Comparison of Outcomes and Safety of "Facilitated" Versus Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction

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Recent studies have documented that use of "facilitated" percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) may be harmful. In-hospital outcomes in 1,553 consecutive patients with STEMI without cardiogenic shock who underwent PCI at a single tertiary center within 6 hours of presentation were analyzed. The study group included 767 patients who underwent primary PCI who initially presented to the tertiary center and were triaged for emergent PCI and 786 patients who underwent facilitated PCI who were pretreated at a community hospital with a glycoprotein IIb/IIIa platelet inhibitor and/or intravenous thrombolytic therapy before transfer for catheter-based therapy. Compared with patients who underwent primary PCI, the facilitated PCI group had longer door-to-balloon times (162 ± 57 vs 113 ± 61 minutes), higher baseline infarct-vessel TIMI 3 flow rates (52.8% vs 25.4%; p <0.001), and no increase in major adverse in-hospital outcomes. In patients treated with door-to-balloon times >90 and ≤150 minutes, patients who underwent facilitated PCI had fewer composite major adverse clinical events (combined mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and nonhemorrhagic stroke, and nonintracranial TIMI major bleeding) compared with patients who underwent primary PCI (relative risk 0.50, 95% confidence interval 0.26 to 0.96, p = 0.034). In conclusion, facilitated PCI can be safely used to increase pharmacologic reperfusion before catheter-based therapy in patients with STEMI without an increase in clinical hazard and with fewer major adverse clinical events in patients treated with door-to-balloon times >90 and ≤150 minutes. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:316–321)

Recent studies have shown that use of "facilitated" percutaneous coronary intervention (PCI) in the treatment of patients with ST-segment elevation myocardial infarction (STEMI) offered no advantage over primary PCI and may be harmful.[1–3] The present study retrospectively examined the safety and efficacy of this approach in a real-world setting using data from a single tertiary center that has used combined pharmacologic and mechanical reperfusion for the last 8 years. The specific facilitated PCI regimens evaluated included use of a glycoprotein IIb/IIIa inhibitor and/or an intravenous thrombolytic agent, alone or in combination, before transfer for planned emergent PCI.

Methods

From an institutional database of 1,982 patients with STEMI treated at Hartford Hospital, Hartford, Connecticut, from January 2000 to March 2008, we analyzed in-hospital outcomes for 1,553 consecutive patients who presented without cardiogenic shock and underwent catheter-based revascularization within 6 hours of initial evaluation. The study group included 767 patients who presented directly to the Hartford Hospital emergency department and were urgently referred to the catheterization laboratory for PCI (primary PCI group) and 786 patients initially treated at 1 of 7 referring community hospitals with a glycoprotein IIb/IIIa platelet inhibitor and/or intravenous thrombolytic therapy and then transferred directly to the catheterization laboratory for catheter-based therapy (facilitated PCI group). Patients who underwent facilitated PCI and developed cardiogenic shock during the time of interhospital transfer were not excluded. Pharmacologic agents administered to the facilitated PCI group, alone or in combination, included eptifibitide, abciximab, or tirofiban as glycoprotein IIb/IIIa inhibitors and reteplase, tenecteplase, or alteplase as intravenous thrombolytics.

Entry of data elements into the Hartford Hospital STEMI database was specifically defined using criteria established by the American College of Cardiology National Cardiovascular Data Registry.[4] In-hospital death was defined as all-cause mortality. Recurrent myocardial infarction was defined as recurrent ischemic symptoms with cardiac enzyme confirmation of new or additional myocardial necrosis. Nonintracranial major and minor bleeding were defined in patients who did not undergo coronary artery bypass grafting according to the Thrombolysis In Myocardial Infarction (TIMI) classification.[5]

The use of all medications at community hospitals and Hartford Hospital before, during, and after PCI was at the

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Table 1
Baseline characteristics and in-hospital treatment

Variable	PCI		p Value
	Facilitated (n = 786)	Primary (n = 767)	
Age (yrs)	59.8 ± 12.7	62.5 ± 13.6	<0.001*
Body mass index (kg/m^2)	28.6 ± 5.6	28.1 ± 5.2	0.14
Men	569 (72.4%)	552 (72.0%)	0.85
Race			
Caucasian	656 (83.5%)	627 (81.7%)	0.006*
African-American	11 (1.4%)	30 (3.9%)	
Other	119 (15.1%)	110 (14.3%)	
Diabetes mellitus	128 (16.3%)	148 (19.3%)	0.12
Treatment for dyslipidemia	428 (54.5%)	411 (53.6%)	0.73
Current smoker	338 (43.0%)	269 (35.1%)	0.001*
Hypertension	416 (52.9%)	445 (58.0%)	0.04*
Body mass index ≥40 kg/m^2	32 (4.2%)	18 (2.4%)	0.06
Chronic lung disease	87 (11.1%)	86 (11.2%)	0.93
Previous stroke/transient ischemic attack	21 (2.7%)	32 (4.2%)	0.10
Renal insufficiency	37 (4.7%)	50 (6.5%)	0.12
Peripheral vascular disease	26 (3.3%)	28 (3.7%)	0.71
Previous myocardial infarction	80 (10.2%)	82 (10.7%)	0.74
Previous PCI	82 (10.4%)	89 (11.6%)	0.46
Previous coronary bypass surgery	20 (2.5%)	36 (4.7%)	0.023*
Time to presentation (min)	185 ± 242	196 ± 240	0.40
Extent of coronary artery disease			
1 Vessel	335 (42.6%)	298 (38.9%)	0.14
2 Vessels	257 (32.7%)	246 (32.1%)	
3 Vessels	165 (21.0%)	180 (23.5%)	
Left main	29 (3.7%)	43 (5.6%)	
Infarct vessel location			
Left main	25 (3.2%)	30 (3.9%)	0.18
Left anterior descending	279 (35.5%)	266 (34.7%)	
Circumflex	103 (13.1%)	121 (15.8%)	
Right coronary artery	369 (46.9%)	332 (43.3%)	
Primary/adjunctive intervention			
Stent	741 (94.3%)	709 (92.4%)	0.15
Drug-coated stent	375 (75.3%)	320 (72.7%)	0.37
Intra-aortic balloon pump	14 (1.8%)	19 (2.5%)	0.34
Temporary pacer	9 (1.1%)	4 (0.5%)	0.18
Thrombectomy device	95 (12.1%)	104 (13.6%)	0.39
Arteriotomy closure device	731 (93.0%)	687 (89.6%)	0.02*
Periprocedural medications			
Aspirin	756 (96.2%)	735 (95.8%)	0.72
Clopidogrel	209 (26.6%)	187 (24.4%)	0.32
Unfractionated heparin	750 (95.4%)	730 (95.2%)	0.82
Glycoprotein IIb/IIIa inhibitor	747 (95.0%)	724 (94.4%)	0.57
Low-molecular-weight heparin	19 (2.4%)	7 (0.9%)	0.02*
Direct thrombin inhibitor	17 (2.2%)	18 (2.3%)	0.50
Post-PCI medications			
Aspirin	770 (98.0%)	749 (97.7%)	0.68
Clopidogrel or ticlopidine	761 (96.8%)	731 (95.3%)	0.13
β Blocker	750 (95.4%)	721 (94.0%)	0.21
Angiotensin-converting enzyme inhibitor	604 (76.8%)	575 (75.0%)	0.39
Statin	720 (91.6%)	699 (91.1%)	0.74

* Statistically significant.

discretion of the treating physician. Standard recommendations for antiplatelet, antithrombin, and thrombolytic dosing regimens were made available for all community and tertiary-care physicians, with an appropriate list of contraindications. Recommended regimens included pretreatment of all patients with aspirin (325 mg orally), thienopyridines (clopidogrel 300 mg or ticlopidine 500 mg orally) in aspirin-allergic patients, and unfractionated heparin (60 to 80 U/kg intravenous bolus followed by 14 U/kg/hour). For physicians prescribing glycoprotein IIb/IIIa inhibitor and/or thrombolytic therapy, standard dosing regimens were recommended for abciximab, eptifibitde, tirofiban, reteplase, tenecteplase, and alteplase. Reduced use of unfractionated heparin (40- to 60-U/kg intravenous bolus) was recommended with concomitant glycoprotein IIb/IIIa inhibitor and/or thrombolytic use, and reduced-dose reteplase (5 units followed by 5 units) was recommended with concomitant glycoprotein IIb/IIIa inhibitor use. Following the evolution of trial-based data, the recommendation for pretreatment with clopidogrel (300 to 600 mg orally) in addition to aspirin was made in 2006.

All PCIs were performed using standard angioplasty and stenting techniques with appropriate monitoring of activating clotting times and platelet activation depending on adjunctive pharmacotherapy use. Mechanical thrombectomy, distal embolization protection devices, and femoral arteriotomy closure devices were available to all interventional physicians throughout the time course of patient treatment.

The primary objectives of this study were to compare in-hospital mortality and a composite of in-hospital major adverse clinical events, including mortality, recurrent myocardial infarction, urgent repeated target-vessel PCI, hemorrhagic and nonhemorrhagic stroke, and nonintracranial TIMI major bleeding, between the primary PCI and facilitated PCI groups. Secondary objectives included intergroup comparisons of baseline and post-PCI TIMI 3 flow in the infarct vessel. We also compared mortality and composite in-hospital adverse outcomes in both groups as a function of door-to-balloon time.

All data were presented as mean ± SD and percentages. Differences in proportions were analyzed using chi-square test or Fisher's exact test, whereas differences in normal continuous variables were analyzed using independent Student's t test. Analysis of variance was used for >2 group comparisons of continuous data. Post hoc comparisons used

Table 2
Use of community hospital pharmacotherapy in the facilitated PCI group

Variable	Facilitated PCI (n = 786)
Glycoprotein IIb/IIIa inhibitor alone	204 (26.0%)
Eptifiditide	155 (19.7%)
Abciximab	47 (6.0%)
Tirofiban	2 (0.3%)
Lytic alone	86 (10.9%)
Reteplase	61 (7.8%)
	33 (4.2%)*
	28 (3.6%)†
Tenecteplase	11 (1.4%)
Alteplase	14 (1.8%)
Combined glycoprotein IIb/IIIa and lytic	496 (63.1%)
Eptifibitide-retapase	276 (35.1%)
	261 (33.2%)*
	15 (1.9%)†
Eptifibitide-tenecteplase	25 (3.2%)
Eptifibitide-alteplase	11 (1.4%)
Abciximab-reteplase	173 (22.0%)
	173 (22.0%)*
Abciximab-tenecteplase	1 (0.1%)
Abciximab-alteplase	6 (0.8%)
Tirofiban-reteplase	2 (0.3%)
	1 (0.1%)*
	1 (0.1%)†
Tirofiban-tenecteplase	0 (0.0%)
Tirofiban-alteplase	2 (0.3%)

* Half-dose reteplase.
† Full-dose reteplase.

a step-down Holm's Bonferroni correction. Relative risks with 95% confidence intervals were generated. All reported p values were 2 sided. Analyses were performed using SPSS software, version 15.0 (SPSS Inc., Chicago, Illinois). The study was designed by all the authors and approved by the Hartford Hospital Institutional Review Board.

Results

Compared with the facilitated PCI group, patients who underwent primary PCI were older, less likely to be Caucasian and current smokers, and had an increased incidence of hypertension and previous coronary bypass surgery (Table 1). In addition, patients who underwent primary PCI had slightly lower use of low-molecular-weight heparin and arteriotomy closure devices. Otherwise, the 2 groups were well matched with respect to baseline demographics and in-hospital treatment strategies.

Table 2 lists glycoprotein IIb/IIIa inhibitors and thrombolytic agents administered at community hospitals in the facilitated PCI group. Facilitated regimens included use of glycoprotein IIb/IIIa inhibitor agents alone (n = 204; 26.0%), lytic agents alone (n = 86; 10.9%), or combined glycoprotein IIb/IIa inhibitors and thrombolytic agents (n = 496; 63.1%). Glycoprotein IIb/IIIa inhibitors, used alone or in combination, included eptifibitide (n = 467; 59.4%), abciximab (n = 227; 28.8%), and tirofiban (n = 6; 0.8%). Thrombolytic agents, used alone or in combination, included reteplase (n = 512; 65.1%), tenecteplase (n = 37; 4.7%), and alteplase (n = 32; 4.1%). In the 512 patients

Table 3
Procedural and in-hospital clinical outcomes

Variable	PCI		p Value
	Facilitated (n = 786)	Primary (n = 767)	
Door-to-balloon (min)	162 ± 57	113 ± 61	<0.001*
TIMI flow before PCI			
0	227 (28.9%)	450 (58.7%)	<0.001*
1	39 (5.0%)	44 (5.7%)	
2	105 (13.4%)	78 (10.2%)	
3	415 (52.8%)	195 (25.4%)	
TIMI flow after PCI			
0	7 (0.9%)	9 (1.2%)	0.50
1	1 (0.1%)	1 (0.1%)	
2	14 (1.8%)	22 (2.9%)	
3	764 (97.2%)	735 (95.8%)	
Procedural complications			
Intubation	13 (1.7%)	14 (1.8%)	0.80
In-laboratory cardiogenic shock	9 (1.1%)	12 (1.6%)	0.47
No reflow	108 (13.7%)	90 (11.7%)	0.24
Distal embolization	19 (2.4%)	36 (4.7%)	0.02*
Side-branch occlusion	30 (3.8%)	29 (3.8%)	0.97
In-hospital outcomes			
Death	16 (2.0%)	19 (2.5%)	0.56
Recurrent myocardial infarction	1 (0.1%)	3 (0.4%)	0.37
Emergent bypass surgery	6 (0.8%)	6 (0.8%)	0.97
Emergent repeated PCI	5 (0.6%)	9 (1.2%)	0.24
Hemorrhagic stroke	3 (0.4%)	0 (0.0%)	0.25
Nonhemorrhagic stroke	2 (0.3%)	2 (0.3%)	0.98
Renal failure with dialysis	1 (0.1%)	3 (0.4%)	0.31
TIMI major bleeding	32 (4.1%)	32 (4.2%)	0.92
TIMI minor bleeding	97 (12.3%)	104 (13.6%)	0.48
Transfusion	60 (7.6%)	70 (9.1%)	0.29
Vascular complications	20 (2.5%)	15 (2.0%)	0.43

* Statistically significant.

treated with reteplase, a half dose was administered to 468 patients (91.4%), whereas a full dose was administered to 44 (8.6%).

Door-to-balloon time increased significantly from a mean of 113 ± 61 minutes in the primary PCI group to 162 ± 57 in the facilitated PCI group (Table 3). During the 8-year course of the study, door-to-balloon times <90 and <120 minutes were achieved in 42.7% and 63.9% of patients who underwent primary PCI, respectively. Initial TIMI 3 flow in the infarct vessel was higher in the facilitated PCI group versus the primary PCI group (52.8% vs 25.4%; p <0.001), although the 2 groups did not differ with respect to the incidence of final TIMI 3 flow. There was no difference between the 2 groups with respect to in-hospital mortality, recurrent myocardial infarction, emergent repeated target-vessel PCI, emergent bypass surgery, hemorrhagic or nonhemorrhagic stroke, renal failure requiring dialysis, nonintracranial TIMI major or minor bleeding, use of red blood cell transfusion, or vascular complications.

Table 4 lists angiographic data and in-hospital clinical outcomes in the facilitated PCI group subdivided according to pretreatment drug regimens. Initial TIMI 3 flow in the infarct vessel was significantly higher in the lytic-alone group (51.8%) and combined glycoprotein IIb/IIIa inhibitor–lytic group (60.9%) compared with the glycoprotein IIb/IIIa inhibitor–alone group (34.2%). Minor bleeding was

Table 4
Subgroup analysis of outcomes in the facilitated PCI group

Variable	Glycoprotein IIb/IIIa Inhibitor Alone (n = 204)	Lytic Alone (n =86)	Combined Glycoprotein IIb/IIIa Inhibitor and Lytic (n = 496)	p Value	p Value
Procedural data					
Pre-PCI TIMI 3 flow	68 (34.2%)	44 (51.8%)	300 (60.9%)	<0.01	<0.01†‡
Post-PCI TIMI 3 flow	199 (98.0%)	81 (94.2%)	484 (97.4%)	0.18	
In-hospital outcomes					
Death	7 (3.4%)	2 (2.3%)	7 (1.4%)	0.22	
Recurrent myocardial infarction	0	0	1 (0.2%)	0.75	
Emergent repeated PCI	0	2 (2.3%)	3 (0.6%)	0.08	
Hemorrhagic stroke	0	0	3 (0.6%)	0.42	
Nonhemorrhagic stroke	0	0	2 (0.4%)	0.56	
TIMI major bleeding	12 (5.9%)	0	20 (4.0%)	0.07	
TIMI minor bleeding	33 (16.3%)	4 (4.7%)	60 (12.1%)	0.02	0.02†
Transfusion	21 (10.3%)	5 (5.8%)	34 (6.8%)	0.23	
Vascular complications	7 (3.4%)	4 (4.7%)	9 (1.8%)	0.19	

† Glycoprotein IIb/IIIa alone versus lytic alone.
‡ Glycoprotein IIb/IIIa alone versus combined glycoprotein IIb/IIIa and lytic.

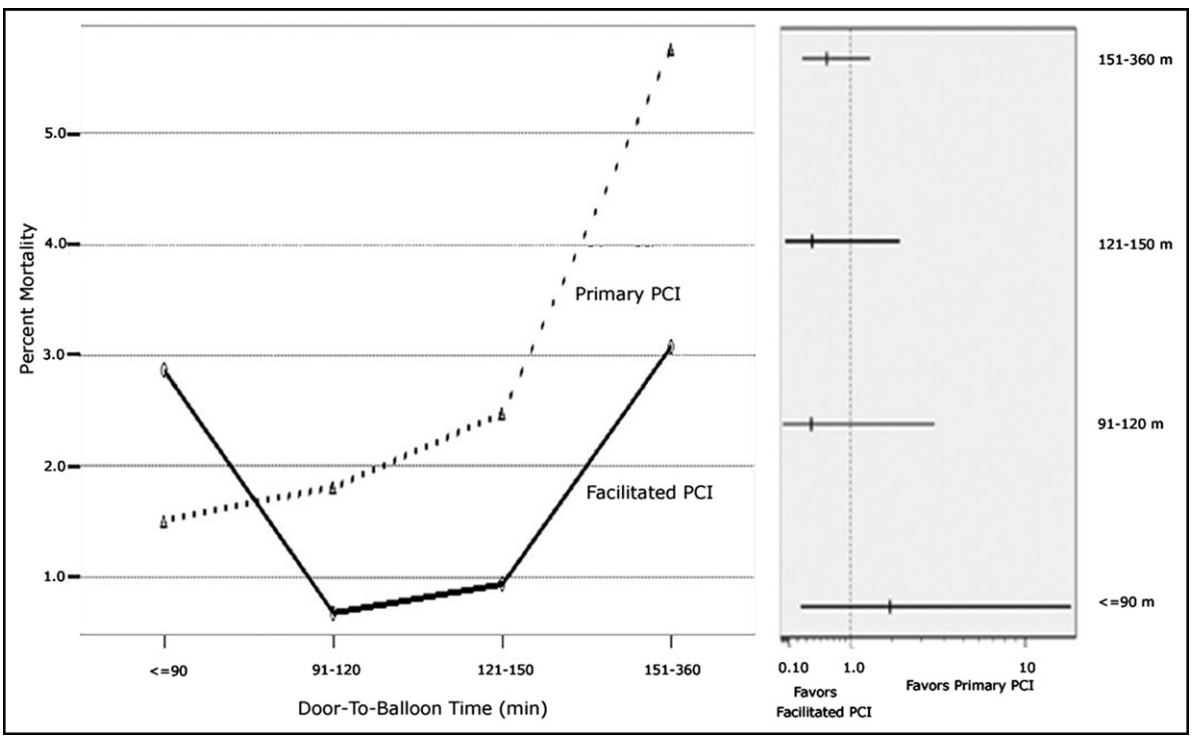

Figure 1. Relation between door-to-balloon time and in-hospital mortality for the primary and facilitated PCI groups.

significantly higher in the glycoprotein IIb/IIIa inhibitor–alone group versus the lytic-alone group, with no differences among the 3 facilitated regimens for all other in-hospital outcomes.

Figure 1 shows the relation between in-hospital mortality and door-to-balloon time in the 2 study groups. Mortality increased progressively and significantly with longer door-to-balloon times in the primary PCI group. Mortality was higher in the facilitated PCI group at door-to-balloon times <90 minutes, but thereafter remained lower than for the primary PCI group at door-to balloon intervals of 91 to 360 minutes.

Figure 2 shows the relation between door-to-balloon time and the composite adverse end point between the 2 study groups. There was no difference in incidence of the composite end point of combined in-hospital mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and nonhemorrhagic stroke, and nonintracranial TIMI major bleeding between the 2 study groups (facilitated PCI 49 events; 6.2%; primary PCI 59 events; 7.7%). However, subgroup analysis showed a significant decrease in composite events in patients who underwent facilitated PCI with PCI with door-to-balloon times >90 and ≤150 min-

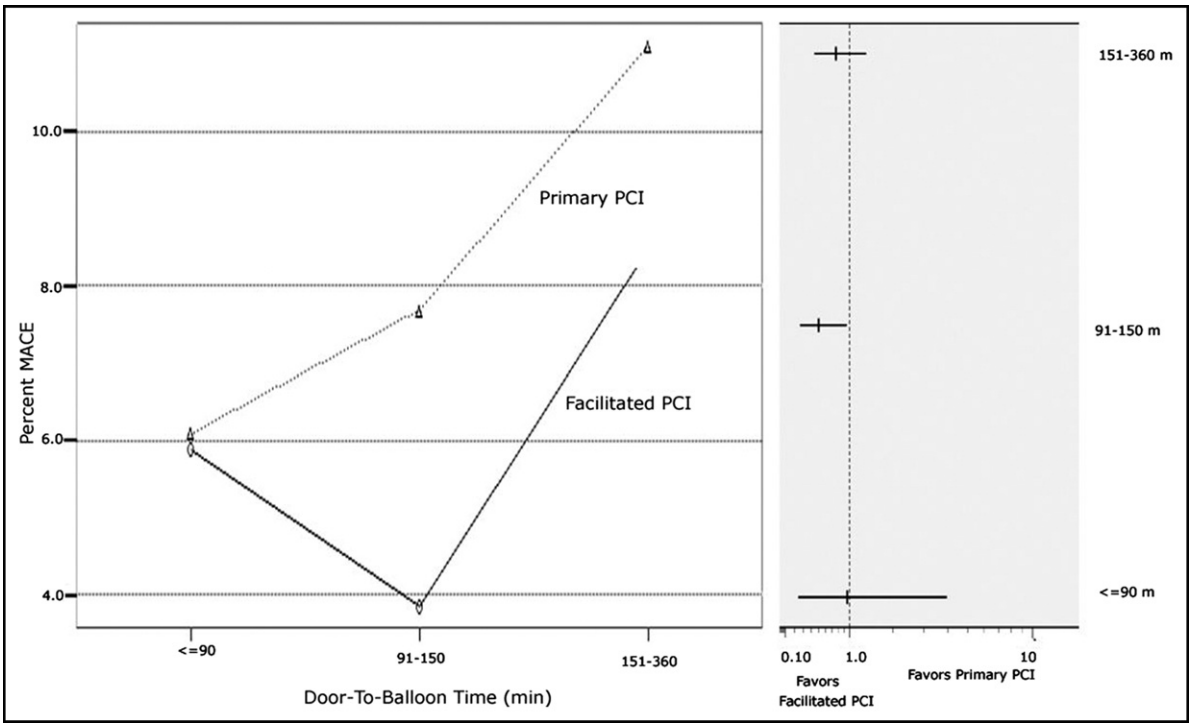

Figure 2. Relation between door-to-balloon time and composite major adverse clinical events (MACEs). In patients treated with door-to-balloon times >90 and ≤150 minutes, patients who underwent facilitated PCI had fewer composite MACEs (combined mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and nonhemorrhagic stroke, and nonintracranial TIMI major bleeding) compared with the primary PCI group (relative risk 0.50, 95% confidence interval 0.26 to 0.96, p = 0.034).

utes (relative risk 0.50, 95% confidence interval 0.26 to 0.96, p = 0.034).

Discussion

This single-center retrospective study showed the safe and efficacious use of a facilitated PCI approach to treat a large cohort of community hospital patients with STEMI. Compared with primary PCI, use of facilitated PCI was associated with a higher incidence of baseline TIMI 3 flow in the infarct vessel and no increase in adverse in-hospital events. Moreover, facilitated PCI was associated with a lower incidence of composite adverse events, including mortality, recurrent myocardial infarction, emergent repeated PCI, hemorrhagic and nonhemorrhagic stroke, and nonintracranial TIMI major bleeding, in patients undergoing catheter-based intervention with door-to-balloon times >90 and ≤150 minutes. By extending the therapeutic window for beneficial catheter-based revascularization, use of facilitated PCI in this study reduced the deleterious clinical impact of delayed PCI associated with initial presentation to a community hospital.

Given the recognized benefit of early reperfusion and the inherent delay associated with interhospital transfer of patients with STEMI for PCI, the concept of using facilitated PCI to achieve early pharmacologic reperfusion before mechanical revascularization has been debated for nearly 2 decades.[6–18] However, recent studies failed to show a clinical benefit of this approach and have documented evidence of patient harm. The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention-4 (ASSENT-4) PCI trial assessed the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) impact of facilitated PCI with full-dose tenecteplase versus primary PCI alone using a primary end point of 90-day death, cardiogenic shock, or congestive heart failure. The trial was terminated early because of worse outcomes in the facilitated-PCI arm, including higher rates of recurrent myocardial infarction, repeated target-vessel revascularization, and stroke and in the primary trial end point.[1] Similarly, the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial randomly assigned 2,452 patients to 1 of 3 treatments arms, including primary PCI with in-laboratory abciximab, abciximab-facilitated PCI, or half-dose reteplase/abciximab–facilitated PCI. At 90 days, there were no differences in the study subgroups with respect to the trial's composite end point of all-cause mortality, readmission for heart failure, ventricular fibrillation, or cardiogenic shock. Moreover, compared with the primary PCI group, there was evidence of increased TIMI major and minor bleeding in the reteplase/abciximab-facilitated PCI group, as well as increased TIMI major or minor bleeding in the abciximab-facilitated PCI group.[2]

One possible explanation for the contrary observations of the present study compared with ASSENT-4 PCI and FINESSE outcomes was the observed incidence of TIMI 3 flow in the infarct vessel before the performance of PCI in the facilitated PCI subgroups. Compared with a 52.8% incidence of baseline TIMI 3 flow in the facilitated PCI group

in the present study, the pre-PCI TIMI 3 flow rate was 43.5% in the Tenectplase-facilitated ASSENT-4 PCI arm, 15% in Tenecteplase the abciximab-facilitated FINESSE arm, and 36% in the abciximab/reteplase-facilitated FINESSE arm. Possible factors underlying the improved pre-PCI TIMI 3 flow in the present study compared with the ASSENT-4 PCI and FINESSE trials included (1) a longer interval between administration of facilitating agents and performance of PCI, allowing the glycoprotein IIb/IIIa inhibitor and/or lytic agents to exert maximal thrombolysis and infarct vessel recanalization before catheter-based intervention; (2) overall higher use of thrombolytic therapy in the present study compared with FINESSE; and (3) overall higher use of glycoprotein IIb/IIIa inhibitor agents in combination with thrombolytics compared with ASSENT-4 PCI.

Apart from improved baseline TIMI 3 flow rates, the specific use of periprocedural medications and adjunctive mechanical technologies in the present study may have obviated the adverse clinical outcomes noted in other facilitated PCI trials. The high use of stenting and periprocedural glycoprotein IIb/IIIa inhibitor agents in both the facilitated and primary PCI groups may explain the observed low incidence of recurrent myocardial infarction and emergent repeated PCI in both study groups. Similarly, the concomitant and periprocedural glycoprotein IIb/IIIa inhibitor use in the facilitated PCI group may have obviated any thrombolytic-induced platelet aggregation. Finally, the high periprocedural use of glycoprotein IIb/IIIa inhibitor agents and arteriotomy closure devices in both study groups may explain the similar incidences of blood loss related specifically to vascular access site bleeding.

As a retrospective registry report, the present study was limited by lack of randomization, accrual of data during an 8-year period, and wide variation in the use of different adjunctive pharmacotherapies with >10 different combinations of glycoprotein IIb/IIIa inhibitors and thrombolytics studied. Although all consecutive patients were included and treatment groups were not preselected, referral bias cannot be eliminated as a confounding factor. However, except for these limitations, this study allowed for the evaluation of a large cohort of patients with STEMI with prolonged door-to-balloon times with sufficient power to detect statistical differences in adverse outcomes. Ethical considerations in the design of present randomized trials, as well as anticipated difficulties in patient recruitment, would be expected to limit future investigations from documenting the potential benefits of facilitated PCI observed in the present study.

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