Reperfusion Strategies

Comparison of Facilitated Versus Primary Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction

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Primary Versus Tenecteplase-Facilitated Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Acute Myocardial Infarction (ASSENT-4 PCI): Randomized Trial

Van de Werf F, the ASSENT-4 PCI Investigators

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Comparison of Primary and Facilitated Coronary Interventions for ST-Elevation Myocardial Infarction: Quantitative Review of Randomized Trials

Keeley EC, Boura JA, Grines CL

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Rapid reperfusion of the infarct-related artery in patients presenting with ST-elevation myocardial infarction (STEMI) limits infarct size ("time is muscle"), increases myocardial salvage, preserves left ventricular function, and improves survival. STEMI is considered a true medical emergency, analogous to major trauma and aortic dissection, where even minutes of delay in initiating appropriate treatment confers higher risk for mortality. Based on current trial data and guidelines,[1,2] there are 2 proven reperfusion strategies for patients with STEMI—namely, full-dose fibrinolysis or primary percutaneous coronary intervention (PCI).

The goals of reperfusion therapy are to restore thrombolysis in myocardial infarction (TIMI) 3 flow in the infarct-related artery as rapidly as possible and to maintain patency over the ensuing hours to days. The Achilles' heel of fibrinolysis is that TIMI 3 flow is achieved in only 60% to 70% of those treated at 90 minutes; furthermore, many patients have absolute or relative contraindications due to bleeding risk. The major limitation with primary PCI arises from the multiple delays in our systems between first medical contact and balloon inflation in the catheterization laboratory. Hence, there has been intense interest in whether a combination approach of fibrinolysis followed by immediate PCI—so-called fibrinolytic-facilitated PCI—can restore TIMI 3 flow more rapidly prior to mechanical intervention of the ruptured atherosclerotic plaque, and consequently improve clinical outcomes.

Review of Recent Facilitated PCI Trials

The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial tested the hypothesis that full-dose fibrinolytic (tenecteplase)-facilitated PCI is more effective than standard primary PCI in patients with STEMI who experience a delay in reperfusion therapy.[3] The trial was a randomized, open-label study that planned to enroll 4000 patients, but was terminated early by the data and safety monitoring board after enrollment of 1667 patients because of higher in-hospital mortality in the facilitated PCI group compared to the primary PCI group (6% versus 3%; $P = .0105$).

Between November 10, 2003 and April 22, 2005, 1667 patients with STEMI of less than 6 hours duration with an anticipated delay to reperfusion of 1 to 3 hours were randomized to full-dose tenecteplase-facilitated PCI (n = 829) or standard primary PCI (n = 838). The facilitated versus primary PCI groups exhibited similar baseline characteristics, including age (60 years versus 61 years), Killip class ≥ II (9% versus 7%), presence of congestive heart failure (5% versus 5%), heart rate (74 beats per minute versus 76 beats per minute), systolic blood pressure (134 mm Hg versus 134 mm Hg), and anterior infarction (49% versus 46%). TIMI 3 flow before PCI was achieved in 43% of the fibrinolytic-facilitated PCI group compared to 15% of the primary PCI group ($P < .0001$). Despite higher rates of TIMI 3 flow before PCI, the incidence of the primary endpoint—namely, death or congestive heart failure or shock within 90 days—was 19% in the facilitated PCI group versus 13% in the primary PCI group (relative risk 1.39; 95% CI, 1.11-1.74; $P = .0045$). Results for single clinical endpoints are shown in Table 1 and causes of death are shown in Table 2. The higher in-hospital mortality observed in the facilitated PCI group

Table 1
Single Clinical Endpoints Within 90 Days

Clinical Endpoint	Tenecteplase-Facilitated PCI (n = 829)	Primary PCI (n = 838)	*P* Value
Death	55/823 (7%)	41/831 (5%)	.1412
Congestive heart failure	97/807 (12%)	75/818 (9%)	.0640
Shock	51/807 (6%)	39/817 (5%)	.1933
Reinfarction	49/805 (6%)	30/820 (4%)	.0279
Repeat target vessel revascularization	53/805 (7%)	28/818 (3%)	.0041

PCI, percutaneous coronary intervention. Data from Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI).[3]

Table 2
Causes of Death Within 90 Days

Clinical Endpoint	Tenecteplase-Facilitated PCI (n = 55)	Primary PCI (n = 40)*
Reinfarction	4	4
Cardiogenic shock	22	17
Arrhythmia or sudden death	1	3
Asystole or cardiac arrest	6	5
Cardiac rupture or electromechanical dissociation	8	5
Stroke or intracranial hemorrhage	8	0
Other cardiac event	1	3
Other non-cardiac event	5	3

*Cause of death missing for 1 patient assigned to primary PCI.
PCI, percutaneous coronary intervention. Data from Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI).[3]

compared to the primary PCI group was largely attributable to higher rates of total stroke (15/829 [1.8%] versus 0; $P < .0001$) and hemorrhagic stroke (8/829 [1.0%] versus 0; $P = .0037$). Although the rates for total and hemorrhagic stroke observed in the facilitated PCI group are comparable to those in previous fibrinolytics trials,[4,5] these adverse events were not seen in the primary PCI group.

The ASSENT-4 trial patient population presented relatively "early" with a median time from symptom onset to randomization of 140 minutes in the facilitated PCI group and 135 minutes in the standard primary PCI group ($P = .5545$). The median time from symptom onset to tenecteplase administration was 153 minutes. The median time from symptom onset to balloon inflation was 263 minutes for the facilitated PCI group versus 255 minutes for the primary PCI group ($P = .7042$). With regard to the observed delays to reperfusion, there are 2 categories. The first is patient-dependent—namely, patient awareness and activation of the healthcare system. The duration of patient-related delay regrettably remains on average 2 to 3 hours and was consistent in this trial as noted in the symptom onset to randomization time interval. The second component of the overall delay is hospital-dependent—namely, delays in processes and systems for delivering treatment effectively and efficiently. The surrogate measure for this interval is door-to-balloon (DTB) time, which has been considered to be a reflection of the overall quality of care at a specific institution. In this trial, the time interval from randomization to first balloon inflation was 115 minutes for the facilitated PCI group and 107 minutes for the primary PCI group ($P = .7042$).

In prespecified subgroup analyses including variables such as age, gender, Killip class, infarct location, time from symptom onset to randomization, and time from symptom onset to first balloon inflation, no subgroups benefited from fibrinolytic-facilitated PCI as measured by mortality, shock, or congestive heart failure within 90 days. The ASSENT-4 investigators concluded that a full-dose fibrinolytic-facilitated PCI for patients presenting within 2 to 3 hours of symptom onset was associated with higher adverse events including in-hospital death and total stroke compared with standard primary PCI. The benefits of achieving higher rates of TIMI 3 flow before PCI with fibrinolytic-facilitated PCI were

outweighed by the increased risk for death, reinfarction, and stroke. The higher risk of adverse events associated with facilitated PCI may be explained by fibrinolytic-induced platelet activation, intramural coronary hemorrhage, myocardial hemorrhage leading to ventricular free-wall rupture, hemorrhagic stroke, and other systemic bleeding exacerbating supply and demand mismatch.

In the same volume of *Lancet*, Keeley and colleagues[6] reported a grouped analysis of 17 randomized trials (including ASSENT-4) comparing facilitated and primary PCI among 4504 patients. The pooled trials utilized 3 facilitation strategies—glycoprotein IIb/IIIa inhibitor alone, fibrinolytic alone, and combination therapy. Overall, the facilitated approach achieved higher rates of initial TIMI 3 flow compared with primary PCI (37% versus 15%; $P = .0001$). However, the facilitated approach demonstrated higher mortality (5% versus 3%; $P = .04$), non-fatal reinfarction (3% versus 2%; $P = .006$), major bleeding (7% versus 5%; $P = .01$), total stroke (1.1% versus 0.3%; $P = .0008$), and hemorrhagic stroke (0.7% versus 0.1%; $P = .0014$) compared to primary PCI. The higher rates of adverse events were primarily observed among the trials utilizing a fibrinolytic-based regimen. Among the 8 facilitated PCI trials that utilized a fibrinolytic agent, all the point estimates for death and major bleeding trended in favor of primary PCI, save for the Grupo de Analisis de la Cardiopatia Isquemica Aguda (GRACIA) 2 trial, which had a non-significant trend favoring facilitated PCI.[7] Among the 9 facilitated trials utilizing a glycoprotein IIb/IIIa inhibitor alone, the facilitated approach did not show significant benefit or harm compared to primary PCI for death (3% versus 3%; $P = .94$), non-fatal reinfarction (1% versus 1%; $P = .53$), major bleeding (7% versus 5%; $P = .30$), total stroke (0 versus 0.4%; $P = .34$), and hemorrhagic stroke (0 versus 0.2%; $P = .68$). The authors concluded that based on the results of ASSENT-4 and the pooled analysis, a facilitated PCI strategy offers no benefit over primary PCI and should not be utilized outside the context of a randomized trial. Furthermore, a facilitated PCI strategy utilizing a fibrinolytic-based regimen increased the risk of death, reinfarction, and bleeding, and should be avoided. A strategy of a half-dose fibrinolytic-facilitated PCI with and without a glycoprotein IIb/IIIa inhibitor (abciximab) is currently being tested in the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, and results are expected within the next 2 to 3 years. (The clinicaltrials.gov number is NCT00046228.)

Choice of Reperfusion in STEMI—the Evidence for Fibrinolytics

Fibrinolysis is most effective for STEMI patients who present within 1 to 3 hours of symptom onset—what has been coined the "golden first hour." The Fibrinolytic Therapy Trialists' (FTT) grouped analysis of 58,600 patients randomized to fibrinolysis or a control group showed that fibrinolysis saved 39 lives per 1000 patients treated within 1 hour of symptom onset and 30 lives per 1000 patients treated within 2 to 3 hours of symptom onset.[8] In the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial, prehospital fibrinolysis for patients within 2 hours of symptom onset demonstrated a trend for improved mortality (2.2% versus 5.7%; $P = .058$) and significantly decreased risk for cardiogenic shock compared to primary angioplasty.[9] Patients treated with a fibrinolytic agent should be transferred immediately to a PCI facility because an invasive approach after failed reperfusion, termed *rescue PCI*,[10] has been shown to be beneficial, and in the GRACIA-1 trial, routine angiography demonstrated overall benefit in decreasing recurrent ischemic events, even among stable patients with apparently successful reperfusion.[11]

Choice of Reperfusion in STEMI—the Evidence for Primary PCI

The benefits from primary PCI can be attributed to improved myocardial salvage (from achieving higher rates of TIMI 3 flow) and to lower risk of reinfarction and reocclusion (from mechanical stabilization of ruptured plaques). Primary PCI is also safer, with lower risk of bleeding complications, particularly intracranial hemorrhage and myocardial rupture. At hospitals with PCI-capability "24-7," primary PCI has become the preferred reperfusion strategy for all STEMI patients, save for the rare exception where vascular access is not possible.

Initial trials that demonstrated the benefits of primary angioplasty achieved rapid reperfusion with DTB of 90 minutes or less. The Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO IIb) substudy demonstrated a direct relationship between time from randomization to angioplasty and 30-day mortality as follows: $\leq$ 60 minutes, 1.0% mortality; 61 to 75 minutes, 3.7% mortality; 76 to 90 minutes, 4.0% mortality; and $\geq$ 91 minutes, 6.4% mortality ($P = .001$).[12,13] Cannon and colleagues[14] analyzed a prospective observational registry of 27,080 patients (Second National Registry Myocardial Infarction [NRMI 2]) and showed that the multivariate adjusted odds of

mortality were 40% to 60% higher if DTB was longer than 2 hours.

In 2003, Keeley and colleagues[15] pooled and analyzed 23 randomized trials with 7739 patients randomized to primary PCI or fibrinolysis. The authors concluded that primary PCI is preferable to fibrinolysis and demonstrated lower rates of death (7% versus 9%; P = .0002), reinfarction (3% versus 7%; P = .0001), and stroke (1% versus 2%; P = .0004). Boersma and colleagues[16] have recently updated and confirmed the finding that primary PCI is the preferred reperfusion strategy when it is performed rapidly, by experienced operators and institutions, and at facilities with PCI capability and availability. Nonetheless, this pooled analysis assumed that times to treatment for both strategies, fibrinolysis versus primary PCI, were equivalent and did not take into account delays resulting from the transfer of patients to PCI-capable hospitals.[17] The issue of availability refers to having systems and processes to overcome hospital-dependent delays from medical contact to balloon inflation during the daytime and off-hours.[18]

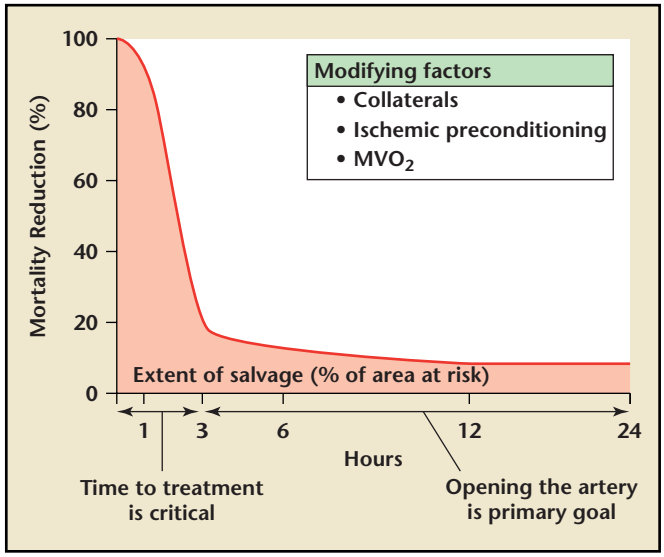

Figure 1. *Relationship between mortality reduction and myocardial salvage. MVO_2, mixed venous oxygen. Data from Gersh BJ et al[21] and Stone GW and Gersh BJ.[22]*

Guidelines and Recommendations

The guidelines recommend primary PCI for STEMI patients if DTB time is < 90 minutes or if the difference between DTB and door-to-needle time is < 60 minutes.[1,19] Are these DTB times achievable in current clinical practice? A report from the National Registry of Myocardial Infarction (NRMI 3/4) registry showed that for patients who require interhospital transfer for primary PCI, the median DTB was 180 minutes, and only 4.2% of patients achieved a DTB < 90 minutes.[20]

The relationship between mortality reduction and myocardial salvage as a function of time from symptom onset to reperfusion has been recently described (Figure 1).[21,22] In this modeling of mortality reduction and myocardial salvage, the choice of reperfusion for STEMI depends on 4 key variables:

- Duration of onset of symptoms.
- Anticipated delays for primary PCI.
- Patient-specific STEMI clinical risk and hemodynamic status.
- Patient-specific bleeding risk.

For patients who present with symptom duration of less than 2 to 3 hours, time-to-reperfusion is most critical, be it fibrinolysis or primary PCI. Moreover, every 30-minute delay from symptom onset to reperfusion is associated with an 8% increase in relative mortality at 1 year.[23] If DTB of < 90 minutes can be reliably achieved, then primary PCI would be the preferred approach. However, if the total delays incurred to diagnose STEMI, to activate the system, and to transport by ground or air ambulance to a PCI-capable facility exceed 60 minutes, then consideration should be given to fibrinolysis as the preferred approach. Patients treated with fibrinolysis should also be immediately transferred to a PCI-capable facility for rescue PCI if there is reperfusion failure.

For patients who present with symptom duration greater than 2 to 3 hours, then time-to-reperfusion is less important and opening the artery becomes the primary goal. Primary PCI is the best option and should be pursued as quickly as possible for all patients, except when transfer to a PCI-capable and available facility is not possible, inclement weather prohibits transport, or severe peripheral arterial disease precludes vascular access.

Future priorities for investigations should focus upon the acceptable limits of the total ischemic time prior to primary PCI before fibrinolysis should be recommended and what strategies can effectively shorten the time between symptom onset and balloon inflation. One potential strategy focuses upon "earlier diagnosis of STEMI," including:

- Pre-hospital electrocardiogram and ambulance triage directly to the catheterization laboratory, bypassing the emergency room.

- Earlier patient activation of the system through increased awareness of signs and symptoms of acute myocardial infarction.

A second and concomitant approach emphasizes "earlier treatment after diagnosis," including:

- Systems and networks to expedite transfer to a PCI-capable and available facility.
- Development of programs for primary PCI at hospitals with a catheterization laboratory but without on-site surgical backup.[24,25]

In 2006, after decades of carefully constructed randomized trials, we know what variables are important and what treatments (and timing) are beneficial for STEMI patients from an evidenced-based standpoint. The key to success is how we implement regional STEMI care systems and overcome current gaps and barriers for optimal STEMI patient care. Implementation should be flexible and take into account logistical issues that can vary significantly from each community, region, and country. These issues, such as the feasibility and training required for routine acquisition of pre-hospital electrocardiograms, the role for pre-hospital administration of fibrinolytics versus primary PCI within urban and rural areas, and the timing and role of universal coronary angiography after "apparently" successful fibrinolytic therapy, warrant further clinical trial observations.

The key to optimal reperfusion therapy is dependent not only upon the nature of the therapy but on the efficacy of its delivery. The logistical constraints entailed are highly variable—locally, regionally, and nationally. ■

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