Recalibrating Reperfusion Waypoints

There falls a shadow, as T. S. Eliot noted, between the conception and the creation. In the annals of innovation, new ideas are only part of the equation. Execution is just as important.

—Walter Isaacson (Steve Jobs, p. 98)

The realization that thrombus was the cause and not the consequence of acute myocardial infarction was a transformative pathophysiologic insight.1 An even more stunning observation was the subsequent discovery that restoration of coronary patency could salvage ischemic myocardium and improve clinical outcomes in ST-elevation acute myocardial infarction (STEMI).2,3 Assertive clinical investigations of both the content and process of STEMI care over the subsequent 4 decades has demonstrated that the ultimate success of reperfusion is modulated by the timeliness, efficiency, and efficacy with which it is applied. Whereas contemporary guidelines indicate that primary percutaneous coronary intervention (PCI) is the preferred strategy for STEMI, most patients with STEMI do not present to a primary PCI (PPCI) center, and ≈50% are walk-ins who do not utilize emergency medical services.4–6 Accordingly, persisting delays—attributable to both patients and the healthcare system—in achieving timely PCI (ie, within 60 to 90 minutes of symptoms to first medical contact) are common and exact a price of excess morbidity and mortality.7,8 Advances in fibrinolytic, anti-thrombotic, and antiplatelet therapies, coupled with improved pre- and in-hospital systems of care, have evolved dramatically pari passu with these clinical realities. Accumulating contemporary evidence indicates that early fibrinolytic therapy followed by timely PCI, where appropriate, achieves clinical outcomes at least as good as PPCI in the common circumstance, where delay to PPCI is >60 to 90 minutes from first medical contact.9,10

In this issue of Circulation,11 the EARLY-MYO trial (Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Elevation Myocardial Infarction) investigators provide another waypoint to help navigate the continuing reperfusion journey. Using a noninferiority design, they targeted a composite reperfusion end point of both thrombolysis in myocardial infarction flow and perfusion grade 3 combined with ST segment resolution ≥70% after PCI.11 They randomized 344 low-risk East Asian patients with STEMI ≤6 hours of symptom onset to either a pharmaco-invasive (PhI) strategy with half-dose alteplase or PPCI and found the primary end point to be 34.2% versus 22.8% for PhI versus PPCI, respectively (P=0.05 for noninferiority and P=0.022 for superiority). Given that the angiographic end point was after PCI and the ST segment resolution assessment was ≈60 minutes after PCI in both treatment groups, it can be argued that this later assessment of reperfusion in the PhI group (≈7 hours after the PPCI group)
favored the PhI patients. However, ancillary support for their findings is evident in the prespecified secondary endpoints of magnetic resonance imaging determined infarct size and left ventricular function (the latter also by quantitative echocardiography) which were similar. Wisely, and to avoid bias in this necessarily open trial, all of the primary and secondary endpoints were analyzed in independent core laboratories and blinded to treatment assignment. Although clearly underpowered for definitive assessment, the clinical outcomes of mortality regarding myocardial infarction, heart failure, and stroke were similar: shock was not reported. Despite enrolling patients with prior stroke (4.1%), no intracranial hemorrhage occurred, but an excess of minor bleeding occurred in the PhI patients.

Some features of this trial deserve further comment. The patients were low risk, none were >75 years of age, and randomization presumably began in hospital. The total ischemic time in the PhI group was relatively long (ie, 210 minutes), and the approximate PCI-related delay was ≈70 minutes. By contrast, in the STREAM study (Strategic Reperfusion Early After Myocardial Infarction), the ischemic times for the PhI patients were much shorter (ie, 100 minutes).10 Although the EARLY-MYO protocol specified aspirin and clopidogrel, apparently some patients received ticagrelor. It would be helpful to know whether any of the PhI patients received ticagrelor. It is important to note that radial vascular access was almost exclusively used in both groups. Thrombus aspiration was frequent, especially in the PPCI group, but we do not know whether nonculprit interventions occurred in the 61% of patients with multivessel disease. A key novel aspect of the current study is the use of half-dose alteplase in a PhI strategy. This was not weight adjusted in this rather low-body-weight population (median 70 kilograms, 75th quartile 76 kg), nor was a conventional step-down infusion at 30 minutes used. Nonetheless, this regime achieved good pre-PCI reperfusion rates, with only 25% of patients requiring timely rescue PCI. The comparable efficacy to PPCI of the EARLY-MYO PhI strategy supports prior observations in the ≥75-year-old cohort of the STREAM study and those acquired from the Minnesota registry.12,13 Whether these data reflect a differing dose-response relationship in this ethnic group, as suggested by Ross et al,14 is unknown and the subject of further study in STREAM-2 (ClinicalTrials.gov. Unique identifier: NCT02777580). Two additional observations in the current study are of interest. Despite achieving good thrombolysis in myocardial infarction epicardial perfusion after PCI in both groups, considerably less success was attained at the myocardial perfusion level. Myocardial hemorrhage was seen in ≈50% of the patients on magnetic resonance imaging but appeared similar in both the PhI and PPCI groups. Before accepting that the EARLY-MYO PhI strategy is safe, it is important to note that <20 patients in the PhI group were females, and the upper 95% confidence interval limit around the 0% estimate of intracranial hemorrhage could range from 1.46% to 2.20%.

In the Table, we have summarized some key outstanding issues that deserve attention in the care of all patients with STEMI, irrespective of where they are treated. The EARLY-MYO study has provided a welcome and commendable new piece to the reperfusion puzzle. These investigators from Shanghai and other Chinese centers remind us of 2 effective modes of reperfusion in the large majority of patients with STEMI in all regions of the world who cannot or do not undergo timely PCI in an expert 24/7 facility. This option is not inferior—and on occasion is even superior—to PCI, nor need it be relegated to rural centers or developing countries given the persisting delays in transfer of patients with STEMI for PPCI from non-PCI centers and the attendant unfavorable outcomes.7,8 Not all things come to those who wait, especially in early presenters and those with a large territory at risk where acceptable PCI-related delays are recommended to be even shorter (ie, 60 minutes).5 Developing a balanced reperfusion portfolio which recognizes that one size does not fit all is imperative. Rather, we need to provide best care for the right patient at the right time and place, thereby heeding the still current American College of Cardiology/American Heart Association adage: “The appropriate and timely use of some form of reperfusion therapy is likely more important than the choice of therapy. Greatest emphasis is to be placed on the delivery of reperfusion therapy to the individual patient as rapidly as possible.”15 In this comprehensive way, we can strike the optimal balance between innovation and execution.

**Table.** Issues in STEMI Care Deserving Future Investigation

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<th>Question</th>
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<td>Is half-dose fibrinolytic right for all PhI patients, and does ethnicity matter in dose selection?</td>
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<td>Is concomitant ticagrelor therapy more effective than clopidogrel, and is it safe when used with fibrinolysis?</td>
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<td>What is the optimal window for invasive assessment in a PhI strategy?</td>
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<td>What is the role of concomitant nonculprit vessel intervention?</td>
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<td>Is PCI necessary in successfully reperfused patients with noncritical culprit stenosis?</td>
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<td>How can we better address failure of microperfusion after reperfusion therapy?</td>
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<td>How can we improve outcomes in cardiogenic shock?</td>
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<td>What community interventions work best—across international borders—to enhance effective prehospital utilization?</td>
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<td>How do we improve survival from STEMI-mediated sudden out-of-hospital death?</td>
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<td>What is the future of cell- and gene-based therapy?</td>
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<td>Given the decline in STEMI mortality, how do we best assess reperfusion efficacy within a composite clinical end point?</td>
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PCI indicates percutaneous coronary intervention; PhI, pharmaco-invasive; and STEMI, ST-elevation acute myocardial infarction.
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FOOTNOTES
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