

# Facilitated Percutaneous Coronary Intervention

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The goal of the initial treatment for ST-segment elevation myocardial infarction is rapid and effective reperfusion. Randomized trials have demonstrated that primary angioplasty is preferred over thrombolysis if done in a timely manner and by an experienced team. However, due to many factors, performance of primary angioplasty within the goal of 90 min is often not possible. A combined strategy of immediate thrombolysis in the emergency room or in the ambulance followed by angioplasty theoretically could provide early reperfusion with subsequent angioplasty to insure complete reperfusion. Over 17 clinical trials have been reported. Compared with thrombolysis, facilitated angioplasty in the most recent trials has been shown to have a more favorable long-term outcome. Trials comparing facilitated angioplasty with full- or half-dose thrombolysis versus primary angioplasty have been far less favorable with the largest trial to date, the ASSENT (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention)-4 trial, demonstrating a worse outcome in the primary end point of death, congestive heart failure, or shock at 90 days. Pending the results of the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial, current data suggest that facilitated angioplasty does not offer any advantage over primary angioplasty and may be harmful. (J Am Coll Cardiol 2006;48:1120–8) © 2006 by the American College of Cardiology Foundation

Despite dramatic improvements in the care for coronary artery disease in the last 25 years, an estimated 1.3 million or more Americans will have acute myocardial infarctions (AMIs) in 2006. The impact of such a high incidence is that 40% of those who experience an AMI in a given year will ultimately die from their coronary artery disease (1). A substantial proportion of these AMIs are due to ST-segment elevation AMI (STEMI) (2). A wealth of randomized controlled trials now guides physicians as to the medical and interventional management of STEMI, particularly in facilities where percutaneous coronary intervention (PCI) is available. However, there remains a chasm in care between those patients presenting with AMI to a PCI-capable hospital compared with those patients presenting to a facility without such resources.

The essential goal of care for AMI remains reperfusion with either a thrombolytic infusion or with rapid PCI. Randomized controlled trials involving thousands of patients as well as registry data have convincingly demonstrated that, when available, timely PCI confers a mortality benefit of 25% to 30% (3,4). However, when a patient presents early in the course of their symptoms, the rapid timing of PCI remains critical. With the conceptual framework that “time delay equals myocardium lost,” the goal has been to achieve reperfusion as quickly as possible because each 30-min delay in reperfusion results in a 7.5% increase in 1-year mortality (5,6). When weighing the choice of strategy, delays in door-to-balloon time for PCI greater than 1 h over when thrombolytic reperfusion would have occurred may negate the mortality benefit of PCI (7). The

strongest predictor of a delay is the need for transfer to a PCI-capable hospital (7,8).

Even though transfer is a potential delay, multiple studies have demonstrated safety with transporting AMI patients for PCI and, as a whole, the data demonstrate a reduction in death/re-infarction/stroke of 42% (9–15). In all of these studies, the transport time was <3 h, and often <90 min—a result that may not be realistically applied generally, where systematic factors may complicate such rapid transport. Thus, a combination strategy, referred to as “facilitated PCI,” may confer benefit by providing early, though potentially partial, flow with thrombolytics followed by transfer for PCI to complete and sustain the reperfusion (16–18). The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of STEMI designate facilitated PCI as a class IIb recommendation with level of evidence B, stating, “Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low (19).” Thus, there is still ambiguity in the guidelines about the utility of facilitated PCI.

While the AHA/ACC guidelines use a broad definition, this review will focus only on facilitated PCI that involves pharmacologic thrombolysis followed by transport for immediate or early mechanical reperfusion with percutaneous transluminal coronary angioplasty (PTCA) and/or stenting. Other strategies such as rescue PCI (intervention after failed thrombolysis with recurrent symptoms, sustained ST-segment elevations, or cardiogenic shock) or adjuvant pharmacologic therapy with glycoprotein IIb/IIIa inhibitors will not be addressed in this article (20–25).

Articles for review were identified by searching the PubMed database using the keywords “facilitated angioplasty” and “facilitated PCI.” Abstracts from the 2005 AHA meeting were searched. Further papers were found by

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#### Abbreviations and Acronyms

AHA/ACC	= American Heart Association/ American College of Cardiology
AMI	= acute myocardial infarction
ECSG	= European Cooperative Study Group
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty
STEMI	= ST-segment elevation acute myocardial infarction
TNK	= tenecteplase
t-PA	= tissue plasminogen activator

searching the bibliographies of the identified articles. The search resulted in 5 major groupings of studies: early trials, studies of thrombolytics alone versus of thrombolytics and PCI, and studies of PCI alone versus thrombolytics and PCI, meta-analyses, and latest trials.

#### EARLY TRIALS

With the initial trials of PTCA versus thrombolytics in AMI, there was the recognition that time was essential and that there could be potential synergistic benefits to combining the rapidity of thrombolysis and the improved reperfusion of PTCA. Thus, some of these early studies in the late 1980s and early 1990s examined the role of facilitated PCI in the pre-stent era.

The TAMI (Thrombolysis and Angioplasty in Myocardial Infarction) study randomized 197 AMI patients after receiving intravenous tissue plasminogen activator (t-PA) to either immediate PTCA or to deferred PTCA (26,27). With the exception of a higher rate of emergent PCI in the deferred PTCA group (16% vs. 5%;  $p = 0.01$ ), there were no differences in outcomes between the 2 groups. A second, smaller study, took patients who had been randomized to either t-PA or placebo to the catheterization laboratory and further randomized those in the t-PA group with >50% stenosis to either PTCA or no PTCA (28). The only difference between the groups was an improvement in infarct-zone regional wall motion in the combined t-PA and PTCA group. These 2 initial studies demonstrated again the increased vessel patency after t-PA, but showed only minimal or no benefit to subsequent emergent angioplasty after t-PA.

A substudy of the Thrombolysis In Myocardial Infarction (TIMI)-II study entitled TIMI-IIA examined the role of immediate compared with delayed PTCA after t-PA in 389 patients (29,30). This study confirmed the findings of the early studies showing no difference in the primary end point of ejection fraction at 1 year. However, in contrast to the previous studies, TIMI-IIA did show a significant increase in complications with the combination of t-PA and immediate PTCA, with higher rates of bleeding (20.0% vs. 7.2%;

$p < 0.001$ ) and coronary artery bypass surgery (16.4% vs. 7.7%;  $p = 0.01$ ).

The European Cooperative Study Group (ECSG) seconded the TIMI-IIA concerns about safety of t-PA with immediate angioplasty (31). The ECSG study was terminated early due to lack of demonstrated benefit and a non-significant trend toward increased mortality in the immediate invasive group (32). A subgroup analysis of the ECSG study suggested that re-occlusion and re-infarction were responsible for the lack of benefit of the early invasive strategy after t-PA and that perhaps procedural improvements in PTCA would lead to a benefit of immediate PTCA after thrombolysis (33). Similar results were also found in a study of streptokinase with and without immediate PTCA with no significant difference in outcome or mortality (34).

Among these early trials, the TAMI-5 trial provided the most substantial support for facilitated PCI with an improvement in wall motion as well as in composite clinical outcomes without increased complication rates (35). This study, however, was not powered to show mortality benefit and excluded many patients with poor prognoses who might have benefited from the aggressive strategy. A meta-analysis of the early trials showed no early mortality benefit to facilitated PCI; however, there was a cautious suggestion that perhaps early PTCA after thrombolytics improved mortality in the 6- to 52-week window (36). The authors comment that perhaps the early indifference in mortality was due to procedural complications, but that survivors of the initial period had better long-term outcomes with the earlier aggressive reperfusion strategy. The high bleeding rates seen in the facilitated group in these trials are noteworthy given the recognized adverse consequences of bleeding on mortality (37,38).

The early trials left many questions unanswered as to the benefit of facilitated PCI. While safety concerns lingered, there were hints in these studies that perhaps the combination reperfusion approach saved myocardium and, with technical improvements of intervention, facilitated PCI could perhaps be shown to be a beneficial strategy. Entering into the era of stents, improved antiplatelet agents, and greater operator experience, multiple study groups set forth to expand on the data provided by the TAMI, TIMI-IIA, ECSG, and TAMI-5 trials.

#### THROMBOLYTICS VERSUS FACILITATED PCI

In the late 1990s and early 2000s, with the debate still active over thrombolysis as opposed to direct PCI for AMI, trials were undertaken to examine thrombolysis compared with the combination approach of facilitated PCI (Table 1). Moreover, these trials served to give important guidance to hospitals without on-site PCI capability, where physicians would give thrombolytics and then debate whether or not to

**Table 1.** Thrombolytic Versus Facilitated PCI

Authors	Titles	Year	Study Type	No. of Patients Lytic Alone	No. of Patients Facilitated	Short-Term		p Value
						Lytic Alone	Death Facilitated	
Vermeer et al. (12)		1999	Prospective randomized	75	74	6.7%	8.1%	NS
Widimsky et al. (13)	PRAGUE	2000	Prospective randomized	99	100	14.0%	12.0%	NS
Herrmann et al. (39)	GUSTO-4 SPEED	2000	Retrospective	162	323	3.7%	3.4%	1.00
Schweiger et al. (40)	TIMI 10B-TIMI 14	2001	Retrospective	738	1,200	OR 0.51		0.09
Scheller et al. (43)	SIAM III	2003	Prospective randomized	81	82	9.9%	4.9%	0.179
Fernandez-Avilés (44)	GRACIA-1	2004	Prospective randomized	252	248	2.0%	2.0%	0.84
Watanabe (41)	FAST-3	2004	Registry	—	—	—	—	—
Le May et al. (45)	CAPITAL AMI	2005	Prospective randomized	84	86	3.6%	2.3%	0.68

CAPITAL AMI = Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction study; FAST = Femoral Artery Stenting trial; GRACIA 1 = Routine Invasive Strategy within 24 Hours of Thrombolysis Versus Ischemia-Guided Conservative Approach for Acute Myocardial Infarction with ST-Segment Elevation trial; GUSTO-4 SPEED = Facilitation of Early Percutaneous Coronary Intervention After Reteplase with or without Abciximab in Acute Myocardial Infarction trial; OR = odds ratio; PCI = percutaneous coronary intervention; PRAGUE = Primary Angioplasty in Patients Transferred from General Community Hospitals to specialized PTCA Units with or without Emergency Thrombolysis trial; SIAM = Southwest German Interventional Study in Acute Myocardial Infarction; TIMI 10B-TIMI 14 = Thrombolysis in Myocardial Infarction 10B and 14 trials.

transport their patients to a tertiary care center for immediate PCI.

Expanding on the concept that facilitated PCI can detect and treat those patients whose arteries have failed to fully re-canalize with thrombolytics, a subgroup analysis of 323 patients in the GUSTO-4 SPEED (Facilitation of Early Percutaneous Coronary Intervention After Reteplase With or Without Abciximab in Acute Myocardial Infarction: Results From the SPEED [GUSTO-4 Pilot]) trial who underwent PCI after receiving abciximab with either t-PA or placebo compared with 162 patients who did not receive early PCI (39). While the SPEED trial incorporated multiple thrombolytic dosing regimens and had the limitation that the decision to perform PCI was left to the discretion of the treating physician, it did show a statistically significant decrease in major clinical outcomes from 29.6% to 14.6% with PCI compared with no PCI. There was no difference in bleeding rates. The authors suggested that the improvement stemmed from the use of abciximab, stents, appropriate heparinization, and improved operator experience; however, they cautioned that larger, dedicated studies were needed. Those studies would take several years and are yet to be published.

Another retrospective analysis, this one of the TIMI-10B and TIMI-14 trials, compared those patients who received interventions with those who did not after thrombolysis (40). Patients who received adjunctive PCI, on vessels with TIMI flow grade 2 or 3, had lower rates of death or recurrent AMI than those patients who received no intervention and had TIMI flow grade 2 or 3. A non-randomized prospective study from Japan examined immediate adjuvant PCI after either alteplase or pamiteplase in patients with either TIMI flow grade 0, 1, or 2 (41). The study showed no differences when patients were segregated by age range.

The first new randomized prospective study of thrombolytics versus facilitated PCI in the stent era came from the

Netherlands as part of a transport for AMI study (12). Patients were randomized to 1 of 3 groups: alteplase, alteplase with transport for PCI, or direct transfer for PCI with no thrombolysis. Because this study was designed for safety and feasibility, it did not show any significant differences between the groups, though it did confirm previous studies demonstrating that there was improved coronary flow in those patients who had received PCI.

A similar trial was performed in the Czech Republic with the PRAGUE (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis) study examining transport and a similar randomization approach to the Netherlands study (13,42). While also designed for safety and feasibility, the PRAGUE study randomized 300 patients and was able to demonstrate a significant decrease in the primary end point of death/re-infarction/stroke with facilitated PCI compared with thrombolysis alone from 23% to 15% ( $p < 0.02$ ). However, the study also showed that transport for PCI alone, without thrombolysis, led to an even lower combined end point of only 8% ( $p < 0.02$ ). Moreover, in the facilitated PCI group, there were significantly more fatal bleeding complications compared with either the thrombolysis or PCI alone groups (7.2% vs. 0% vs. 0%;  $p < 0.001$ ).

The SIAM-III (Southwest German Interventional Study in Acute Myocardial Infarction) randomized 110 patients who had received reteplase to either immediate PCI with stenting or to the same intervention 2 weeks later (43). Using a combined primary end point of death, re-infarction, ischemic events, or target lesion revascularization, this study showed a significant improvement from the thrombolysis group of 50.6% to 25.6% in the facilitated PCI group. There were no differences in bleeding risks. A major difference between the SIAM-III trial and the PRAGUE study was time; in the PRAGUE study the median time from admission to balloon opening was 108 min, while in the SIAM-

**Table 1.** Continued

Short-Term			Short-Term			Short-Term		
Lytic Alone	Reinfarction Facilitated	p Value	Lytic Alone	Revascularization Facilitated	p Value	Lytic Alone	Bleeding Facilitated	p Value
9.3%	5.4%	NS	30.7%	23.0%	NS	11.0%	21.0%	Not reported
10.0%	7.0%	NS	14.1%	7.0%	NS	0.0%	7.2%	<0.001
4.9%	1.2%	0.03	9.3%	1.6%	0.001	8.6%	6.5%	0.46
	OR 0.45	0.06	—	—	—	—	—	—
2.5%	2.4%	0.685	2.5%	2.4%	0.685	7.4%	9.8%	0.400
2.0%	1.0%	0.98	12.0%	2.0%	<0.0001	1.6%	1.6%	NS
—	—	—	—	—	—	—	—	—
13.3%	4.7%	0.06	50.6%	13.9%	<0.001	13.1%	23.3%	0.11

III trial the goal was less than 6 h, with an average time from thrombolysis to angiography of 3.5 h.

Recognizing that some of the early trials lacked applicability in current practice, 2 more recent studies looked at thrombolysis versus modern PCI with the expanded arsenal of stents and glycoprotein IIb/IIIa inhibitors. The GRACIA-1 trial (Randomized Trial Comparing Stenting Within 24 h of Thrombolysis Versus Ischemia-Guided Approach to Thrombolysed AMI With ST-Segment Elevation) randomized 500 patients who had received t-PA for AMI to either PCI within 24 h or to a conservative ischemia-guided approach (44). The study showed a 1-year improvement in death/re-infarction/revascularization from 21% to 9% in the facilitated PCI group. The CAPITAL AMI (Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction) study took the approach of the GRACIA-1 trial another step further by using the more effective new thrombolytic tenecteplase (TNK) with modern PCI (45). The study enrolled 170 patients and primarily showed a reduction at 6 months in recurrent unstable ischemia from 20.7% in the TNK group to 8.1% in the facilitated PCI group ( $p = 0.03$ ).

Importantly, both the GRACIA-1 and CAPITAL AMI trials showed no difference in major bleeding complications. These larger, more recent trials have helped to understand thrombolytics versus facilitated PCI. However, the developing picture that primary PCI, when available, was the standard of care set the stage to ask the question of whether there was benefit when comparing primary PCI to facilitated PCI.

### PCI VERSUS FACILITATED PCI

Some of the trials comparing primary coronary intervention to facilitated PCI trials overlapped with some of the thrombolytics versus facilitated PCI trials by consisting of 3 arms: thrombolytics alone, PCI alone, and facilitated PCI. Due to compelling concerns about the increased bleeding complications seen with facilitated PCI, some of the more recent trials tried to attenuate that risk by varying the

dosage of thrombolytics. Thus, some studies examined full-dose thrombolytics (Table 2) and some examined reduced-dose thrombolytics (Table 3) in conjunction with PCI compared with PCI alone.

**Full-dose thrombolytics.** Two of the first trials were the previously mentioned studies from the Netherlands and the Czech Republic (12,13). While both of these studies focused on safety and feasibility of transport in AMI, they did provide insights that there was not a dramatic benefit to facilitated PCI and, in the PRAGUE study, that direct PCI without thrombolytics had better outcomes as well as fewer complications. Because the initial PRAGUE study found facilitated PCI to be inferior to transport for immediate PCI alone, the Czech study group did not include facilitated PCI in their follow-up PRAGUE-2 trial (14).

Except for these 2 transport trials, there exists only a limited amount of recent data regarding facilitated PCI with full-dose thrombolytics. A small study from Japan randomized 39 patients to either alteplase or placebo before PCI (46). As seen in previous studies, the thrombolytic group had greater TIMI flow grade and lower percentage stenosis; however, perhaps limited by its size, the study did not demonstrate any change in follow-up angiography, target lesion revascularization, or in clinical outcomes.

A retrospective study by Möckel et al. (47) looked at their patients receiving either tirofiban or a variety of fibrinolytics before PCI and found both increased rates of both major bleeding and major adverse events with the group of PCI facilitated by thrombolytics. Two recent abstracts showed a randomized trial that demonstrated improved ST-segment recovery with facilitated PCI compared with either thrombolytics alone or PCI alone and a retrospective study that showed no benefit nor harm with facilitated PCI (48,49). In general, the more recent research has focused on reduced-dose thrombolytics; however, the largest and latest trial of facilitated PCI with full-dose thrombolytics, ASSENT (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention)-4, will be discussed in the following text (50).

**Table 2.** Primary PCI Versus Full-Dose Facilitated PCI

Authors	Titles	Year	Study Type	No. of Patients Lytic Alone	No. of Patients Facilitated	Short-Term		p Value
						Lytic Alone	Death Facilitated	
Vermeer et al. (12)		1999	Prospective randomized	75	74	6.7%	8.1%	NS
Widimsky et al. (14)	PRAGUE	2000	Prospective randomized	101	100	7.0%	12.0%	NS
Kurihara et al. (46)		2004	Prospective randomized	20	19	0.0%	0.0%	NS
Möckel et al. (47)		2005	Retrospective	44	35	4.5%	20.9%	0.028
ASSENT Investigators (50)	ASSENT-4	2006	Prospective randomized	838	829	5.0%	7.0%	0.1412

ASSENT = Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention. Other abbreviations as in Table 1.

**Reduced-dose thrombolytics.** Support for reduced-dose thrombolytics was bolstered with the 1999 publication of the PACT (Plasminogen Activator-Angioplasty Compatibility) trial, testing the hypothesis that a lower-dose of a short-acting thrombolytic would attenuate some of the adverse effects seen in prior trials while maintaining the benefits of early reperfusion (51). The PACT trial randomized 606 patients to either a 50-mg bolus of recombinant t-PA or to placebo followed by urgent PCI. Consistent with prior studies, there was better initial coronary flow in those patients who received thrombolytics; however, TIMI flow grade 3 was equal in the 2 groups after PCI. While overall measures of left ventricular performance were equal between the 2 groups, a subgroup analysis showed improved left ventricular function in those who had TIMI flow grade 3 on initial images compared with those who had TIMI flow grade 3 only after intervention. The authors concluded that their regimen of a short-acting, fibrin-selective thrombolytic in reduced dose created earlier revascularization and subsequent improved left ventricular performance.

In the interim, while waiting for larger randomized trials, several smaller studies were released. Following up on the first trial, the GRACIA-2 trial compared facilitated PCI in the 3- to 12-h window to primary PCI in less than 3 h (52,53). Aside from improved perfusion, no significant outcome differences were observed between the 2 groups although none of the studies were sized to look at mortality. However, with an average time to catheterization of 5.89 h in the facilitated arm compared with 1.08 h in the primary PCI group, the authors viewed the absence of differences between groups as evidence that facilitated PCI was a safe and equally effective alternative to primary PCI when external factors such as geographic distance prohibited early intervention.

A small registry of 200 patients added more support to this concept by showing promising outcomes in patients transported with a combination of abciximab, reduced doses of alteplase, and PCI (54). The same group from Poland recently reported on a larger registry comparing transferred facilitated PCI to primary PCI patients and showed similar clinical outcomes, though higher rates of moderate and severe bleeding (5.5% vs. 2.3%) and hemorrhagic stroke

(0.6% vs. 0.0%), in the facilitated PCI group (55). Another transport registry, this time from Minnesota, showed equivalent 30-day outcomes of death, stroke, and re-infarction between direct and facilitated PCI, with remarkably short door-to-balloon times of 117 min for patients 60 to 200 miles from the interventional center, though bleeding complication data have not been published yet (56).

While these preceding 3 studies have looked at transporting for PCI, another potential advantage with facilitated PCI is that, even in an interventional center, using a thrombolytic to create early reperfusion may convert the emergent need for PCI into an urgent need, thereby allowing the PCI to occur during daytime hours. Night-time presentation for PCI has been associated with worse outcomes (57). A registry giving facilitated PCI to those arriving in off hours and direct PCI to those arriving during on hours showed with facilitated PCI an improvement in corrected post-intervention TIMI frame count, a trend toward increased bleeding, and no difference in primary clinical outcomes (58). In that study, even the off-hours facilitated PCI group had a low door-to-balloon time of 72 min. An investigation of a longer delay compared abciximab, half-dose recombinant t-PA, and PCI in either <2 h, or PCI in the window from 12 to 72 h showed no difference between groups (59). These studies suggest that even in centers capable of performing PCI, facilitating PCI through the use of reduced-dose thrombolytics, may have a role in allowing more time to perform the intervention, especially in off hours, without any worsening of outcomes.

Though many of these studies have shown essential equivalency of facilitated PCI to direct PCI, 2 more recent studies question not only the efficacy of facilitated PCI, but also its safety. The ADVANCE MI (ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction) trial sought to enroll 5,640 patients in 30 centers; however, it was terminated early due to slow recruitment (60). Even with its limited enrollment of 148 patients, the primary end point at 30 days of death or new/worsening heart failure was increased in the intention-to-treat facilitated PCI arm as was the rate of bleeding complications. Due to the limited

**Table 2.** Continued

Short-Term			Short-Term			Short-Term		
Lytic Alone	Reinfarction Facilitated	p Value	Lytic Alone	Revascularization Facilitated	p Value	Lytic Alone	Bleeding Facilitated	p Value
1.3%	5.4%	NS	6.0%	23.0%	NS	11.0%	21.0%	Not reported
1.0%	7.0%	<0.03	6.9%	7.0%	NS	0.0%	7.2%	<0.001
5.0%	5.8%	NS	31.6%	17.6%	NS	0.0%	0.0%	NS
0.0%	2.9%	NS	2.3%	0.0%	NS	2.3%	11.4%	NS
4.0%	6.0%	0.0279	3.0%	7.0%	0.0041	4.4%	5.6%	0.3118

number of patients in the trial, results must be interpreted with caution. However, lack of benefit with facilitated PCI was also seen by examining infarct size in the 253-patient BRAVE (Bavarian Reperfusion Alternatives Evaluation) study, which randomized patients with abciximab and PCI to either half-dose reteplase or no thrombolytic (61).

With the wide range of results, no clear conclusions can yet be drawn from the studies with reduced-dose thrombolytics.

### LATEST TRIALS

Two recent trials have sought to definitively answer the question raised by nearly 2 decades of previous studies: is PCI facilitated by thrombolysis safe and effective? The ASSENT-4 PCI trial randomized patients to PCI with or without full-dose TNK with a primary end point of 90-day death, cardiogenic shock, or congestive heart failure (50). After randomizing 1,667 patients, the trial was terminated early in April 2005 by the Data Safety Monitoring Board due to worse outcomes observed in the facilitated PCI arm. The TNK plus PCI patients had significantly higher rates of repeated myocardial infarction (6% vs. 4%;  $p = 0.0279$ ), repeat target vessel revascularization (7% vs. 3%;  $p = 0.0041$ ), stroke (1.8% vs. 0%;  $p < 0.0001$ ), and, in the primary trial, end point of death, congestive heart failure, or shock (18% vs. 13%; relative risk 1.3, 95% confidence interval 1.11 to 1.74;  $p = 0.0045$ ).

Limitations of the study were that it was stopped before the pre-specified number of patients was enrolled and that the randomization-to-balloon times were similar in both groups at less than 120 min. Potentially, the rapid timing from TNK-to-balloon of 104 min played a role in the worse outcomes, whereas benefit might be seen if there were to be a longer delay between thrombolytic and PCI. Regardless of these limitations, the ASSENT-4 trial raises serious concerns about continued use of facilitated PCI.

Following up on the ASSENT-4 trial, the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial is randomizing patients going for immediate PCI to 1 of 3 groups: abciximab plus reduced-dose reteplase, abciximab alone, or placebo (62). This study has the additional advantage of investigating a lower-dose thrombolytic. While results from the FINESSE trial should be forthcoming, enrollment has not yet completed. The

medical community will have to wait to see whether this large, randomized trial confirms the results of the ASSENT-4 trial, or if it demonstrates benefit in the setting of a reduced-dose thrombolytic.

### META-ANALYSES

Combining the data from all of the preceding trials presents a daunting task. Aside from the differences in control groups and dosing of thrombolytics, the facilitated PCI trials differed in type of thrombolytic, the use of glycoprotein IIb/IIIa inhibitors, the use of stents and other more advanced PCI technologies, the timing of the intervention, the indications for PCI, and in the outcome measures analyzed. Despite these limitations, 3 meta-analyses attempted to collate this plethora of data.

One analysis found equivocal data to support PCI after thrombolysis, with the later, stent-era trials favoring intervention after thrombolytics (63). This analysis does point out that the largest randomized trials showed no benefit to early PCI after thrombolysis. A recently presented meta-analysis of 5 trials focused on just comparing facilitated PCI with primary PCI, and found results consistent with many of the individual trials: an improvement in TIMI flow grade 3 upon arrival to the catheterization lab after thrombolytics, though no difference in 30-day mortality, and a trend toward increased major hemorrhage with the facilitated approach (64).

Finally, a meta-analysis, incorporating the recent ASSENT-4 trial data, found even worse outcomes with facilitated PCI (65). While this article analyzed a broader definition, including studies of PCI assisted with glycoprotein IIb/IIIa, their analysis of 6 trials of thrombolytic-facilitated PCI did show improved initial TIMI flow grade 3 in the combination group, though similar TIMI flow grade 3 after PCI was performed. However, when assessing clinical outcomes, facilitated PCI was associated with increased rates of short-term death (5% vs. 3%;  $p = 0.04$ ), non-fatal MI (3% vs. 2%;  $p = 0.006$ ), and target vessel revascularization (4% vs. 1%;  $p = 0.010$ ). Among this subgroup of the meta-analysis, there was a non-significant trend toward an increase in major bleeding with facilitated PCI.

**Table 3.** Primary PCI Versus Reduced-Dose Facilitated PCI

Authors	Titles	Year	Study Type	No. of Patients Lytic Alone	No. of Patients Facilitated	Short-Term		p Value
						Lytic Alone	Death Facilitated	
Ross et al. (51)	PACT	1999	Prospective Randomized	304	302	3.3%	3.6%	0.81
Dudek et al. (54)		2003	Registry	—	200	—	3.5%	—
Kastrati et al. (61)	BRAVE	2004	Prospective Randomized	128	125	1.6%	1.6%	NS
Maioli et al. (58)		2005	Retrospective	99	113	6.1%	6.3%	0.195
ADVANCE MI Investigators (60)	ADVANCE MI	2005	Prospective Randomized	74	74	0.0%	6.8%	0.03

ADVANCE MI = Addressing the Value of Facilitated Angioplasty after Combination Therapy or Eptifibatid Monotherapy in Acute Myocardial Infarction trial; BRAVE = Bavarian Reperfusion Alternatives Evaluation trial; PACT = Randomized Trial Comparing Primary Angioplasty with a Strategy of Short-Acting Thrombolysis and Immediate Planned Rescue Angioplasty in Acute Myocardial Infarction; PCI = percutaneous coronary intervention.

## DISCUSSION

The reasoning behind facilitated PCI is sound, and finding a mechanism to achieve the earliest reperfusion is a reasonable goal. It seems only logical that achieving temporizing reperfusion with thrombolytics followed by definitive reperfusion with PCI would save the most myocardium. The first main reason pushing forward the use of facilitated PCI is the limited access that some areas of the country have to PCI-capable centers. The delay in transport to a hospital with interventional capability could mean myocardium lost and increased infarct size, an outcome hopefully improved with early thrombolytic reperfusion. The second main driving force pushing forward facilitated PCI is that, even in centers with 24-h interventional catheterization laboratories, there remain delays in door-to-balloon times, particularly for off hours. National Registry of Myocardial Infarction data from 2002 suggest that only 37% of patients are achieving a door-to-balloon time of <90 min (66). An infusion of a thrombolytic in the emergency department could create enough reperfusion so as to turn back the ticking clock of myocardium being lost, and allow more time for either the interventional team to arrive at the hospital, or potentially, for the patient to await intervention during the daytime (18).

The data for facilitated PCI have been mixed at best, and the more recent trials suggest worse outcomes with facilitated PCI. The main drawback, noted in the earliest trials, was the increased rates of bleeding with the facilitated PCI approach. Having thrombolytic agents in the vascular system followed by an arterial puncture and further anticoagulation has led to both minor and major bleeding complications. After the early trials, some of these bleeding complications were decreased, thought to be secondary to smaller sheaths, improved anticoagulation regimens, and the experimentation with reduced-dose thrombolytics. However, the more recent trials, ADVANCE MI and ASSENT-4, have again demonstrated higher bleeding risks, suggesting that this complication has not gone away. The association between bleeding, anemia, and transfusion, and a poor short- and long-term outcome is strong and mounting. It seems likely that the excess bleeding seen with

the combined approach may have contributed to the lack of benefit with facilitated PCI.

The initial trials showing efficacy when comparing facilitated PCI to thrombolytics were mostly retrospective studies. Later randomized studies, such as the SIAM III, GRACIA-1, and CAPITAL AMI trials, did show benefit, but potentially the benefit came from the patients receiving PCI rather than from the combined approach. In fact, the PRAGUE study did show that, with transport for STEMI, lone PCI demonstrated better outcomes than either lone thrombolytics or facilitated PCI. Perhaps these trials of combination therapy versus thrombolytics simply re-demonstrated that PCI, even with the addition of thrombolytics and the time delay with transport for PCI, provided better results than thrombolytics alone.

When evaluating the subsequent trials of facilitated PCI versus primary PCI, the largest trials showed some surrogate improvements, though no benefit to clinical outcomes. Many of these trials attempted to show equivalence between facilitated PCI and primary PCI to demonstrate that, even with transport time or delay for on-hours interventions, there would be equivalent results. While some of the studies did show equivalence, the most recent and definitive study, ASSENT-4, reached adverse outcomes in its primary as well as secondary end points before the study had even enrolled 50% of the planned patients. The meta-analyses collated the various smaller trials and showed similar results to the ASSENT-4 trial: earlier TIMI flow grade 3 in those patients that receive facilitated PCI, though worse clinical outcomes and trends toward increased bleeding.

Though the results of the FINESSE trial are not yet available, unless they provide convincingly contradictory results to the ASSENT-4 trial, the issue of thrombolytic-facilitated PCI should be laid to rest as a theoretically interesting strategy that, in reality, was shown through multiple studies to be detrimental to the care of AMI.

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**Table 3.** Continued

Short-Term			Short-Term			Short-Term		
Lytic Alone	Reinfarction Facilitated	p Value	Lytic Alone	Revascularization Facilitated	p Value	Lytic Alone	Bleeding Facilitated	p Value
2.6%	3.0%	0.80	7.2%	7.3%	0.98	13.5%	12.9%	0.84
—	1.0%	—	—	1.5%	—	—	3.0%	—
0.0%	0.8%	NS	—	—	—	1.6%	5.6%	0.16
—	—	—	1.0%	0.0%	0.560	3.0%	6.2%	0.226
2.7%	1.4%	0.33	—	—	—	10.8%	23.0%	0.05

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