Strategies that enhance functional reperfusion and translate into better clinical outcomes for ST-segment elevation myocardial infarction (STEMI) remain the holy grail of reperfusion therapy. In the absence of complete understanding of the vascular and cellular processes that are initiated with plaque rupture and thrombotic coronary artery occlusion, we have had to rely on therapies that shorten the duration of occlusion as well as result in effective thrombolysis. Because the initial events of a myocardial infarction appear to be mediated by acute thrombosis, it would seem logical that effective therapy would focus on pharmacologic strategies that would directly result in clot lysis, and/or enhance intrinsic fibrinolysis. Thrombolytic agents administered soon after the onset of an acute myocardial infarction achieve reperfusion in a majority of patients and save lives. Moreover, fibrin-specific thrombolytic agents achieve higher rates of vessel patency and are associated with lower mortality rates than non–fibrin-specific agents such as streptokinase. Finally, the ease of administration and life-saving characteristics of thrombolytics thrust this therapy into position as a first-line treatment for an acute myocardial infarction in the 1980s and 1990s, and as a Class I, Level of Evidence: A, recommendation for STEMI (1).

However, although the majority of patients receiving thrombolytics achieve angiographic and clinical evidence of reperfusion, a sizable minority achieve neither. This latter group remains a clinical challenge and is the Achilles heel of thrombolytic therapy. Although associated with inherent delays compared with administration of thrombolitics intravenously, primary percutaneous coronary intervention (PCI) achieves higher rates of angiographic and clinical reperfusion than thrombolytic therapy and has supplanted thrombolytic therapy as first-line treatment for acute myocardial infarction (when there are not substantial delays in obtaining primary PCI) (2).

The clinical success of these 2 reperfusion strategies depends not only on achieving recanalization/reperfusion of an occluded vessel, but also on maintenance of patency with adjunctive anticoagulant and antiplatelet therapy. A thorough review and discussion of the clinical evidence evaluating the relative benefits of different adjunctive strategies is beyond the scope of this editorial. However, it is important to understand that a strictly pharmacologic approach to an acute myocardial infarction results in complex and dynamic effects of thrombosis and fibrinolysis that were not entirely understood when thrombolytic therapy was initially proposed and introduced into clinical practice. The most important facet of this complex interaction of fibrinolysis with the coagulation system is the prothrombotic effects of fibrinolytics, with activation of platelets accompanying fibrinolysis. This will become important as shall be discussed.

It is also important to recognize that epicardial reperfusion as measured traditionally by Thrombolysis In Myocardial Infarction (TIMI) flow grade, or TIMI frame count (3), is not synonymous with tissue perfusion, that is, at the myocyte (4,5). This is evidenced by the variability in clinical outcomes of patients with TIMI flow grade 3, or the restoration of normal epicardial flow (6). Within this group are patients who have clinical outcomes similar to patients who had less successful restoration of epicardial flow. These patients are characterized by TIMI flow grade 3 epicardial flow but absence of myocardial blush, a surrogate for tissue perfusion at the microvascular level (6). The mechanisms responsible for this apparent dichotomy in epicardial and microvascular flow are under active clinical investigation, but remain incompletely elucidated. Potential mechanisms include the presence of embolized platelet-rich thrombi, leukocyte activation, and local accumulation of inflammatory mediators.

With the inherent delays in PCI and lack of universal availability, strategies to initiate the process of reperfusion before facilitated PCI, or more simply “drip and ship,” have gained great enthusiasm. Several large randomized control trials have been designed and completed to test the hypothesis that pharmacologic therapy could be given quickly after the initial identification of an acute myocardial infarction, while the patient is being prepared for PCI (7,8). Quite surprisingly, these studies have consistently observed just the opposite. That is, patients receiving facilitated PCI did not fare better, and if full-dose thrombolytics and glycoprotein IIb/IIIa inhibitors (GPI) were given, there was a substantially higher rate of bleeding, including fatal bleed-
ing. These results have puzzled investigators and clinicians, who have scrambled for explanations.

Some would point out that similar observations were made in the TIMI II-A (Thrombolysis In Myocardial Infarction, phase II-A) trial in which thrombolytic therapy followed by early catheterization and PCI (<48 h) was accompanied by higher adverse rates of clinical outcomes than if the PCI were performed after 48 h (9). However, TIMI II-A was completed in the pre-GPI era, and it was presumed that inadequate platelet inhibition was responsible for the apparent poor results observed in TIMI II-A given the now well-recognized platelet activation by thrombolytics (10). An alternative explanation has been suggested by Stone and Gersh (11), who suggested that the lack of benefit of facilitated PCI versus primary PCI alone for STEMI could be explained by the delays in PCI inherent to randomized central trials. In support of this, they point out that median time from symptom onset to balloon angioplasty was 3.5 h for all trials in aggregate. The potential for myocardial salvage is much less at this time than within the first hour or 2, so it should not be surprising that differences in outcomes were not detected.

In this issue of the Journal, Zalewski et al. (12) present a substudy of the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention) trial comparing primary PCI for STEMI to tenecteplase-facilitated PCI. These investigators retrospectively reviewed all angiograms obtained from patients enrolled in the ASSENT-4 PCI trial (13). They assessed vessel patency using TIMI flow grade and frame counts and evaluated for the presence of thrombus. For this, the investigators defined thrombus burden as a composite measure of TIMI thrombus grade (>2), slow flow without dissection or embolus, and/or angiographic evidence of distal embolization. The principal observation of this post hoc analysis was that despite a higher incidence of infarct vessel patency at the time of the initial angiogram with facilitated PCI, at case end these patients had a higher thrombus burden than those who underwent primary PCI alone. Moreover, facilitated PCI combined with thrombus burden was an independent predictor of higher mortality at 90 days (odds ratio: 2.43, 95% confidence interval: 1.30 to 4.51). The investigators speculated that the prothrombotic characteristics of tenecteplase with suboptimal antiocoagulation and antplatelet therapies led to resistant thrombus that was more likely to impair tissue perfusion despite the apparent higher rates of initial restoration of epicardial flow than primary PCI alone (10).

These observations from the ASSENT-4 PCI trial provide important insights into the potential mechanisms responsible for the lack of benefit overall of the facilitated PCI strategy in ASSENT-4 PCI. Data from several lines of clinical investigation indicate that distal embolization is associated with impaired tissue perfusion, and that impaired tissue perfusion is associated with worse clinical outcomes, all things otherwise being equal. Thus, the greater thrombus burden and distal embolization in those undergoing facilitated PCI would be expected to have worse clinical outcomes than in those without these features, in other words, primary PCI alone. Although the exact composition of these "resistant thrombi" were not evaluated in this study, the investigators postulated that they might be similar to the highly organized and fibrin-rich thrombi recovered from distal embolic protection devices at the time of primary PCI (14). Although this hypothesis is appealing, it is difficult to understand why patients receiving thrombolytics (facilitated PCI) should have thrombus of similar composition to patients not receiving thrombolytics (primary PCI with embolic protection), in whom fibrinolytic-mediated platelet activation should not be present. Further studies will need to determine if these resistant thrombi are erythrocyte- or platelet-rich, or a combination of both, and what causative role they may have in limiting tissue perfusion.

Another point of potential concern in accepting the role of resistant thrombi as the sole, if not principle, explanation for the apparent lack of benefit of facilitated PCI is that no benefit was observed in 3 trials in which half-dose lytics were administered along with full-dose GPI. Presumably, GPI coadministration should have neutralized fibrinolytic-mediated platelet activation in these studies. Yet, no apparent benefit with regard to clinical outcomes were observed in these 3 trials using this strategy (7,15,16). Clearly, these observations from ASSENT-4 PCI are hypothesis-generating and should stimulate further clinical evaluation into the role and importance of thrombus burden during treatment of patients with STEMI.

Despite some uncertainties about the role resistant thrombi have in mediating adverse outcomes in patients in ASSENT-4 PCI, these observations complement information concerning the role of thrombi and clinical outcomes from studies evaluating adjunctive thrombectomy during primary PCI for STEMI. Interest emerged in thrombectomy when it became apparent that distal embolization was commonly observed during primary PCI (17), and that this was a predictor of worse outcomes. Disappointingly, neither studies designed to minimize or prevent distal emboli using embolic protection devices (18) nor use of mechanical thrombectomy were associated with improved clinical outcomes (19). Nonetheless, use of manual thrombectomy devices appears to have a favorable effect on clinical outcomes with a reduction in the incidence of both distal emboli and mortality (20,21). The mechanisms responsible for the apparent disparate results with manual thrombectomy compared with mechanical thrombectomy or use of embolic protection devices are uncertain. The observation that the incidence of distal embolization is reduced with mechanical thrombectomy and perfusion is improved, yet overall survival is not changed, suggests that there are complex interactions between the vascular and coagulation systems that require further basic and clinical evaluation. The observations from the ASSENT-4 PCI angiographic study and the experience with adjunct manual thrombec-
tomy suggest that focus on importance of residual thrombus and/or distal embolization in influencing clinical outcomes during therapy for STEMI is appropriate and should continue to be pursued.

Like many potentially important observations, the findings from this ASSENT-4 PCI angiographic study raise many questions as well. Determining the exact nature of these resistant thrombi will be important to direct appropriate preventive or therapeutic strategies. Other important questions are: How generalizable are these findings? Do they apply to all facilitated PCI strategies? These questions are germane in that facilitated PCI strategies have employed different thrombolytic, anticoagulant, and antiplatelet therapies, yet all have failed to demonstrate superiority over simple primary PCI for STEMI. Finally, it is much easier to determine macroscopic evidence of thrombus (i.e., what we see on an angiogram); but it is microvascular perfusion coupled with intact cellular and myocyte function that ultimately determines the benefit of any reperfusion strategy. These ASSENT-4 PCI observations point us in an important direction of clinical investigation, but we have a long way to go before we achieve adequate understanding of the dynamics of functional and effective reperfusion in the setting of an acute myocardial infarction.

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