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The Impact of Place of Enrollment and Delay to Reperfusion on 90-Day Post-Infarction Mortality in the ASSENT-4 PCI Trial

Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention

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Objectives We have performed a retrospective analysis of the data stratified by time to treatment and by enrollment site: percutaneous coronary intervention hospitals (PCIH), nonpercutaneous coronary intervention hospitals (NoPCIH), or in a pre-hospital setting (PreH).

Background The ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial intended to test the hypothesis that in ST-segment elevation myocardial infarction (STEMI) patients an upfront fibrinolytic bolus before PCI ("facilitated PCI") compared with primary PCI would benefit STEMI patients facing a long pre-PCI delay.

Methods Seven hundred forty-nine patients (45%) presented directly to PCIH, 578 (34%) presented to NoPCIH, and 334 (20%) were randomized and initially treated in the PreH setting.

Results Patients in the PreH-facilitated group had the shortest delays (pain-to-fibrinolytic treatment 125 min) and the lowest 90-day mortality (3.1%). Among patients randomized to primary PCI, the shortest time from pain to first balloon was similarly in the PreH group (223 min). They had the lowest mortality of the primary PCI patient groups (4.1%). The highest mortality (8.4%) was in patients presenting to a PCIH and assigned to the facilitated strategy. Their pain-to-lysis time was 174 min and pain-to-PCI time 266 min (or 92 min after lysis).

Conclusions Few patients fit the target population, long delays to PCI for whom facilitated PCI was designed. Patients treated early after pain onset in the PreH setting do well after a facilitated approach. Despite limitations of post hoc subgroup analysis, these observations suggest caution in extrapolating the results of the ASSENT-4 trial to the "real world" where many patients might have potentially short pain-to-fibrinolysis time but are facing a long transport time to primary PCI. (J Am Coll Cardiol Intv 2009;2:925–30) © 2009 by the American College of Cardiology Foundation

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Acute ST-segment elevation myocardial infarction (STEMI) patients are frequently selected for reperfusion by percutaneous coronary intervention (PCI) (1), despite the possibility or probability of a substantial delay before the procedure can be effected (2). Long delays have been consistently shown to decrease and eventually eliminate the mortality advantage that timely PCI might otherwise have over fibrinolytic reperfusion (3–5). Such delays are commonly due to the need for a transfer from a community hospital without PCI facilities to a tertiary

See page 931

care hospital (6,7). Many communities are successfully reorganizing their approach to possible STEMI patients by establishing streamlined management protocols and by creating networks consisting of both hospitals and emergency systems designed to decrease these delays and comply with current U.S. and European guidelines: PCI within 90 min of presentation or within 60 min in younger patients and those experiencing an anterior wall infarction (8–16). Nonetheless, as a result of distance, traffic, weather, and other unanticipated transfer issues, long delays cannot be completely avoided.

Abbreviations and Acronyms

NoPCIH = nonpercutaneous coronary intervention hospitals

PCI = percutaneous coronary intervention

PCIH = percutaneous coronary intervention hospitals

PreH = pre-hospital setting

STEMI = ST-segment elevation myocardial infarction

An approach to mitigate the effects of such delays has been the immediate administration of pharmacological therapies that can achieve reperfusion before or during transfer (generally referred to as "facilitated PCI"). The PCI would then be accomplished as soon as possible thereafter for the purpose of "rescuing" drug failures and by dilating and commonly stenting significant residual stenosis of the infarct artery, thus diminishing the occurrences of recurrent myocardial infarction and further episodes of ischemia (17). Various antithrombotic and fibrinolytic agents and combinations have been examined for utility in this indication; however, a recent quantitative review (18) and meta-analysis (19) each concluded that none of the published fibrinolytic-based, facilitated protocols improved upon the results of standard primary angioplasty. These reports have given rise to the general understanding that a routine, facilitated approach to STEMI is not helpful. The basis for this position, however, is composed dominantly of information from the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction with Percutaneous Coronary Intervention) trial patients (17), representing 56% and 62% of the sample sizes in the review and meta-analysis, respectively. Therefore, it might be instructive to examine some relationships in the study, particularly regarding place of patient enrollment and various measures of delay as they might have affected 90-day mortality.

The ASSENT-4 trial was intended to evaluate the use of a fibrinolysis-based, facilitated approach for patients in whom delays to primary PCI of 1 to 3 h were anticipated (17). It was also expected that most enrolled patients would be those presenting to a community hospital (NoPCIH), but those presenting to a PCI-capable institution (PCIH) were not excluded. The current report is a retrospective analysis undertaken when differences in outcome were perceived according to the type of enrolling site and the time intervals common to each site. These findings might modify the impressions held of the ASSENT-4 trial (17) and lead to some revision in thinking regarding what ASSENT-4 did and did not demonstrate.

Methods

The trial methodology and principal end points have been previously published (17). Briefly, 1,667 STEMI patients within 6 h of pain onset were selected for PCI but not expected to have the intervention earlier than 60 min or later than 180 min. They were enrolled in PCIH, NoPCIH, and in pre-hospital settings (PreH). They were randomized to either the facilitated group, which received open-label, full-dose weight-adjusted tenecteplase and an IV bolus of unfractionated heparin (60 IU/kg but not more than 4,000 IU dose) but no heparin infusion and no glycoprotein IIb/IIIa antagonist except for bail-out circumstances or they were randomized to standard primary PCI, in which glycoprotein receptor use was not restricted and left to the preference of the interventionalist.

Data were collected on all patients regarding the following time intervals: pain to randomization at first medical contact (by emergency responders with pre-hospital fibrinolytic capabilities or performed at the first hospital reached), randomization to initiation of fibrinolytic bolus, randomization to first balloon inflation of the infarct-related artery (1), and pain onset to initiation of fibrinolysis and pain onset to first balloon inflation.

The ASSENT-4 trial was prematurely terminated after 1,667 patients had been enrolled, and events after 30 days of follow-up were available to the Data Safety Monitoring Board for 1,320 patients. Analysis then showed an imbalance of in-hospital deaths (6.5% and 3.4% in the facilitated and primary PCI groups, respectively, $p < 0.01$). The pre-specified primary end point of the trial was the combined frequency of death, shock, or congestive heart failure 90 days after the index STEMI. The mortality rate at 90 days was: facilitated PCI, 6.7%; and primary PCI, 5.0% ($p = 0.14$). The other components of the primary end point also trended in favor of primary PCI, but none were

Table 1. Baseline Characteristics According to Place of Randomization

	PCIH (n = 749)	NoPCIH (n = 578)	PreH (n = 334)	p Value
Age, yrs	59 (51–69)	61 (52–71)	60 (51–69)	0.07
Female	21.5%	26.6%	19.5%	0.02
Previous MI	13.8%	9.7%	11.5%	0.07
Previous PCI	10.2%	5.6%	9.4%	0.007
Previous CABG	3.4%	0.9%	1.2%	0.004
Smoker	46.6%	46.0%	47.5%	0.9
Hypertension	47.9%	47.8%	43.4%	0.35
Hypercholesterolemia	35.6%	30.3%	35.9%	0.06
Diabetes mellitus	20.3%	13.5%	13.2%	<0.01
Killip class >II	7.5%	9.5%	7.5%	0.18
Anterior MI	50.3%	48.2%	45.8%	0.37

p values by analysis of variance for age and chi-square for other variables.

CABG = coronary artery bypass grafting; MI = myocardial infarction; NoPCIH = nonpercutaneous coronary intervention hospitals; PCI = percutaneous coronary intervention; PCIH = percutaneous coronary intervention hospitals; PreH = pre-hospital setting.

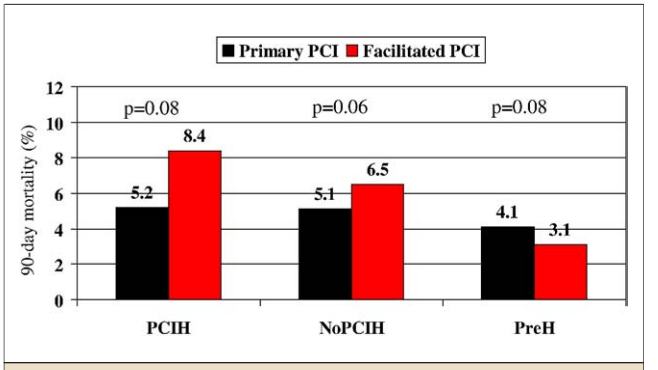

Figure 1. Mortality After 90 Days According to Place of Enrollment Comparing Primary and Facilitated PCI

p values for chi square. NoPCIH = nonpercutaneous coronary intervention hospitals; PCI = percutaneous coronary intervention; PCIH = percutaneous coronary intervention hospitals; PreH = pre-hospital setting.

statistically significant (shock 6.1% vs. 4.8%, p = 0.27, and heart failure 12.1% and 9.4%, p = 0.08). When combined, 19% of facilitated and 14% of primary PCI patients had at least 1 component of the combination (p = 0.01). The primary publication of this trial included data on key time intervals, but comparison was only between the 2 randomized groups. In this report we analyzed time delays by site of enrollment and treatment assigned.

Descriptive statistics were summarized as medians with 25th and 75th percentiles for continuous variables, and the Mann-Whitney *U* test was used for comparisons of groups. For categorical variables, the data were summarized in percentages, and the chi-square test was used.

Results

The plurality–749 (45%) patients–were enrolled in PCIH. Five hundred seventy-eight (35%) entered the trial at community hospitals (NoPCIH) and were then transferred for intervention, and 334 patients (20%) were randomized in the pre-hospital setting (PreH). Table 1 shows the baseline variables in the 3 groups. The antithrombotic therapies administered in the 6 groups are given in Table 2. Figure 1 depicts the 90-day mortality by site of enrollment and treatment assignment. Table 3 shows the time delays for both treatment assignments and for the 3 randomization sites. The rates of patients with a delay of more than 120 min between randomization and PCI were 24% in PCIH, 67% in the NoPCIH, and 24% in the PreH. The median PCI-related delay (time from fibrinolysis to PCI in facilitated PCI patients) was over 2 h in the NoPCIH (transferred) patients but fewer than 100 min in the other 2 groups.

In primary PCI patients, time from pain onset to PCI related most closely to outcome. In patients enrolled at PCIH it was 258 min, and the 90-day mortality was 5.2%. Patients in NoPCIH had a short time from pain to randomization (135 min), but the delay imposed by transfer led to a pain-to-PCI time of 273 min. The mortality rate of this group was 5.1%. The interval from pain onset to PCI was shortest in PreH patients (203 min), and they had the lowest PCI group mortality rate in that treatment assignment (4.1%).

In the facilitated PCI group the mortality appears to correlate best with time from pain to fibrinolytic bolus. The longest pain-to-lytic time was in patients enrolled at PCI-capable hospitals (174 min), and the mortality rate was highest (8.4%). The lowest mortality rate (3.1%) was in PreH patients with tenecteplase bolus delivered at a median of 125 min after the onset of pain (Table 3). The results

Table 2. Antithrombotic Therapies According to Treatment Assignment and Place of Randomization

	PCIH		NoPCIH		PreH	
	Facilitated PCI	Primary PCI	Facilitated PCI	Primary PCI	Facilitated PCI	Primary PCI
Aspirin	89%	91%	76%	76%	79%	81%
Clopidogrel	88%	93%	90%	92%	93%	97%
GP IIb/IIIa inhibitors	15%	52%	12%	48%	17%	69%
Unfractionated heparin	100%	100%	100%	100%	100%	100%

GP = glycoprotein; other abbreviations as in Table 1.

Table 3. Time Intervals in Patients With Primary or Facilitated PCI According to Place of Randomization

	Symptom Onset to Randomization	Randomization to Lysis	Randomization to PCI	Symptom Onset to Lysis	Symptom Onset to PCI	90-Day Mortality
Primary PCI						
PCIH	160 (110;248)	na	95 (80;115)	na	258 (207;341)	5.2%
NoPCIH	135 (90;185)	na	140 (105;165)	na	273 (227;345)	5.1%
PreH	105 (70;160)	na	99 (75;122)	na	203 (154;258)	4.1%
Facilitated PCI						
PCIH	160 (110;234)	10 (6;15)	105 (88;123)	174 (123;252)	266 (215;340)	8.4%
NoPCIH	130 (86;190)	12 (7;18)	145 (114;176)	142 (101;205)	272 (229;350)	6.5%
PreH	105 (75;172)	10 (5;16)	107 (81;135)	125 (90;185)	223 (180;310)	3.1%

p value by chi-square for mortality among the 3 primary PCI groups: 0.9. p value by chi-square for mortality among the 3 facilitated PCI groups: 0.06. Values are minutes to first balloon (median and quartiles [Q1;Q3]), except % for mortality (Mort). Individual medians do not necessarily sum to combined medians.
Rand = randomization; 90-d = 90-day; other abbreviations as in Table 1.

with respect to the combined end point and bleeding complications are given in Table 4.

Discussion

The ASSENT-4 PCI trial provides important insights into the relationship of time from symptom onset, PCI-related delays, and impact of facilitation with fibrinolytic therapy. The trial, however, failed to predominantly recruit those patients for whom the concept of facilitated PCI was designed, those admitted to a NoPCIH and therefore for whom a significant delay before PCI might be expected. The inclusion of patients presenting to a PCIH was a practical one, anticipating that the centers doing the procedures would be motivated if they too could be an enrolling site. Furthermore, the protocol was finalized at a time when long pain-to-balloon times and long door-to-balloon times were common, even in PCI-capable centers.

The present report reconfirms the common understandings that delay to reperfusion remains a dominant arbiter of mortality, whether the treatment is direct PCI or PCI after fibrinolysis or fibrinolysis alone (20–23). Facilitated PCI with fibrinolysis administered in the pre-hospital setting within the first 2 to 3 h after infarct onset, then followed with PCI, was associated with the lowest 90-day mortality rate in the trial. These results reconfirm earlier reports about the value of very early fibrinolysis (24,25). Pre-hospital triage as represented here by pre-hospital patients randomized to PCI and taken directly to intervention had the second lowest mortality in the trial and the lowest of the 3 primary PCI subgroups.

One interpretation of the high mortality among facilitated PCI patients admitted directly to a PCI hospital has been that doing the PCI early after fibrinolysis with low levels of antithrombotic adjuncts was injurious and led to multiple problems, including the complications of a lytic-induced prothrombotic environment (26–28). It is noteworthy that the interval between lytic drug and PCI was nearly the same (98 min and 92 min in PreH and PCIH patients, respectively), despite the apparent difference in outcome. Hence the 8.4% mortality rate in the PCIH patient group is without certain explanation.

Recent descriptions of regional STEMI strategies have confirmed the effective use of fibrinolytic therapy when the infarct onset is recent and PCI is not quickly available (14,15,29). Henry et al. (14) employed half-dose tenecteplase before STEMI patients at a community hospital with known long transport times were transferred to the tertiary care hospital in Minneapolis for PCI. During inclement weather or for other reasons to anticipate transport delays, full-dose lysis was employed. Despite baseline variables predictive of high risk, the 421 patients in this protocol had a 30-day mortality of 5.2%. Ting et al. (15) published the Mayo Clinic regional strategy for STEMI patients presenting to any 1 of their 28 non-PCI hospitals in their referral network. For patients

Table 4. Combined End Point After 90 Days and Bleeding Complications

	PCIH		NoPCIH		PreH	
	Facilitated PCI	Primary PCI	Facilitated PCI	Primary PCI	Facilitated PCI	Primary PCI
Death, cardiogenic shock, or CHF	17.9%	11.0%	19.3%	16.2%	19.4%	13.9%
Intracranial bleeding	1.3%	0	0.7%	0	0.6%	0
Major bleeding complications	7.6%	4.3%	3.9%	3.4%	8.0%	6.4%

CHF = congestive heart failure; other abbreviations as in Table 1.

presenting within 3 h of pain onset, treatment was full-dose fibrinolysis. Angiography and possible PCI were deferred for 24 to 48 h, unless there were compelling clinical reasons to intervene earlier. The 30-day mortality was 3.7%. Patients whose symptom-to-presentation time exceeds 3 h were transported for PCI without use of a fibrinolytic and had a 7.1% mortality.

Also recently presented and relevant to the current report are the results of the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) (30) and TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute MI) trials (31). In the FINESSE trial, patients were randomized to 1 of 3 strategies: abciximab at the start of PCI, abciximab at the time of presentation/randomization, and abciximab plus half-dose fibrinolysis bolus at randomization. The median time for pain onset to PCI for all patients was 255 min. There were no significant differences among the groups in the composite end point (90-day death, heart failure, or hospital stay for cardiogenic shock or ventricular fibrillation). The rates were 10.7, 10.8, and 9.8, respectively. There were also no differences in each component of the primary end point. The mortality rates were 4.6%, 5.5%, and 5.2%, respectively. No patient received full-dose fibrinolysis. It should be noted that this trial was prematurely terminated after enrollment of 2,542 patients, which was 82% of the planned 3,000. Termination was due to recruitment problems and not interim analysis differences.

In the TRANSFER-AMI trial, 1,059 patients were treated with fibrinolysis and then randomized to early PCI within 6 h after fibrinolysis or conventional treatment. The results showed that the combined primary end point of death, reinfarction, recurrent ischemia, cardiogenic shock, and heart failure occurred significantly more often in the conventional group (17.2% vs. 11.0%) when planned early PCI followed lysis (relative risk: 0.64, 95% confidence interval: 0.47 to 0.87, $p = 0.004$). The majority of the patients were treated with fibrinolysis within 3 h after symptom onset. There was no increase in bleeding complications in the early PCI group. These results are in line with the findings of the CARESS-AMI (Combined Abciximab Reteplase Stent study in Acute myocardial infarction) trial (32). Here, routine early angiography and PCI after fibrinolysis reduced the incidence of death, reinfarction, and recurrent angina from 10.7% to 4.4% with selective angiography.

The obvious major limitation to the observations in the current report is, although the general plan to do time interval-related analyses was pre-specified, the correlations described in the preceding text were not. We observed differences in baseline variables of patients among 3 randomization locations. Moreover, subgroup analyses might be misleading and are to be considered hypothesis-generating only. For these reasons no probability calculations of the comparisons presented were made. Nonetheless, on the basis of the present ASSENT-4 analyses and other clinical and investigational reports on patients seen in the first 2 to 3 h after STEMI symptom onset, immediate fibrinolysis should remain a consideration when longer delays to PCI are anticipated, with or without plans for subsequent early PCI. An implied conclusion of our analyses is that the ASSENT-4 PCI trial should not be taken as grounds for conclusive rejection of facilitated PCI in all its variations as currently practiced or studied in ongoing investigations.

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