

EDITORIAL COMMENT

Percutaneous Coronary Intervention After Successful Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction

Better Late Than Never*

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Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI) if it can be performed in a timely manner and by experienced operators (1,2). However, in 2009, primary PCI is still unavailable to many patients worldwide and in many rural parts of the U.S. (3). Fibrinolytic therapy is the alternative to primary PCI, but bleeding complications occur in some patients, and as many as 40% are ultimately resistant to infarct artery reperfusion (4). Among selected patients who fail to reperfuse with fibrinolytic therapy, a strategy of emergent transfer to a PCI hospital for rescue PCI has emerged as the standard of care (5). Thus, the definitive goal in contemporary reperfusion therapy is early, complete, and sustained reperfusion, which for decades has been known to result in better short- and long-term outcomes (6).

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Given the logistical challenges related to delivering primary PCI in some settings, investigators have sought to combine the best of both reperfusion therapies with early upstream administration of fibrinolytic therapy, anticoagulants, and antiplatelet agents to establish initial reperfusion, followed by stabilization of the infarct artery with PCI. Facilitated PCI refers to a strategy of PCI performed routinely and emergently after pharmacological reperfusion—even when pharmacological reperfusion has been

successful. Eighteen trials over 3 decades have examined the efficacy and safety of this approach (7) but unfortunately have failed to show an improvement in clinical outcomes when compared with primary PCI. In fact, when full-dose fibrinolytic therapy was used for pharmacological reperfusion, an increased rate of bleeding, nonfatal myocardial infarction, stroke, and death was observed with facilitated PCI. A criticism of these trials was the relatively short time intervals between upstream fibrinolytic therapy and PCI, which have been thought to contribute, at least in part, to adverse events. Given these findings, American and European guidelines have cautioned against the use of facilitated PCI with full-dose fibrinolytic therapy (1,2).

In contrast, trials testing the hypothesis of routine but nonemergent PCI after successful fibrinolytic therapy have shown benefit when compared with fibrinolytic therapy when delays between fibrinolysis and PCI were 3 to 24 h (8,9). This strategy has often been referred to as the pharmacoinvasive approach; the recent TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) is the largest and latest trial to study this approach (10). On average, patients in the pharmacoinvasive arm in the TRANSFER-AMI trial underwent cardiac catheterization and subsequent PCI 3.9 h after receiving full-dose fibrinolytic therapy. Significant improvements were noted in the composite end point of death, reinfarction, recurrent ischemia, new or worsening ischemia, or cardiogenic shock when compared with fibrinolytic therapy and delayed cardiac catheterization. Differences in this end point were driven largely by reductions in reinfarction, recurrent ischemia, and new or worsening heart failure—all events likely improved by stabilization of the infarct artery with PCI. No differences were noted between groups in rates of major bleeding or transfusion.

In this issue of the *Journal*, the NORDISTEMI (Norwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction) by Bøhmer et al. (11) takes these findings a step further. In brief, the trial included 266 patients at rural community hospitals in Norway with expected time delays for primary PCI >90 min. All patients received guideline-based therapy with full-dose fibrinolytic therapy with tenecteplase and adjunctive therapy with enoxaparin and clopidogrel. In addition, 57% of patients received fibrinolytic therapy in the pre-hospital setting. Then, patients were randomly assigned to transfer for planned cardiac catheterization (n = 134) and revascularization as indicated or a conservative ischemia-guided protocol (n = 132) at the community hospital with rescue PCI for failed fibrinolysis. Median time from fibrinolytic therapy to first balloon inflation was 2.7 h in the pharmacoinvasive arm. The primary end point—a composite of death, reinfarction, stroke, or new ischemia at 12 months—occurred in 21% of the pharmacoinvasive group versus 27% of the conservative group (p = 0.19). Excluding the softer end point of new

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ischemia, the secondary composite end point of death, reinfarction, or stroke at 12 months was statistically improved in the early invasive arm (6% vs. 16%; $p = 0.01$). Moreover, overall bleeding rates did not differ between groups despite the relatively short time interval between fibrinolysis and PCI, perhaps a result of the high rate of radial artery access that was used (>80%).

Although far from definitive, this study's findings add importantly to a growing body of evidence that supports routine and nonemergent cardiac catheterization after successful fibrinolytic therapy. For many hospital systems, the delay to primary PCI remains a formidable barrier, and the concept of using PCI as a nonemergent adjunct to fibrinolytic therapy is very appealing. Patients could receive contemporary guideline-based fibrinolytic therapy with first medical contact-to-needle times within 30 min and immediate antiplatelet therapy with clopidogrel. Those without clinical reperfusion could then be emergently referred for rescue PCI, whereas patients with successful reperfusion could undergo cardiac catheterization and revascularization within 24 h. Bøhmer et al. (11) suggest that PCI can be safely delivered as early as 2 to 3 h after fibrinolysis, although earlier treatment might not be superior to longer delays that are still within a 24-h window. The great attraction of this approach is that it would alleviate the intensive resource demand required of STEMI systems of care that attempt to emergently deliver primary PCI to all patients (12).

An immediate consequence of the TRANSFER-AMI and NORDISTEMI trials is that clinicians will more strongly consider recommending routine cardiac catheterization and PCI after successful fibrinolytic therapy in STEMI patients—currently Class IIb and Class IIa recommendations in the American and European guidelines, respectively (1,2). However, the larger implication of these trials is their long-term effect on population-based approaches to reperfusion therapy. Given that the most significant advantages of primary PCI over fibrinolytic therapy are related to reductions in reinfarction and recurrent ischemia, it is interesting to postulate whether a pharmacoinvasive approach among fibrinolytic-eligible patients would result in similar outcomes compared with primary PCI when significant delays to primary PCI exist. For example, the 30-day reinfarction rate between the pharmacoinvasive and fibrinolytic therapy arms in the NORDISTEMI trial (1.5% vs. 5.3%) compares favorably with pooled results reported from a meta-analysis evaluating inter-hospital transfer for primary PCI with fibrinolytic therapy (1.5% vs. 5.1%) (13). This hypothesis has not been studied definitively in a randomized clinical trial, although the large FAST-MI (French registry on Acute ST-elevation Myocardial Infarction) registry from France suggests that, when fibrinolytic therapy is combined with liberal use of PCI, the results are comparable to primary PCI (14). The ongoing STREAM (Strategic Reperfusion With Tenecteplase and Antithrombotic Treatment Early After Myocardial Infarction) trial will provide some answers to this question as well (15).

Throughout the world, STEMI systems of care rely on efficient identification, triage, and delivery of patients to facilities capable of providing timely reperfusion therapy. Although primary PCI remains the preferred strategy, timeliness remains a key limitation to its universal use. Given the geographic challenges that are present in many parts of the world, this limitation is unlikely to be overcome in the immediate future. The approach studied by Bøhmer et al. (11) as well as the trials that preceded it offer a potential paradigm shift for STEMI systems of care—particularly in rural areas—that combines the advantages of fibrinolytic therapy and PCI without the limitations of facilitated PCI. When access to primary PCI is limited, incorporating timely cardiac catheterization of patients after fibrinolysis into STEMI systems of care should be strongly considered.

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