





The comparison of procedural and clinical outcomes of thrombolytic-facilitated and primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction (STEMI): Findings from PROVE/ACS study

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Original Article

Abstract

BACKGROUND: There is still a controversy in the preferred method of reperfusion in acute ST-segment elevation myocardial infarction (STEMI), when the achievement of well-defined "golden time" is difficult. We sought to evaluate the procedural and in-hospital outcomes of the strategy of "thrombolytic administration and rescue or routine percutaneous coronary intervention (PCI)" versus "primary PCI (PPCI)" strategy in acute STEMI.

METHODS: In this observational prospective study, the data of 237 patients with acute STEMI presented or referred to Chamran Cardiovascular Research Center in Isfahan, Iran, were collected (PROVE/ACS study). Baseline characteristics, thrombolysis in myocardial infarction (TIMI) flow grade of infarct-related artery (IRA), left ventricular ejection fraction (LVEF), and in-hospital outcomes were evaluated.

RESULTS: The mean age of patients was 61.4 ± 13.0 years, 86.9% were men, 13.1% were diabetic, and 67.9% had anterior STEMI. Patients in the "thrombolytic then PCI" group were younger, more smoker, more often male with higher body weight and lower systolic blood pressure (SBP). The pre-PCI TIMI flow grade 3 was more often seen in the "thrombolytic then PCI" group (39.4% vs. 21.0%, $P < 0.001$) and less thrombectomy was performed in this group of patients (12.9% vs. 26.7%, $P = 0.011$). Time to reperfusion was significantly longer in PPCI group (182.4 ± 233.7 minutes vs. 44.6 ± 93.4 minutes, respectively, $P < 0.001$). No difference in mortality, mean of LVEF, and incidence of atrial fibrillation (AF) was observed in two groups.

CONCLUSION: If the PPCI strategy could not be performed in the golden time, the strategy of thrombolytic administration and rescue or routine PCI leads to more initial IRA patency and less thrombectomy with similar clinical outcomes.

Keywords: ST Segment Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Thrombolytic Therapy; Treatment Outcome; Reperfusion

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Introduction

ST-segment elevation myocardial infarction (STEMI) is the most serious type of acute coronary syndromes (ACS). Primary percutaneous coronary intervention (PPCI) is the treatment of choice according to the recent guidelines on the management of STEMI if it could be accomplished in the golden time (less than 120 minutes from symptom onset) and in an experienced center.^{1,2}

Decision on the type of reperfusion is made

based on many factors such as the presence of well-defined local STEMI management strategy,

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individual patient factors, team experience, and hospital facilities but "the time elapsed from symptom onset and the time delay to reperfusion" are the main factors for choosing between thrombolytic therapy and PPCI as the preferred reperfusion strategy.²⁻⁴ Some studies have proposed that very early thrombolysis works as PPCI in efficacy and outcomes.⁵⁻⁷ Fibrinolytic-based facilitated percutaneous coronary intervention (PCI) (immediate transfer to PCI after early fibrinolysis) was associated with more patent infarct-related artery (IRA) and better pre-PCI thrombolysis in myocardial infarction (TIMI) flow in most trials.⁷⁻⁹ In the Alliance for Myocardial Infarction Care Optimization (AMICO) registry, this strategy reduced the mortality and combined endpoints.⁹ More recent studies showed increased infarct size and event rates with fibrinolytic-based facilitated PCI compared to PPCI, in spite of better pre-PCI TIMI flow.⁸ The comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial demonstrated lower 5-year mortality in patients with STEMI who received thrombolytic therapy within 2 hours of symptom onset compared with PPCI.¹⁰ In the Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial, fibrinolysis during 3 hours of symptom onset in patients who could not be transferred for PPCI within 1 hour of first medical contact (FMC) was associated with slightly better primary endpoints in spite of increased intracranial hemorrhage (ICH).⁵

Regarding the available data, evaluation of the outcome of each reperfusion strategy in the regions with long distance to PCI-capable hospital is necessary. There is a lack of evidence about the time delay to both reperfusion treatments, procedural (angiographic), clinical, and in-hospital outcomes of acute STEMI in Middle East region, especially in Iran. In this study, we aimed to compare the outcomes of patients with acute STEMI who were managed with thrombolytic therapy then rescue or routine PCI versus PPCI strategy in a referral high-volume PCI-capable hospital in Iran. The findings of such study can provide the valid data to provide local guidelines in the management of acute STEMI.

Materials and Methods

The data of this observational prospective study was derived from "Persian Registry Of cardioVascular disease/Acute Coronary Syndrome (PROVE/ACS)".¹¹ In the STEMI registry, an

observational prospective study from October 2015 to October 2016, the demographic, clinical, laboratory, electrocardiographic (ECG), echocardiographic, and angiographic data and in-hospital course of all patients with acute STEMI presented or referred to the three main hospitals of Isfahan, Iran, were consecutively collected. Follow-up was done until hospital discharge. Medical interview, physical examination, and laboratory assays were performed by trained health personnel, using a validated questionnaire, calibrated instruments, and a standard protocol.¹¹ An external auditor team evaluated the data periodically and randomly. The study protocol was approved by the Research Ethical Committee of Isfahan University of Medical Sciences, Isfahan, and all patients provided written informed consent.

In this study, the data of 237 patients with acute STEMI presented or referred to Chamran Cardiovascular Medical and Research Center in Isfahan, Iran, were used. The acute STEMI diagnosis was made based on the third universal definition of myocardial infarction (MI). Acute STEMI was diagnosed if ST-segment elevation at the J point ≥ 0.1 mv was seen in two contiguous leads. The cut points in V2-V3 leads were defined as ≥ 0.25 mv in men < 40 years, ≥ 0.2 mv in men ≥ 40 years, and ≥ 0.15 mv in women.¹² Patients with glomerular filtration rate (GFR) < 30 and patients who refused coronary angiography were excluded. All demographic, past medical history, physical examination, and ECG data [heart rate, rhythm abnormalities such as atrial fibrillation (AF) and location of STEMI] of the patients were recorded at presentation. History of diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) ≥ 126 mg/dl or already taking anti-diabetic medications. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dl, total cholesterol (TC) ≥ 200 mg/dl, triglyceride (TG) ≥ 150 mg/dl, high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dl in men or < 50 mg/dl in women, or receiving its medications.¹³ The body mass index (BMI) was calculated with this formula: body weight (kg) divided by height (meter) to the power of two.

Participants who used at least one cigarette per day were considered as current smokers. History of heart failure (HF) was defined as left ventricular ejection fraction (LVEF) $\leq 40\%$ or history of admission due to HF symptoms. The presence of left main (LM) stenosis (stenosis $> 50\%$), the number of diseased vessels (stenosis $> 75\%$ diameter), TIMI

flow grade before and after PCI, and procedural outcomes were assessed by two blinded interventional cardiologists. Echocardiography during the first 24 hours of admission was performed with an expert echocardiographer.

Patients with acute STEMI in the study were placed in two groups:

1- Thrombolytic then PCI strategy group (lytic then PCI group): these patients were admitted in a non-PCI-capable hospital at first. In the first hospital, the patients without contraindication to thrombolysis [such as active bleeding, recent ischemic stroke, history of ICH, history of major trauma or surgery within 30 days, uncontrolled hypertension (HTN), chronic oral anticoagulation, active malignancy, and pregnancy] had received loading dose of chewable aspirin (325 mg), clopidogrel (300 mg in patients < 75 years, 75 mg in patients \geq 75 years), and standard dose of thrombolytic agent [either reteplase (10 units + 10 units intravenous (IV) boluses given 30 minutes apart) or streptokinase (1500000 units during 90 minutes) based on local availability] and then had been transferred to the Chamran Cardiovascular Medical and Research Center (a referral high-volume PCI-capable hospital) with an equipped ambulance. In this center, the patients underwent emergent catheterization if the chest pain and ST-segment elevation was not resolved. If there was no residual chest pain and ST-segment resolution of \geq 75% was achieved, the routine PCI strategy, preferably but not exclusively, within 24 hours of symptom onset was performed.

2- PPCI strategy group (PPCI group): these patients were presented to Chamran Cardiovascular Medical and Research Center [by themselves or Emergency Medical System (EMS)] and were transferred for primary PCI, after loading dose of chewable aspirin (325 mg) and clopidogrel (600 mg). At the catheterization laboratory, 5000 units of unfractionated heparin (UFH) was administered in IV form and PCI of the IRA was performed if the culprit lesion in IRA had \geq 75% stenosis or TIMI flow < grade 3. Administration of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, performance of thrombectomy, and type of stent were on the decision of the expert interventional cardiologist team that performed the procedure.

Data entry was done using EPI Info (version 6). Data were analyzed by SPSS software (version 15, SPSS Inc., Chicago, IL, USA). Statistical significance was assessed at a level of 0.05 (two-tailed).

Quantitative variables were represented as mean \pm standard deviation (SD) and compared by independent samples t-test or Mann-Whitney U test where normality assumption did not exist. Normality assumption was checked using Kolmogorov-Smirnov test (K-S test). The Wilcoxon signed-rank test was used to compare changes in TIMI flow before and after PCI in patients with STEMI. Qualitative variables were represented as frequency (percentage) and chi-square test or Fisher's exact test was used whenever appropriate.

Results

The data of 237 patients with acute STEMI were analyzed in two groups of lytic versus PPCI. The mean age of patients was 61.4 ± 13.0 years. Two hundred and six patients (86.9%) were men and 31 patients (13.1%) were diabetic. History of HF and previous MI was observed in 34 (14.7%) and 35 (15.5%) patients, respectively. Of 237 patients, 161 patients (67.9%) had anterior STEMI and in the remaining (76 patients, 32.1%), STEMI occurred in other locations (inferior, lateral, posterior). Baseline characteristics and data of initial presentations of the patients in both groups are presented in table 1. Patients in the thrombolytic group were younger, more smokers, more often men with higher body weight (without difference in BMI) and lower systolic blood pressure (SBP). A trend to more history of HF was observed in PPCI group (18.8% vs. 10.4%, $P = 0.072$) that were more often in killip class of one or two (Table 1).

Table 2 represents comparison of clinical and angiographic outcomes of patients with STEMI in both groups. The time to reperfusion was significantly longer in the PPCI group compared with lytic group (182.4 ± 233.7 minutes vs. 44.6 ± 93.4 minutes, respectively, $P < 0.001$). The prevalence of one, two, and three-vessel disease in the patients with acute STEMI was 107 (45.1%), 80 (33.8%), and 47 (19.8%), respectively. LM stenosis was observed in 3 patients, one had no involved vessels, and 2 (0.8%) were unknown. Thrombectomy was performed in 45 (19.0%) patients [22 (14.9%) of anterior MI vs. 23 (31.5%) of other MI, $P = 0.004$], significantly less often in thrombolytic then PCI group [odds ratio (OR): 0.40, 95% confidence interval (CI): 0.20-0.83]. After adjustment for age and sex, the difference remained significant (OR: 0.37, 95% CI: 0.18-0.77). Mean LVEF of the patients was $37 \pm 12\%$ ($32 \pm 10\%$ in anterior vs. $46 \pm 9\%$ in other MI, $P < 0.001$).

Table 1. Baseline characteristics of patients with ST-elevation myocardial infarction (STEMI)

Baseline variables	Primary PCI (n = 121)	Thrombolytic then PCI (n = 116)	P
Sex (male)	100 (82.6)	106 (91.4)	0.040*
Killip class > 3	1 (4.5)	2 (16.7)	0.270**
DM	35 (32.7)	27 (27.6)	0.420*
Dyslipidemia	34 (37.8)	35 (37.2)	0.930*
Smoking	42 (35.0)	60 (51.7)	0.010*
History of previous MI	21 (18.4)	14 (12.5)	0.210*
HF	22 (18.8)	12 (10.4)	0.070*
AF at entrance	3 (2.5)	2 (1.7)	> 0.999**
History of CABG	2 (1.7)	2 (1.8)	> 0.999**
Location of current MI (anterior)	78 (64.5)	83 (71.6)	0.240*
Weight (kg)	73.5 ± 12.7	78.8 ± 13.3	0.010††
BMI (kg/m ²)	26.3 ± 4.4	26.6 ± 3.9	0.210††
Age (year)	64.8 ± 13.6	57.9 ± 11.4	< 0.001††
Baseline heart rate	79.9 ± 23.7	77.4 ± 21.1	0.470††
Baseline SBP	135.5 ± 27.8	122.7 ± 22.3	< 0.001††
Earliest Hb	14.6 ± 1.9	14.5 ± 1.7	0.620†

Data are presented as mean ± standard deviation (SD) or frequency and percentage

* Chi-square test was used; ** Fisher's exact test was used; † Independent samples t-test was used; †† Mann-Whitney test was used
 PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; MI: Myocardial infarction; HF: Heart failure; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; BMI: Body mass index; SBP: Systolic blood pressure; Hb: Hemoglobin

Table 3 shows the TIMI flow before and after PCI in the study population. The TIMI flow grades after PCI were significantly improved in both groups with more than 95% of all patients with STEMI reaching the TIMI flow grade 2 and 3 after PCI. The pre-PCI TIMI flow grade was significantly better in the group of "thrombolytic then PCI" (TIMI flow grade 3, 39.4% vs. 21.0%, $P < 0.001$).

Three patients died during hospitalization, two of them had anterior MI, and all of them were in the "thrombolytic then PCI" group. There were no reports of significant vascular access site complication and ICH or extracranial hemorrhage.

Discussion

This observational prospective study was a well quality controlled registry with validated data of patients with acute STEMI presented in Chamran Cardiovascular Medical and Research Center in Isfahan. In this study, patients who received thrombolytic therapy then transferred for PCI were younger, mostly men, more smokers, with higher body weight, lower SBP, and a trend to less history of HF compared with PPCI patients. In this group, pre-PCI TIMI flow was better and less thrombectomy was performed. Time to reperfusion was significantly longer in PPCI group. No difference in final LVEF, incidence of arrhythmia, HF, and in-hospital mortality was seen.

Table 2. Clinical and procedural outcome of patients with ST-elevation myocardial infarction (STEMI)

Clinical and procedural variables	Primary PCI	Thrombolytic then PCI	P
Number of diseased vessels	0	1 (0.9)	0.400*
	1	60 (49.6)	
	2	37 (30.6)	
	3	24 (19.8)	
	LM	3 (2.7)	
Identifiable culprit lesion	121 (100)	108 (95.6)	0.030*
Thrombectomy	32 (26.7)	13 (12.9)	0.010**
AF during admission	2 (1.7)	3 (2.8)	0.670*
Any hemodynamic support	2 (1.7)	4 (3.9)	0.420*
Mortality	0 (0)	3 (2.6)	0.120*
Mean time delay to reperfusion (minutes)	182.4 ± 233.7	44.6 ± 93.4	< 0.001††
LVEF	36.0 ± 13.0	37.0 ± 10.0	0.210††

Data are presented as mean ± standard deviation (SD) or frequency and percentage

* Fisher's exact test was used; ** Chi-square test was used; †† Mann-Whitney test was used

PCI: Percutaneous coronary intervention; LM: Left main; AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction

Table 3. Thrombolysis in myocardial infarction (TIMI) flow before and after percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI)

TIMI flow		Primary PCI	Thrombolytic then PCI	P
Before PCI	0	60 (50.4)	27 (27.3)	< 0.001*
	1	18 (15.1)	5 (5.1)	
	2	16 (13.4)	28 (28.3)	
	3	25 (21.0)	39 (39.4)	
After PCI	0	0 (0)	1 (1.0)	0.371**
	1	5 (4.2)	3 (3.0)	
	2	26 (22.0)	29 (29.3)	
	3	87 (73.7)	66 (66.7)	
P		< 0.001††	< 0.001††	-

Data are presented as frequency and percentage

* Chi-square test was used; ** Fisher's exact test was used;

†† Wilcoxon signed-rank test was used

PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction

PPCI is the preferred method of reperfusion if it could be accomplished in a timely fashion.^{1,2} Performing reperfusion in the "golden time" is essential, regarding the flat curve of mortality benefit with reperfusion after the first 3-4 hours of symptom onset.¹⁴ Achievement of reperfusion via PPCI with an experienced operator in the "golden time" in many countries is a problematic issue.

In this observational study, patients in the lytic group had higher baseline risk profile, except for the younger (mean of 6.9 years) age at presentation.

In the Leipzig Immediate Prehospital Facilitated Angioplasty in STEMI (LIPSIA-STEMI) trial, patients with STEMI presented < 3 hours from symptom onset were randomized and compared in two groups: lytic-facilitated PCI (pre-hospital lytic) versus PPCI.⁸ In line with our results, pre-PCI TIMI flow was better in the lytic-facilitated PCI group, but contradictory with our study, the trial showed a trend to worse infarct size, more early and late microvascular obstruction (MVO) in cardiovascular magnetic resonance (CMR), and 30 days event rate in the lytic-facilitated PCI group. The thrombolytic agent that was used in the LIPSIA-STEMI trial was tenecteplase that was not available in our country.

In the STREAM trial, patients within 3 hours of symptom onset who could not underwent PPCI during 1 hour of FMC, were candidate for lytic therapy (tenecteplase) and rescue or routine PCI in 24 hours.⁵ The primary end points of death, shock, congestive HF (CHF), and reinfarction at 30 days in this group were similar with patients in the PPCI group. The increased incidence of ICH in older age

was disappeared after the dose reduction of tenecteplase.⁵ Higher IRA patency, lower time to reperfusion, and similar 12-month outcomes with this pharmaco-invasive strategy was achieved in a Korean study.¹⁵ The results of STEPP-AMI trial (a prospective, observational, multicenter study comparing tenecteplase facilitated PCI versus primary PCI in Indian patients with STEMI) were matched with our study in more IRA patency, less thrombus with similar 30 days and 2 years clinical end points, and major bleeding in lytic-facilitated PCI compared with primary PCI.^{7,16}

In a meta-analysis of lytic-facilitated PCI in comparison with PPCI, lower incidence of cardiogenic shock, higher stroke rates, and similar mortality rates was observed.¹⁷ There are multiple trials and expert opinions that proposed similar outcomes using lytic-facilitated PCI compared with PPCI in patients with acute STEMI for whom PPCI could not be performed in the golden time even in the elderly.^{6,18-20}

This study was a prospective observational report of patients with acute STEMI presented to Chamran Cardiovascular Medical and Research Center with delicate protocols for data collection and external evaluation. In this study, the strategy of "lytic then PCI" had similar clinical outcomes with less performance of thrombectomy and better pre-PCI TIMI flow compared with PPCI strategy. The mortality rate was too low to evaluate the difference statistically. The limitations of this study were the absence of tenecteplase as the preferred specific thrombolytic agent in our center, time delays in performing PPCI, limitations in exact time recall of the patients, and lack of funds for evaluation of infarct size with advanced imaging modalities. The low number of cases and the limited occurrence of adverse events such as mortality and hemorrhagic complications prevented us to find significant difference between groups. Long-term follow-up of the patients will clarify the outcomes in the future.

Conclusion

In the countries that achievement of well-defined "golden time" in PPCI strategy is difficult, the strategy of thrombolytic administration and rescue or routine PCI remains a good alternative option with very promising results in the trials. The concerns about increased stroke and bleeding risk can be eliminated with careful adjustment of the lytic and antithrombotic doses and meticulous patient selection for the strategy. Performance of reperfusion as soon as possible from symptom

onset is essential and the better outcome is accessible with pre-hospital fibrinolysis. The findings of this study can provide the valid data to provide local guidelines in the management of acute STEMI in regions with long distance to a PCI-capable hospital.

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Conflict of Interests

Authors have no conflict of interests.

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