subgroup (significantly lower than the rate of 10.4% in patients with a baseline TIMI flow of 0-1). Therefore, this study showing a low mortality rate in patients who underwent successful thrombolysis is encouraging and stresses the potential importance of a pharmacoinvasive treatment strategy, especially in public hospitals and developing countries.

Regardless of achieving a similar optimal final TIMI flow after PCI (as a surrogate endpoint for PCI angiographic success) in both groups, grade 3 myocardial blush was observed significantly less often in non-survivors; thus, myocardial blush grade was also an important independent predictor of mortality. Restoring coronary microcirculation through the use of several available strategies and in light of ongoing studies (e.g., intracoronary abciximab and thrombectomy) has been a challenge for interventional cardiologists over the last several decades. Studies evaluating patients who underwent thrombolytic and mechanical reperfusion during STEMI showed a direct relationship between the degree of myocardial perfusion, as detected by the blush angiographic method, and mortality in short and long clinical follow-up periods (22,23).

Restoring microcirculation extends beyond the restoration of epicardial flow and depends on the optimization of adjunctive therapy, especially antiplatelet and antithrombotic therapy. Compared with the STREAM trial population, we achieved similar rates of final TIMI flow 2-3 even in a setting of a longer pain-to-needle time. Therefore, achieving

**Table 1** - Baseline, clinical, and procedural characteristics of non-survivors vs. survivors.

Variables	Non-survivors (23)	Survivors (375)	p-value
Age (years)	63.78 ± 11.2	57.63 ± 11.5	0.011
Male	13 (56.5%)	260 (69.3%)	0.199
CrCl (<60 ml/min)	10 (43.5%)	63 (16.8%)	0.001
Diabetes mellitus	14 (60.9%)	105 (28%)	0.001
Hypertension	16 (69.5%)	234 (58.7%)	0.330
Dyslipidemia	14 (60.9%)	220 (58.6%)	0.846
Currently smoking	14 (60.9%)	248 (66.1%)	0.797
Anemia	6 (26.1%)	61 (16.3%)	0.222
Anterior AMI	6 (26.1%)	97 (25.9%)	0.981
Inferior AMI + RV	5 (21.7%)	36 (9.6%)	0.075
Killip class III or IV	10 (43.5%)	29 (7.7%)	<0.0001
GRACE risk score	206.2 ± 39.2	144.6 ± 33.7	<0.0001
LVEF (%)	33.9 ± 20.2	49.9 ± 12.5	<0.0001
Pain-to-needle time (h)	4.8 ± 3.1	4.4 ± 3.9	0.69
Needle-to-balloon time (h)	8.0 ± 6.3	17.0 ± 21.1	0.053
Successful thrombolysis	9 (39.1%)	255 (68%)	0.005
Multi-vessel CAD	20 (87%)	240 (64%)	0.024
Final TIMI 2, 3	20 (87%)	343 (91.4%)	0.442
Final Blush 0-2	20 (87%)	143 (38.1%)	<0.0001

CrCl: creatinine clearance; AMI: acute myocardial infarction; RV: right ventricular involvement.

a baseline TIMI flow of 3 along with a myocardial blush grade of 3 should be considered to indicate optimal reperfusion. This finding is in accordance with previous studies demonstrating a normal myocardial blush grade as a predictor of survival and left ventricular recovery in patients who undergo pPCI and rescue angioplasty (24-28).

Hemorrhagic complications are still a concern associated with this strategy. However, no significant difference was observed in randomized trials between this treatment strategy and other treatments (14,20,21). In the STREAM trial, after the amendment of halving the TNK dosage in patients older than 75 years, there was no significant difference in hemorrhagic events between the groups. Hemorrhagic stroke and blood transfusion occurred in 0.5% and 2.9% of patients, respectively; in our study, these rates were 0.5% and 4.0%, respectively.

Although far from ideal because pPCI is considered the standard of care for STEMI patients, a pharmacoinvasive treatment strategy could be an alternative for achieving short pain-to-balloon times and, coupled with a structured healthcare network, could represent a highly important improvement in public health management of STEMI in Brazil. The present study is a step forward in adjusting the healthcare system in accordance with global standards to optimally assist the largest possible number of patients.

This study has several limitations. It was an observational and single-center study. A femoral artery approach was used in all cases, and bleeding criteria may underestimate the actual impact of this important complication on mortality. In addition, the use of radial access in pPCI has been associated with lower mortality rates (29,30). The multivariate analysis performed in this study cannot exclude residual confounding due to unmeasured or

unknown variables. Finally, the generalizability of this study is limited because it can only be applied to STEMI patients who undergo a pharmacoinvasive treatment strategy according to the methods described in our protocol.

In this real-world, prospective study that included STEMI patients who underwent a pharmacoinvasive treatment strategy, in-hospital mortality rates were low at 5.8%. The GRACE score, LVEF, and myocardial blush grade were powerful predictors of mortality after administration of this pharmacoinvasive treatment strategy in the contemporary reperfusion era.

## ■ AUTHOR CONTRIBUTIONS

Falcão FJ wrote the manuscript. Alves CM was responsible for data analysis and interpretation. Barbosa AH was responsible for angiographic analysis. Caixeta A performed critical revision of the manuscript for important intellectual content. Sousa JM performed the statistical analysis. Souza JA, Gonçalves Júnior I, and Stefanini E were responsible for data analysis. Amaral A, Wilke LC, and Perez FC were responsible for data acquisition. Carvalho AC assisted with the study design and reviewed the final version of the manuscript.

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**Table 2** - Independent predictors of mortality according to multivariate logistic regression analysis.

Variables	OR	p-value	95% CI
GRACE score	1.057	0.001	1.023-1.091
LVEF	0.930	0.001	0.890-0.972
Final Blush 0-2	8.857	0.02	1.339-58.570





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