

## EDITORIAL COMMENT

# The Ideal Reperfusion Strategy for the ST-Segment Elevation Myocardial Infarction Patient With Expected Delay to Percutaneous Coronary Intervention

## Paradise Lost or Paradise Renamed?\*

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In the 20 years since the ISIS-2 (Second International Study of Infarct Survival) was published, therapy for ST-segment elevation myocardial infarction (STEMI) has undergone a remarkable evolution (1). The demonstration of benefit of fibrinolysis versus placebo in the ISIS-2 study, the preferred fibrinolytic agent, and the superiority of primary percutaneous coronary intervention (PCI) over fibrinolysis were all driven primarily by the results of large, randomized, multicenter clinical trials. A clear consensus now exists

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that primary PCI is the preferred reperfusion strategy for STEMI patients, if performed in a timely manner (2). Among remaining controversies in care for patients with STEMI, 2 stand out: the time after which primary PCI is no longer preferred (door-to-balloon 90 vs. 120 min, or possibly longer), and the ideal reperfusion strategy for the STEMI patient with an expected delay to PCI. Do the data available from randomized clinical trials answer these questions?

Facilitated PCI has always been an attractive strategy, combining the theoretical advantages of fibrinolytic therapy and PCI (3,4). Unfortunately, several meta-analysis/systematic reviews demonstrated no advantage of facilitated PCI over primary PCI, and even possible harm (5–7). Two papers

published in this issue of *JACC: Cardiovascular Interventions* indicate the conclusion “Facilitated Angioplasty: Paradise Lost” (8) may in fact have been premature.

Both reports represent retrospective analyses from the 2 largest and most influential facilitated PCI trials (9,10). In fact, the 2 trials provide the strongest evidence against a facilitated PCI strategy. Herrmann et al. (11) performed a retrospective analysis of the 2,452 patients randomized in the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial stratified by presentation to a spoke (non-PCI center) or hub site, symptom to randomization time, and Thrombolysis In Myocardial Infarction (TIMI) risk score. As expected, overall mortality was directly related to TIMI risk score. Patients with a TIMI risk score  $\geq 3$ , presentation to a spoke hospital, and symptom to randomization time  $< 4$  h had a significant improvement in the 90-day composite end point (death, ventricular fibrillation after 48 h, cardiogenic shock, and congestive heart failure), as well as 1-year survival when randomized to combination facilitated PCI (half-dose reteplase and abciximab). As the authors note, this is exactly the patient population expected to benefit from facilitated PCI (11). A number of key points are made in the retrospective analysis of the 1,667 STEMI patients enrolled in the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) trial (12). Few patients actually fit the target population for which facilitated PCI was designed, and the results of the ASSENT-4 PCI trial are actually more closely related to the time to treatment than the treatment strategy. The authors conclude that “the ASSENT-4 PCI trial should not be taken as grounds for conclusive rejection of facilitated PCI in all its variations as currently practiced or studied in ongoing investigations” (12). Despite the inherent risks of retrospective analysis, both papers provide insight into the challenges of trial design (in particular, the balance between inclusion/exclusion criteria and enrollment expectations) and the extrapolation of clinical trial results into clinical practice.

The insightful reanalysis from the authors of these 2 important trials combined with the results of 2 recently published prospective randomized clinical trials should refocus our attention on a key question: what is the ideal reperfusion strategy for the STEMI patient with expected delay to PCI? The CARESS-AMI (Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction) trial was a prospective multicenter trial that randomized 600 high-risk STEMI patients  $\leq 75$  years of age to half-dose reteplase and abciximab with immediate transfer for PCI compared with transfer only for persistent ST-segment elevation or clinical deterioration. The primary outcome, a composite of death, reinfarction, or refractory ischemia at 30 days was significantly reduced in the pharmacoinvasive PCI group (4.4%) compared with the standard care/rescue PCI group (10.7%) (13). The TRANSFER-AMI (Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) trial

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randomized 1,059 high-risk STEMI patients at non-PCI centers to full-dose tenecteplase with immediate transfer for PCI versus tenecteplase with transfer for rescue PCI if the patients had persistent ST-segment elevation, chest pain, or hemodynamic instability (14). The primary end point—a composite of death, reinfarction, and recurrent ischemia, new or worsening CHF, or cardiogenic shock within 30 days—was significantly reduced in patients assigned pharmacoinvasive PCI (11%) compared with patients receiving standard care/rescue PCI (17%). Thus, both trials were similar in that a pharmacoinvasive PCI strategy was superior to the current guideline-recommended strategy of fibrinolysis plus rescue PCI in patients with an expected delay to PCI. Is pharmacoinvasive PCI simply facilitated PCI renamed?

The terminology itself leads to considerable confusion. What are the fundamental differences between facilitated and pharmacoinvasive PCI? The pharmacologic regimen has varied, and the ideal regimen remains unclear for both. The major differences are the time to PCI and the trial design. *Facilitated PCI* trials in general have had shorter time to PCI and have compared the combination of fibrinolysis and/or IIB/IIIa inhibitors plus immediate PCI to PCI alone. *Pharmacoinvasive PCI* trials have been more likely to randomize patients at non-PCI hospitals and have compared the combination of fibrinolysis and/or IIB/IIIa inhibitors followed by early PCI to fibrinolysis alone with an ischemia-guided rescue PCI strategy. The evidence is mounting that a routine invasive strategy after fibrinolytic therapy is not only safe and effective but the preferred approach (15). Like the ideal pharmacologic regimen, the ideal time to PCI post-fibrinolysis remains unclear.

Herrmann et al. (11) suggest the conclusions of their study are exploratory and require validation in a prospective, randomized trial. Theoretically, the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial itself was well designed to be that trial, but was plagued and ultimately halted by slow enrollment. Therefore, the trial was underpowered to answer the question, especially considering that 60% of patients were enrolled at PCI centers and not “spoke” hospitals. In both the FINESSE and ASSENT-4 studies, the patients most likely to benefit from facilitated PCI (patients who present early with expected delays to PCI) were under-represented. The design and successful completion of such a trial will be extremely challenging. With the focus on time to treatment, it has become increasingly difficult to perform a randomized placebo-controlled STEMI trial in the U.S. “spoke” hospitals at distances from a PCI hospital that lead to door-to-balloon times >120 min are predominately small, rural, or community hospitals frequently without cardiologists on site and lacking sophisticated research structures. The annual number of STEMI patients presenting to these “spoke” hospitals is small, and therefore a large number of hospitals will be needed. These may be insurmountable issues,

especially in the U.S. In the absence of a well-designed clinical trial, what are our current options for the STEMI patient with expected delay to PCI, and how many patients does this represent?

It is important to emphasize that patients presenting to a PCI hospital and those with short transfer times should receive primary PCI as fast as possible with a goal door-to-balloon time of <120 min. The current focus on increasing timely access to PCI makes this an obtainable goal for the majority of STEMI patients (16,17). Still, the number of STEMI patients treated with delays >120 min is substantial. In the most recent data from the American College of Cardiology/National Cardiovascular Data Registry, 82% of transferred patients had a door-to-balloon time >120 min (18). In the Minneapolis Heart Institute Level 1 regional STEMI network, 34% of transferred patients have a door-to-balloon time >120 min, including 52% of patients transferred from hospitals 60 to 210 miles from the PCI center (19). Based on the FINESSE trial investigators criteria of patients presenting to a spoke hospital with symptoms to randomization ≤4 h and TIMI risk score ≥3, 40% to 50% of transferred patients in our regional STEMI network would benefit from a pharmacoinvasive approach.

Five distinct options available for the STEMI patient with expected delay to PCI are listed in Table 1. We believe there is sufficient evidence to support immediate transfer of STEMI patients to a PCI center and the benefit of having a standardized approach to STEMI care, which would eliminate option numbers 1 and 5. The CARESS-AMI and TRANSFER-AMI trials as well as a number of smaller trials indicate the pharmacoinvasive approach (early invasive strategy after fibrinolysis) is superior to full-dose fibrinolytic with a rescue PCI strategy (13–15). Therefore, in our opinion, the remaining options are a pharmacoinvasive strategy or primary PCI “no matter how long it takes” or “as fast as possible.” Unfortunately, currently available data do not provide conclusive evidence, but the results from the FINESSE trial investigators indicate that in high-risk STEMI patients who present early to a non-PCI center, the pharmacoinvasive strategy may be preferred. Therefore, paradise may not be lost, just renamed.

**Table 1. Reperfusion Options for the Patients With Expected Delays**

1	Full-dose fibrinolytic, admission to the non-PCI hospital with selective transfer for rescue PCI
2	Full-dose fibrinolytic, routine transfer to PCI hospital with aggressive rescue PCI
3	Facilitated or pharmacoinvasive PCI
4	Primary PCI (no matter how long it takes)
5	Any of the above depending on the PCI facility available and the cardiologist on call

PCI = percutaneous coronary intervention.

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