Comparison of In-Hospital Outcomes With Low-Dose Fibrinolytic Therapy Followed by Urgent Percutaneous Coronary Intervention Versus Percutaneous Coronary Intervention Alone for Treatment of ST-Elevation Myocardial Infarction

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In patients with acute ST-elevation myocardial infarction (STEMI), a strategy of prehospital reduced dose fibrinolytic administration coupled with urgent percutaneous coronary intervention (PCI), termed FAST-PCI strategy, has been found to be superior to primary PCI (PPCI) alone. A coordinated STEMI system of care that includes FAST-PCI should offer better outcomes than a system in which prehospital diagnosis of STEMI is followed by PPCI alone. The aim of this study was to compare the in-hospital outcomes for patients treated with the FAST-PCI approach with outcomes for patients treated with the PPCI approach in a common system. The in-hospital data for 253 STEMI patients (March 2003−December 2009) treated with a FAST-PCI protocol were compared with 124 patients (January 2010−August 2011) treated with PPCI strategy alone. In-hospital mortality was the primary comparator. Stroke, major bleeding, and reinfarction during index hospitalization were also compared. The in-hospital mortality was significantly lower with FAST-PCI than with PPCI (2.77% vs 10.48%, p = 0.0017). Rates of stroke, reinfarction, and major bleeding were similar in the 2 groups. There was a lower frequency of pre-PCI Thrombolysis In Myocardial Infarction 0 flow (no patency) seen in patients treated with FAST-PCI compared with the PPCI patients (26.7% vs 62.7%, p <0.0001). Earlier infarct artery patency in the FAST-PCI group had a favorable impact on the incidence of cardiogenic shock on hospital arrival (3.1% vs 20.9%, p <0.0001). In conclusion, compared with a PPCI strategy in a common STEMI system of care, the FAST-PCI strategy was associated with earlier infarct artery patency and lower incidence of cardiogenic shock, as well as with reduced in-hospital mortality. **(Am J Cardiol 2013;111:1576−1579)**

The mainstay of ST-elevation myocardial infarction (STEMI) treatment has been immediate reperfusion of the culprit artery to limit or prevent myocardial damage. The faster that reperfusion can be accomplished the better because ischemic time is directly proportional to both infarct size and mortality. Despite many advances in management strategies, a uniform system of care for STEMI patients that routinely accomplishes rapid reperfusion does not exist in many areas of the United States. A possible effective solution may be offered by the combination of reduced dose fibrinolytic therapy administered on the scene to eligible STEMI patients before transport to the hospital, followed by immediate percutaneous coronary intervention (PCI) on hospital arrival. This has been termed fibrinolytic acceleration of STEMI treatment combined with urgent PCI (FAST-PCI) approach.[1] In a pooled analysis of almost 3,000 patients treated with either FAST-PCI or primary PCI alone (PPCI), patients treated with the FAST-PCI approach had >40% reduction in 30-day mortality without any bleeding penalty.[1] The purpose of this study was to investigate changes in adverse outcomes of STEMI patients during a pause in the FAST-PCI strategy at our institution due to fibrinolytic unavailability and the consequent shift to a solely PPCI approach.

Methods

The protocol we have followed for more than 6 years using prehospital administration of a reduced-dose fibrinolytic agent followed by urgent PCI has been described previously.[1] Patients with STEMI were identified before transport to our STEMI center hospital. They were given a regimen of reduced-dose reteplase (10 U intravenously), aspirin (325 mg orally), clopidogrel (600 mg orally), and heparin (60 U/kg, up to 4,000 U intravenously). Glycoprotein IIb/IIIa inhibitors were used according to local practice or at the discretion of the treating physician (Figure 1).

At the end of 2009, the manufacturer suspended delivery of the fibrinolytic we used (reteplase), causing our center to shift to a PPCI approach. Under this PPCI strategy, patients

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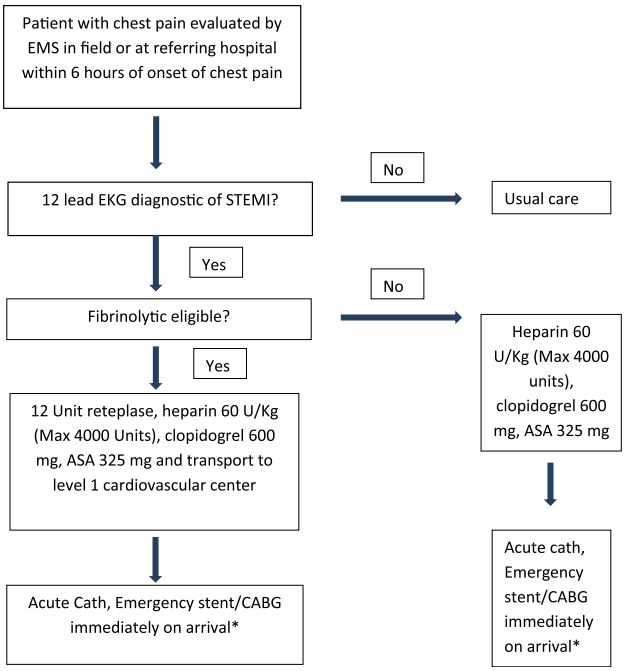

Figure 1. Algorithm for management of patients, FAST-PCI protocol. * Glycoprotein IIb/IIIa given at discretion of operator.

with STEMI were still identified in the field, either at the scene or in local referral hospitals. Adjunctive agents including aspirin, clopidogrel, and heparin, but without a fibrinolytic, could be administered and patient transport initiated, all in a similar manner as when the FAST-PCI protocol was in place. Urgent PCI on hospital arrival was also performed in a similar manner and by the same operators as under the FAST-PCI protocol.

From October 1, 2003, to December 31, 2009, 253 patients were identified in the field or at STEMI-referring hospitals by paramedics, nurses, or physicians and treated according to the FAST-PCI approach. After January 1, 2010, a pause in the FAST-PCI protocol due to fibrinolytic unavailability made PPCI the standard approach again for STEMI patients. From January 1, 2010, to August 31, 2011, 124 STEMI patients were treated according to a PPCI strategy. We examined data on STEMI patients treated under the previous FAST-PCI or the subsequent PPCI protocols. Total ischemic time was defined as the time from onset of symptoms to first intracoronary therapy (first balloon inflation or thrombus aspiration). Door-to-balloon time was defined as the time from patient's arrival in the emergency department to first intracoronary balloon inflation. In-hospital clinical data for the 2 groups were compared. The primary end point comparison for this analysis was all-cause in-hospital mortality. Secondary end points were other in-hospital adverse outcomes such as reinfarction, major bleeding, and stroke. Reinfarction was defined as new significant Q waves in 2 contiguous leads different from those affected by initial MI, re-elevation of creatinine kinase-MB to higher levels than normal (or by another 50%, if already higher than normal), and re-elevation of CK-MB to >3 or >5 times upper limits of normal after angioplasty or surgery, respectively. Major

Table 1
Baseline characteristics and hospital course of patients treated with prehospital low-dose FAST-PCI and with PPCI alone

Variable	FAST-PCI (n = 253)	PPCI (n = 124)	p Value
Age (yrs)	58.1 ± 12.1	58.3 ± 11.6	0.878
Men	185 (73%)	90 (73%)	0.911
Previous PCI	30/253 (11.8%)	29/124 (23.5%)	0.003
Previous myocardial infarction	38/252 (15.1%)	15/123 (12.1%)	0.460
Previous coronary bypass	5/253 (1.9%)	2/123 (1.6%)	0.813
Hypertension	162/253 (64%)	75/123 (60.9%)	0.564
Diabetes mellitus	78/252 (30.9%)	32/124 (26%)	0.324
Smoker	170/250 (68%)	75/121 (61.9%)	0.251
Hyperlipidemia	122/251 (48.6%)	55/124 (44.3%)	0.479
Creatinine	1.0 ± 0.2	1.1 ± 0.6	0.017
Killip class IV at presentation (shock)	8/253 (3.1%)	26/124 (20.9%)	<0.0001
Ischemic time (min)	173.5 ± 81.9	193.8 ± 99.1	0.07
Door-to-balloon (min)	26.9 ± 12.2	44.7 ± 34.2	<0.0001
TIMI 0 flow at presentation	65/243 (26.7%)	74/118 (62.7%)	<0.0001
TIMI 3 flow at presentation	109/243 (44.8%)	26/118 (22%)	<0.0001
3-vessel coronary disease	29/253 (11.4%)	29/124 (23.3%)	0.002
Peak creatine kinase (IU/L)	1,826.5 ± 1,946.1	2,220.2 ± 2,401.8	0.09
Culprit vessel LAD	85/239 (35.5%)	58/121 (47.9%)	0.023
Glycoprotein IIb/IIIa inhibitors used	88/253 (34.7%)	43/124 (34.6%)	0.983

LAD = left anterior descending coronary artery.

bleeding was defined as bleeding resulting in substantial hemodynamic instability requiring intervention. Bleeding requiring blood transfusion but not associated with hemodynamic compromise was considered moderate and not severe. Development of a new neurologic deficit not present on initial screening examination or diagnosed by a neurologist or new intracranial bleeding diagnosed by computed tomography or magnetic resonance imaging were the criteria for stroke. Categorical variables were expressed as number and percentage of patients; statistical differences were analyzed using chi-square and Fisher exact tests. All continuous variables were expressed using mean and SD. Student t test was used to assess differences. A p value <.05 was considered statistically significant.

Results

Table 1 shows the patient demographics, clinical features, and angiographic details for the 2 groups. The groups were comparable, although a higher percentage of the PPCI group had a history of previous PCI. Notably, PPCI patients had a higher frequency of Killip Class IV (shock) at hospital arrival compared with FAST-PCI patients, and they had a higher frequency of occluded arteries (pre-PCI Thrombolysis In Myocardial Infarction [TIMI] 0 flow grade) on initial angiography. Approximately one-third of patients in both groups received glycoprotein IIb/IIIa inhibitors. A higher proportion of PPCI patients had 3-vessel coronary disease compared with FAST-PCI patients.

Table 2
Comparison of in-hospital outcomes of patients treated with prehospital low-dose FAST-PCI and with PPCI alone

	FAST−PCI (n = 253)	PPCI (n = 124)	p Value
Mortality	7 (2.77%)	13 (10.48%)	0.0017
Stroke	2 (0.79%)	4 (3.22%)	0.094
Bleeding (GUSTO Major)	5 (1.98%)	0 (0%)	0.176
Reinfarction	1 (0.39%)	2 (1.61%)	0.253

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial.

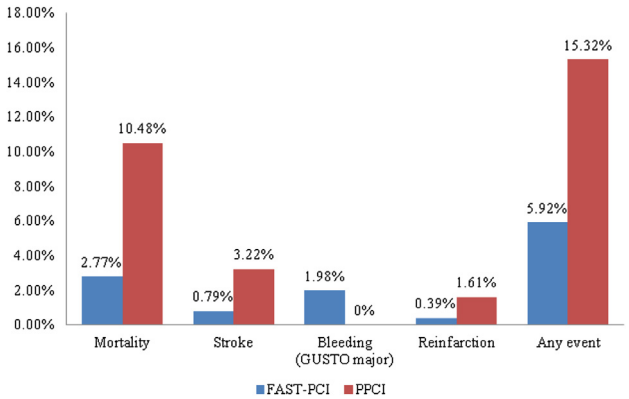

Figure 2. Comparison of adverse events between FAST-PCI and PPCI patients groups.

Both door-to-balloon time and total ischemic time were measured for all patients. Longer door-to-balloon time was noted for the PPCI group compared with the FAST-PCI group (44.7 ± 34.2 vs 26.9 ± 12.2 minutes, p <0.0001), although for both groups, these door-to-balloon times were brief. Total ischemic time was slightly longer in the PPCI group. These time differences appeared to represent the delaying effects of endotracheal intubation and hemodynamic stabilization with inotropes and/or intraaortic balloon counterpulsation in the patients with cardiogenic shock.

Table 2 and Figure 2 show in-hospital adverse events in the 2 groups. The mortality for the FAST-PCI patients was approximately one-fourth that of the PPCI patients (2.77% vs 10.48%, p = 0.017). The rates of stroke, reinfarction, and major bleeding were low and did not differ between the 2 groups.

Discussion

Our main finding is that when our prehospital reduced dose fibrinolytic program was interrupted, and PPCI once again became the standard treatment plan for STEMI patients, in-hospital mortality increased. Our results with these 2 strategies are similar to those reported by the Alliance for Myocardial Infarction Care Optimization (AMICO).[1] The AMICO study found that prehospital half-dose fibrinolytic administration followed by urgent PCI resulted in lower 30-day mortality compared with PPCI, without a penalty of increased major bleeding complications. The 30-day mortality rate was 3.8% with FAST-PCI in AMICO compared with 6.4% with PPCI (p = 0.002). The in-hospital mortalities we report here are similar to those rates. Additionally, AMICO demonstrated that prehospital administration of half-dose fibrinolytic was safe and appeared to recanalize infarct arteries in approximately 80% of patients before PCI and frequently before hospital arrival.[1] Another study, the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial also evaluated prehospital fibrinolysis versus primary PCI.[2] Similar to our findings, shock was less frequent in the prehospital fibrinolysis group, suggesting that this prehospital treatment and its attendant more rapid onset of reperfusion may be beneficial in reducing this serious factor.[2]

Stone and colleagues studied the association between earlier infarct artery patency and patient survival. They reported in the Primary Angioplasty in Myocardial Infarction trial a striking relationship between initial TIMI flow grade and 6-month survival.[3] Patients presenting with TIMI grade 3 flow before PCI had 0.5% mortality at 6 months. With a slower initial grade of TIMI 2 flow present, mortality increased to 2.8%, and was 4.4% when only TIMI 0 to 1 flow was present initially (p = 0.009). Patients with TIMI 3 flow at initial angiography also had significantly lower in-hospital mortality, less new-onset heart failure and hypotension, and shorter hospital stays.[3] New information also suggests a strong correlation between shortened time from onset of symptoms to reperfusion and improved outcomes. Steg and colleagues demonstrated that in STEMI patients treated within the first 2 hours with prehospital fibrinolysis, the 30-day mortality was 2.2%, in contrast to patients treated with PPCI within the first 2 hours, who experienced a mortality of 5.7% (p = 0.058).[2] There was a 55-minute advantage in terms of reduction in time to treatment in patients treated with prehospital fibrinolysis versus primary PCI. Additionally, patients treated with prehospital fibrinolysis had no cardiogenic shock develop, compared with a 3.6% incidence of shock in the primary PCI group (p = 0.007).[2] A recent report by Thiele et al of reduced dose prehospital fibrinolysis followed by urgent PCI, compared with prehospital fibrinolysis alone, suggests that significant myocardial salvage occurs with the addition of urgent PCI to the prehospital fibrinolysis regimen. Patients in the prehospital fibrinolysis with PCI arm experienced a reduced infarct size (5.3% vs 10.4%, p = 0.001) compared with those patients treated with prehospital fibrinolysis alone.[4]

Reteplase has been used as the fibrinolytic of choice in the FAST-PCI protocol at our institution. Early experience with reteplase suggested that it achieved clot lysis faster than tissue plasminogen activator (t-PA) both in vivo and in vitro.[5,6,7] Subsequent investigations in the RAPID I and II trials confirmed that reteplase reopened arteries approximately 30 minutes faster and 20% more effectively in humans compared with t-PA.[8,9] A meta-analysis of the RAPID I and II trials demonstrated a 30-day mortality advantage in patients treated with reteplase (and who also achieved TIMI 3 flow in the infarct related artery before intervention): 2.6 % compared with 5.7% in patients treated with t-PA (p <0.01).[10] When our supply of reteplase was interrupted because of manufacturing changes and we moved to a strategy of PPCI alone for STEMI, we found that patient outcomes were not as favorable.

We recognize there are limitations to this study. Patients with STEMI were not randomized between FAST-PCI and PPCI treatment groups. Instead, these were sequentially treated groups because of the nature of the supply interruption. Unmeasured confounders are likely present inasmuch as there were some clinical differences between the 2 groups. Only simple comparative analyses were performed because the group sizes were too small to permit more sophisticated comparisons using propensity scores or other adjustments. Nevertheless, the same operators and the same system were at work for both groups, reducing the impact of such differences. We conclude that a change from a strategy of coordinated prehospital administration of fibrinolytics coupled with urgent PCI for STEMI to a primary PCI strategy was associated with an increase in in-hospital mortality. A coordinated STEMI system of care that includes the administration of prehospital fibrinolytics offers better outcomes than a system with prehospital STEMI diagnosis followed by primary PCI alone.

Disclosures

The authors have no conflicts of interest to disclose.

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