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EDITORIAL COMMENT

Facilitated Percutaneous Coronary Intervention

Still Searching for the Right Patients*

Bruce R. Brodie, MD

Greensboro, North Carolina

Primary percutaneous coronary intervention (PCI) has become the preferred reperfusion strategy for ST-segment elevation myocardial infarction (STEMI) but has been limited by delays to PCI. There has been great progress in the development of systems of care for reducing delays to PCI, and most STEMI patients in the United States and most of Europe are now treated with primary PCI. However, there are circumstances where delays to primary PCI are too long, and alternative reperfusion strategies are needed.

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Facilitated PCI has been an attractive alternative reperfusion strategy for patients with long delays to PCI and has been evaluated in a number of clinical trials. Facilitated PCI is the use of pharmacological therapy (usually fibrinolytic therapy or half-dose fibrinolytic therapy plus glycoprotein IIb/IIIa platelet inhibitors) administered as soon as possible after the onset of symptoms to establish early reperfusion followed by emergent transfer to a PCI facility for planned emergent PCI. Despite the intuitive appeal of facilitated PCI, its benefit has not been supported by 2 large randomized trials. The ASSENT-4 PCI (Assessment of Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) trial (1) randomized 1,667 STEMI patients to facilitated PCI with tenecteplase (TNK) versus primary PCI alone. The trial was stopped early due to an increased mortality in the facilitated arm, and the final outcomes showed higher rates of death or heart failure (the primary endpoint), more ischemic events, and more intracranial hemorrhage with TNK-facilitated PCI. There were several limitations in the study design that may explain the lack of benefit of facilitated PCI in this trial. Clopidogrel was not used in either group, and only 10% of the facilitated group received glycoprotein IIb/IIIa platelet inhibitors. Without adequate platelet inhibition, there was dyssynergy between fibrinolytic therapy, which activates platelets, and PCI resulting in increased ischemic events. Furthermore, the patients expected to benefit most from facilitated PCI (patients presenting early after the onset of symptoms with long delays to PCI) were not well represented in the study. The median time from symptom onset to randomization was relatively long (150 min), and the median time from randomization to balloon was relatively short (115 min).

The other major facilitated PCI trial, the FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) trial, randomized 2,452 STEMI patients into 3 arms: 1) facilitated PCI with abciximab; 2) facilitated PCI with combination half-dose reteplase plus abciximab; and 3) primary PCI with abciximab given at the time of PCI (2). Despite a higher frequency of TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 on initial angiography and better ST-segment resolution in the combination facilitated group, there were no differences in the primary endpoint of death, heart failure, or shock between the 3 groups, and there was increased bleeding in the combination facilitated group. Unlike ASSENT-4 PCI, this trial provided good platelet inhibition, but, like ASSENT-4 PCI, patients expected to benefit most were not well represented in the trial. The time from symptom onset to drug was relatively long at 165 min, and the time from drug administration to balloon was relatively short at 90 min. A post hoc analysis of patients expected to benefit most, high-risk patients presenting early at spoke hospitals with long delays to PCI, found lower 1-year mortality in the combination facilitated PCI arm compared with the other 2 groups (3). However, these patients comprised only 16% of the FINESSE population.

In this issue of *JACC: Cardiovascular Interventions*, Thiele et al. (4) present the results of The LIPSIA-STEMI Trial (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction), which evaluates the impact of facilitated PCI with TNK compared with primary PCI on infarct size measured by magnetic resonance imaging. The investigators designed this trial in a very thoughtful way in an attempt to avoid some of the limitations of earlier facilitated PCI trials. All patients were treated with clopidogrel and aspirin to provide adequate platelet inhibition, and patients expected to benefit most from facilitated PCI—patients presenting early after the onset of symptoms with long delays to PCI—were selected for inclusion. As anticipated, facilitated PCI resulted in a higher frequency of infarct artery patency on initial angiography, but unfortunately, this did not translate into any reduction in infarct size. Facilitated PCI also did not decrease microvascular obstruction or improve myocardial salvage, did

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From the Department of Medicine, University of North Carolina Teaching Service, Moses Cone Heart and Vascular Center, and The LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina. Dr. Brodie is on the Speakers' Bureau for The Medicines Company and Medrad/Possis.

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not improve ST-segment resolution, and did not improve clinical outcomes.

What went wrong? Why was there no benefit with facilitated PCI in a group of STEMI patients expected to benefit? The investigators offer several possible explanations. The delays to PCI, both time to PCI and door-to-balloon time, were slightly longer (20 to 25 min) in the facilitated group, which could influence outcomes. Glycoprotein IIb/IIIa platelet inhibitors were used less frequently in the facilitated group compared with the primary PCI group (29% vs. 88%), which could influence microvascular reperfusion. The study was successful in enrolling patients presenting early (symptom-to-door time was 55 min), but the delays to PCI were much shorter than expected. Door-to-balloon times were <90 min in the primary PCI group. Allowing time to administer TNK and time for TNK to achieve reperfusion, the estimated times to reperfusion with facilitated PCI were no faster than with primary PCI. This appears to be the likely reason there was no improvement in infarct size with facilitated PCI.

In retrospect, it is not surprising that this trial and previous facilitated-PCI trials have not shown benefit. Reperfusion therapy has the maximum benefit in improving myocardial salvage and survival when reperfusion can be achieved within the first 2 to 3 h after the onset of symptoms (5). After 2 to 3 h, reperfusion is still beneficial, but the benefits are much less time-dependent and are related less to myocardial salvage and more to the benefits of an open artery. We have shown that delays to primary PCI influence mortality primarily in high-risk patients presenting early after the onset of symptoms (<90 min) (6). In these patients, short door-to-balloon times can achieve reperfusion within the time window of maximum benefit. In patients who present later, even rapid door-to-balloon times do not achieve reperfusion within the time period for maximal benefit, and incremental delays to reperfusion have little impact on outcomes. If facilitated PCI is to achieve benefit over primary PCI, it must achieve reperfusion much faster than primary PCI does and must achieve reperfusion within 2 to 3 h. Most STEMI patients present at 90 to 180 min after the onset of symptoms. Facilitated therapy would be initiated 30 min later and take another 60 min to establish reperfusion. This would establish reperfusion at 180 to 270 min, which is beyond the time window for optimal benefit. Only patients presenting very early (<90 min) would have the potential to achieve reperfusion with facilitated PCI within this time window. Patients presenting later may achieve earlier reperfusion with facilitated PCI compared with primary PCI when there are long delays to PCI, but these time differences after the first 2 to 3 h have little impact on outcomes. Furthermore, because facilitated PCI is associated with increased bleeding, the benefit from earlier reperfusion would have to outweigh the negative impact of increased bleeding, including higher associated mortality. Consequently, we would expect facilitated PCI to benefit only a small minority of patients who are at high clinical risk and present very early (about 16% of STEMI patients), and only those patients in whom there are long delays to PCI (3). Facilitated PCI trials are still searching for these patients.

A relatively new term, pharmaco-invasive strategy, has been used to describe a reperfusion strategy in which fibrinolytic therapy is given at non-PCI hospitals to establish reperfusion and is followed by transfer to a PCI facility for urgent PCI to optimize reperfusion rates and minimize reinfarction. This strategy is similar to facilitated PCI, but has been compared in clinical trials with fibrinolytic therapy rather than with primary PCI. Two relatively large trials (7,8) have shown benefit of the pharmaco-invasive strategy over fibrinolytic therapy alone, and this strategy has received a class IIa indication after fibrinolytic therapy by the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines committees. So when should we consider fibrinolytic therapy with a pharmaco-invasive strategy (i.e., facilitated PCI) over transfer for primary PCI? Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend that fibrinolytic therapy is the preferred reperfusion strategy at non-PCI hospitals unless transfer for primary PCI can be achieved with door-to-balloon times <90 to 120 min. Evidence now suggests that fibrinolytic therapy is best accompanied by a pharmaco-invasive strategy, but a pharmaco-invasive strategy (i.e., facilitated PCI) has not been shown to be beneficial compared with transfer for primary PCI alone, even with long delays to PCI. Many of us believe there are patients who may benefit from facilitated PCI, but it is likely that these patients are a small minority who are fibrinolytic eligible, are at high clinical risk, present very early, and have very long delays to PCI. Determining when the delay to primary PCI is long enough to consider such a strategy and designing trials to enroll these patients has proven to be very difficult. Until that can be done, transfer for primary PCI, even with delays beyond 2 h, appears to provide the best reperfusion strategy for all but a small minority of patients.

Reprint requests and correspondence: Dr. Bruce R. Brodie, Department of Medicine, LeBauer Cardiovascular Research Foundation, 1126 North Church Street, P.O. Box 13586, Greensboro, North Carolina 27401. E-mail: bbrodie89@gmail.com.

REFERENCES

1. The ASSENT-4 PCI Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet 2006;367:569–78.

2. Ellis SG, Tendera M, de Belder MA, et al., for the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205–17.
3. Herrmann HC, Lu J, Brodie BR, et al., for the FINESSE Investigators. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. J Am Coll Cardiol Intv 2009;2:917–24.
4. Thiele H, Eitel I, Meinberg C, et al., for the LIPSIA-STEMI Trial Group. Randomized comparison of pre-hospital–initiated facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention in acute myocardial infarction very early after symptom onset: The LIPSIA-STEMI Trial (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction). J Am Coll Cardiol Intv 2011;4:605–14.
5. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA 2005;293:979–86.
6. Brodie BR, Gersh BJ, Stuckey T, et al. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. J Am Coll Cardiol 2010;56:407–13.
7. Di Mario C, Dudek D, Piscione F, et al., for the CARESS-in-AMI Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. Lancet 2008;371:559–68.
8. Cantor WJ, Fitchett D, Borgundvaag B, et al., for the TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009;360:2705–18.

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