Synergistic Treatment of ST-Segment Elevation Myocardial Infarction With Pharmacoinvasive Recanalization

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Both pharmacologic and mechanical approaches designed to limit infarct size by recanalization of infarct-related arteries have reduced mortality associated with ST-segment elevation myocardial infarction (STEMI). Early efforts to combine the two were attenuated because of complications encountered. Primary percutaneous coronary intervention (PCI) and thrombolysis became viewed as alternative rather than complementary modalities. Time to recanalization and adequacy of restoration of perfusion were found to be pivotal determinants of a favorable outcome with either approach. Because pharmacologic intervention can be initiated immediately in virtually any hospital, it is a promising initial step. Because PCI proffers more complete recanalization, it may be a particularly salutary initial or subsequent step. Because of unavoidable delay often confronting implementation of PCI, optimal advantage may accrue from the use of both approaches in combination. We seek to emphasize the potential synergy by referring to the combined approach as “pharmacoinvasive recanalization” rather than by the conventional term “facilitated PCI.” Virtually all patients with STEMI can benefit from prompt, sustained, and complete coronary recanalization. Thus, investigations focusing on identification of pharmacologic regimens that can safely initiate recanalization as early as possible, minimize bleeding, and broaden the temporal window available for efficacy of subsequent, optimally timed PCI should provide particularly valuable information. (J Am Coll Cardiol 2003;42:646–51) © 2003 by the American College of Cardiology Foundation

Coronary thrombolysis and primary-infarct percutaneous coronary intervention (PCI) for treatment of ST-segment elevation myocardial infarction (STEMI) are generally viewed as alternatives. However, consideration of established principles and much recent information support the view that the two in combination offer potential synergies. We shall refer to the combination, frequently called “facilitated PCI,” as “pharmacoinvasive recanalization” to emphasize the potential synergy and because it is not literally the case that initial thrombolysis actually facilitates PCI.

Elucidation of the importance of time to recanalization in early studies of coronary thrombolysis. Dr. Eugene Braunwald formulated a then-revolutionary hypothesis. He postulated that acute myocardial infarction (AMI) is a dynamic process and that its clinical outcome is determined largely by infarct size. The first laboratory study testing this hypothesis concluded: “Of greatest interest, from the clinical point of view, is the finding that the severity and extent of myocardial ischemic injury resulting from coronary occlusion could be radically altered not only by pretreatment but also by an appropriate intervention as late as 3 h after the coronary occlusion” (1). Two concepts emerged from subsequent clinical studies and trials: 1) restoration of coronary patency improves survival; and 2) recanalization must be induced within a narrow temporal window to be maximally beneficial (2–7).

The Fibrinolytic Therapy Trialists’ Collaborative Group articulated results from clinical trials as follows: 35 lives could be saved per thousand patients with STEMI when treatment was initiated within the first hour after onset of symptoms. By contrast, fewer, 16 per thousand, lives could be saved when treatment had to be delayed for as long as 7 to 12 h (8). American College of Cardiology/American Heart Association (ACC/AHA) AMI guidelines state that “The earlier therapy begins, the better the outcome, with the greatest benefit...when (thrombolytic) therapy is given in the first 3 hours” (9).

Thrombolysis has reduced mortality associated with STEMI. Adjusted hospital mortality decreased by nearly 50% between 1986 and 1997 as shown in the longitudinal Worcester Heart Attack study. During this period the use of thrombolytic agents doubled, even though primary angioplasty was used only minimally in most communities. Although improvement was seen for both young and older patients in the registry study (10), the use of thrombolysis for treatment of elderly patients remained controversial (11–14). A population-based cohort study of Medicare beneficiaries presenting with STEMI during the 1990s indicated that both thrombolysis and primary angioplasty were associated with one-year survival benefits. However, thrombolysis did not confer a clear survival benefit at 30 days (odds ratio, 1.01; 95% confidence interval, 0.94 to 1.09) (13). Ten lives were saved per thousand elderly patients with STEMI according to the Fibrinolytic Therapy Trialists Collaborative Group (8). However, the interpretation remains controversial given the insignificant p value.
**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<td>GUSTO</td>
<td>Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes</td>
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<td>PACT</td>
<td>Plasminogen-Activator Angioplasty Compatibility Trial</td>
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<tr>
<td>PAMI</td>
<td>Primary Angioplasty in Myocardial Infarction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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<tr>
<td>t-PA</td>
<td>tissue-type plasminogen activator</td>
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The importance of complete restoration of myocardial perfusion in studies of coronary thrombolysis and primary PCI. Despite its value, thrombolysis is clearly imperfect. Certain subsets of patients with STEMI (e.g., those with cardiogenic shock) benefit unequivocally only from acute infarct PCI with stenting (15). Thrombolysis fails to induce complete recanalization and reperfusion (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow) in 30% to 40% of patients even with conjunctive antithrombotic and antiplatelet regimens (16,17). In both the Thrombolytic Trial of Eminase in Acute Myocardial Infarction (TEAM)-3 and the European Cooperative Study Group trials, outcome in patients with TIMI 2 flow after thrombolysis was suboptimal and more similar to outcome in patients with persistently occluded culprit arteries than outcome in those with completely recanalized vessels (18,19).

Because of concerns regarding the safety and efficacy of thrombolysis, PCI evolved as an attractive alternative. Its value was supported by results in a small but highly influential 56-patient randomized trial comparing primary angioplasty with intracoronary administration of streptokinase in 1986 (20). Primary angioplasty was superior with respect to recovery of left ventricular function. The Primary Angioplasty in Myocardial Infarction (PAMI) trial, a 395 patient randomized trial, compared primary angioplasty with tissue-type plasminogen activator (t-PA). Early mortality was more favorable with primary angioplasty (2.6% compared with 6.5%, p = 0.06). In 90% of patients undergoing PCI, TIMI grade 3 flow was demonstrable (21).

Unfortunately, however, <25% of hospitals in the U.S. and <10% in Europe have facilities for PCI. This has limited widespread adoption of primary angioplasty (9,22). The community-based Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO) IIb substudy randomized 1,138 patients with STEMI to t-PA or primary angioplasty. The incidence of the primary end point (death, nonfatal reinfarction, or stroke at 30 days) was significantly lower with primary angioplasty (9.6% compared with 13.7%, p = 0.03) (23). Somewhat surprisingly, however, the reduction in mortality was modest (5.7% compared with 7.0%, p = 0.37) compared with the apparently striking reduction seen in the PAMI trial. Neither the GUSTO IIb trial nor the National Registry of Myocardial Infarction-2 data demonstrated statistically improved survival in patients with STEMI treated with primary angioplasty compared with fibrinolytic agents. This observation discouraged widespread adoption of primary angioplasty (24). The apparently greater mortality benefit in PAMI may reflect, in part, inclusion of lower risk patients (25) and the impact of the skill of operators performing a high volume of procedures in the PAMI trial (26).

Longer times to treatment increase mortality after STEMI. In GUSTO IIb, patients with arteries that were opened <60 min after randomization had a 30-day mortality of only 1%. By contrast, mortality was 6.4% when the delay was >90 min (27). Similarly, in National Registry of Myocardial Infarction (NRMI)-2 mortality was 1.6 times higher with primary angioplasty accomplished within 151 to 180 min after admission than that accomplished within <60 min (28). The 1999 update to the ACC/AHA guidelines states: “Interventional cardiologists and centers must operate within a specified corridor of outcomes to include balloon dilation within 90 min (±30) of admission and diagnosis of AMI” (9).

It is instructive to consider the results in two trials comparing primary angioplasty with thrombolysis in the context of time to open artery—Danish Multicenter Randomized Study of Acute Myocardial Infarction (DANAMI)-2 and the Zwolle trial in the elderly (14,29). Both sought to resolve the vexing issues of the frequent delay inherent in the need for transfer of patients to centers that can perform PCI and the relatively reduced benefit of thrombolysis in elderly patients. The DANAMI-2 trial showed a reduction in reinfarction even in patients requiring transfer for primary angioplasty. The Zwolle trial demonstrated reduced one-year mortality in very high risk, elderly patients undergoing primary angioplasty compared with thrombolysis. Should we, therefore, conclude that a “transfer to a trauma center” strategy for PCI is needed, such that all patients with STEMI undergo initial treatment in centers performing PCI (12)? Not necessarily.

Rapidity of time to opening, completeness of restoration of flow, and the promise of pharmacoinvasive recanalization. A combined pharmacoinvasive approach capitalizing on the rapidity of initiation and widespread feasibility of pharmacologic thrombolysis to promptly restore at least some myocardial blood flow, coupled with the more complete restoration achievable with subsequent PCI, merits consideration as an optimal approach. Though this approach is frequently called “facilitated PCI,” we refer to it here as “pharmacoinvasive recanalization” (Fig. 1).

Unfortunately, the benefit of primary PCI is limited—frequently by unavoidable delay. The median door-to-
balloon times in DANAMI-2 for both on-site (90 min) and transported patients (~110 min) (29–31) do not mesh closely with overall clinical experience in the U.S. The NRMI data show a mean time of 111 min for the entire patient group and 198 min for those requiring transfer (30,32). In the Zwolle trial, the mean time was remarkably close with overall clinical experience in the U.S. The NRMI data show a mean time of 111 min for the entire patient group and 198 min for those requiring transfer (30,32). In the Zwolle trial, the mean time was remarkably low, 59 ± 19 min (14). By contrast, the U.S. Medicare experience shows an interval more than twice as long (143 min) (13). Primary PCI can restore flow virtually completely in >90% of patients. Thus, it is clearly superior to coronary thrombolysis with respect to this pivotal variable when it can be performed in a 90 ± 30 min time window (31,32). However, in general, this constraint cannot be met in community practice settings. Single centers have reduced door-to-balloon times for primary PCI (33). System-wide approaches (requiring major efforts on the part of personnel in communities, emergency rooms, transport systems, and primary angioplasty centers) might make timely primary angioplasty more universally available (12). Yet, nationally, it has been possible to reduce door-to-balloon times by only 8 min during the past decade (30,34).

In part because of recognized though different limitations of each approach, many trials have compared PCI with thrombolysis (32). They were designed to settle the debate of “either-or” that had been forged by the historically based presumption that “routine, immediate angioplasty does not provide an improved outcome after thrombolytic administration...” (31). This antipodal view of early PCI and thrombolysis evolved because of a historical lack of clear-cut superiority of either and a high incidence of adverse events encountered with the two combined in early trials (35–38). Recent results require reconsideration of the historically based assumptions (39–42). They indicate that adverse event rates can be diminished with the use of clot-selective fibrinolytic agents, improved antiplatelet agents, and advances in PCI, including the use of stents (Table 1).

### Recognition of potential synergies

The Plasminogen-Activator Angioplasty Compatibility trial (PACT) trial randomized patients with STEMI to initial treatment with “half dose” t-PA (50 mg) compared with placebo. All were transferred to the catheterization laboratory for assessment for immediate PCI as well. The initial thrombolysis doubled the incidence of the presence of TIMI grade 3 flow at the time of initial angiographic assessment (from 15% to 33%). The combined recanalization strategy was not compromised by early reocclusion or bleeding (40). Induction of a higher incidence of TIMI grade 3 flow before PCI is relevant to clinical outcome. Thus, mortality was fivefold greater with primary angioplasty when therapy before PCI had not induced TIMI grade 3 flow at the time of initial angiography in the PAMI trials (43). Favorable findings regarding regular use of PCI after thrombolysis in PACT and, subsequently, in the Strategies for Patency Enhancement in the Emergency Department (SPEED) and TIMI 10B/14B substudies (39–42) (Table 1) are not reflected in current ACC/AHA guidelines for management of STEMI. It is unfortunate, in our view, that the guidelines presently classify routine use of angiography and PCI within 24 h of thrombolysis for treatment of STEMI as a class III contraindication (9). We believe that results in future trials, coupled with information already available, are likely to require modification of this guidance.

#### Elucidation of the efficacy of pharmacoinvasive recanalization

Future trials of treatment of STEMI may be of particular value if they focus on both the crucial importance of combined rapidity of recanalization and the completeness of restoration of myocardial blood flow. When PCI is performed early after administration of thrombolytic drugs, it is generally called “facilitated PCI.” Yet, PCI is not simplified by antecedent therapy with thrombolytic agents. It may be rendered more difficult. We believe that the focus of research should deviate from the decade-long “either-or” debate to elucidation of the best strategy of pharmacoinvasive recanalization by addressing the following five questions:

### Table 1. Selected Studies Supporting the Concept of PharmacoInvasive Recanalization

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>PACT</th>
<th>SPEED</th>
<th>TIMI 10B/14B</th>
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<tbody>
<tr>
<td>Publication date</td>
<td>1999</td>
<td>2000</td>
<td>2001</td>
</tr>
<tr>
<td>Total trial (n)</td>
<td>606</td>
<td>528</td>
<td>1,938</td>
</tr>
<tr>
<td>Early PCI after lytic (n)</td>
<td>302</td>
<td>323</td>
<td>719</td>
</tr>
<tr>
<td>Type of early PCI</td>
<td>Rescue PCI: 39%</td>
<td>34%</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>Facilitated PCI: 61%</td>
<td>64%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>Study design: Randomized trial</td>
<td>Substudy</td>
<td>Substudy</td>
</tr>
<tr>
<td></td>
<td>Pre-PCI lytic: 50 mg t-PA</td>
<td>Combo Rx</td>
<td>Combo Rx</td>
</tr>
<tr>
<td></td>
<td>Time to PCI: &lt;120’ from presentation</td>
<td>at 60–90’ angio</td>
<td>at 60–90’ angio</td>
</tr>
<tr>
<td>Advantage of early PCI</td>
<td>Doubled rate of TIMI 3 flow at initial angiogram</td>
<td>Decrease in reinfarction and urgent revascularization</td>
<td>54% reduction in death + recurrent AMI</td>
</tr>
<tr>
<td>Increase in major bleeding due to early PCI</td>
<td>No</td>
<td>No</td>
<td>No</td>
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Angio is protocol driven 60–90 min angiogram after drug dosing. “The PACT trial is a randomized comparison of the two strategies; the SPEED and TIMI 10B/14B comparisons are retrospective analyses from subsets of patients undergoing early PCI in the dose-finding randomized trials. AMI = acute myocardial infarction; Combo Rx = combination therapy and dose finding with thrombolytic agents or/and glycoprotein IIb/IIIa inhibitors; PACT = Plasminogen-Activator Angioplasty Compatibility trial; PCI = percutaneous coronary intervention; SPEED = Strategies for Patency Enhancement in the Emergency Department.”
1) What initial pharmacologic strategy for recanalization can most safely maximize the achievement of TIMI grade 3 flow by the time that initial angiography, undertaken as early as possible, is performed? Candidates include fibrinolysis with clot-selective drugs and the use of conjunctive agents (17), including glycoprotein IIb/IIIa inhibitors, platelet adenosine diphosphate antagonists, low-molecular-weight heparin, direct thrombin inhibitors, and novel anticoagulants such as antagonists of coagulation factors Xa and VIIa. Outcomes were improved with the use of glycoprotein IIb/IIIa inhibitors before primary PCI in the Abciximab Before Direct Angioplasty and Stenting in MI Regarding Acute and Long-Term Follow-Up (ADMIRAL) trial (44,45). Because induction of early TIMI 3 flow is more readily achieved with full-dose than with half-dose fibrinolytic agents or glycoprotein IIb/IIIa inhibition alone (16), such regimens may ultimately prove to be superior with respect to mortality as well.

2) What initial pharmacologic regimen is optimally safe when PCI is initiated very early afterward? The combination of half-dose fibrinolytic agents plus glycoprotein IIb/IIIa inhibitors is an attractive option as judged from results in pilot studies such as TIMI 14 (16). Unfortunately, however, neither Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-III nor GUSTO V demonstrated greater efficacy than that seen with full-dose thrombolytic agents plus low-molecular-weight heparin. In fact, the incidence of bleeding was greater, especially in elderly patients (46,47).

3) Can the temporal window for efficacy of PCI be broadened by employing pharmacologic components as part of the pharmacoinvasive recanalization strategy? Current median times to open artery for non-transferred patients (111 min) and transferred patients (198 min) imply that community practice often cannot fulfill criteria recommended for the timing of primary angioplasty (9,30,31,34). Thus, studies are needed to define outcomes in patients initially treated pharmacologically and for whom mechanical intervention is not practically possible for 3 h or more after onset of symptoms.

4) What is the best treatment strategy for elderly patients? Only 10% of patients with STEMI in randomized trials have been ≥75 years of age (8) because of several considerations, including the limited benefits of thrombolysis in the elderly, the fact that only 40% of elderly patients with STEMI present to hospitals with on-site capability for PCI, and a natural inclination to seek to enroll patients at low risk in randomized trials (8,11,12,25,48). Optimal reduction of mortality after STEMI requires that mortality be reduced in elderly patients. Their mortality is as much as tenfold greater than that of younger patients with STEMI (48). By
broadening the temporal window available for effective PCI and including in studies more hospitals that lack the capacity to perform PCI on their own premises, multicenter studies of pharmacoinvasive recanalization could enroll the elderly in proportions closer to their 30% to 40% representation among all patients with STEMI (10).

5) Can novel secondary end points be used to decrease sizes of populations in trials yet provide sufficient power for detection of improved therapeutic efficacy? Microvascular flow is a powerful indicator and perhaps determinant of prognosis after STEMI. Thus, end points such as TIMI frame count, perfusion grade, and ST-segment resolution are strong descriptors of outcomes (49). Use of such end points should facilitate and may be of importance in evaluating the efficacy of novel approaches such as distal, embolic protection (50), and novel conjunctive and adjunctive pharmacologic regimens.

Conclusions. As judged from established principles regarding determinants of prognosis, the rapidity of recanalization and the magnitude of sustained restoration of perfusion will continue to be pivotal variables in improving treatment of patients with STEMI. We believe that pharmacoinvasive recanalization is a particularly promising approach. Optimizing this modality may render irrelevant the “either-or” debate that has pitted the virtues of thrombolysis against those of PCI.

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