PCI Strategies After Fibrinolytic Therapy

How to choose the appropriate reperfusion strategy.

BY MICHEL R. LE MAY, MD

Survival in patients presenting with ST-segment elevation myocardial infarction (STEMI) depends on early, complete, and sustained reperfusion of the infarct-related artery.[1-3] Pharmacological therapy with the use of fibrinolytic agents can achieve early reperfusion, but complete flow is restored at best in only 60% of patients.[4] Mechanical reperfusion with primary percutaneous coronary intervention (PCI) can restore complete flow in up to 95% of patients and is associated with a lower rate of reocclusion.[4] However, unlike fibrinolytic therapy, which is widely available, primary PCI can only be performed in centers equipped with a catheterization facility. An overview of 23 randomized trials comparing the two strategies reported an absolute 2% survival benefit with primary PCI.[5] In this study, intracranial hemorrhage occurred in 1% of patients treated with fibrinolytic therapy but was virtually eliminated with primary PCI.

Primary PCI holds a survival advantage only if it can be performed in a timely fashion. The principle that "time is myocardium" applies to both fibrinolysis (door-to-needle)[1] and primary PCI (door-to-balloon).[6] Hence, guidelines have been developed to help physicians choose the appropriate reperfusion strategy for patients with STEMI.[7] Although pharmacological and catheter-based strategies may be viewed as separate and competing options in some situations, the coupling of these two strategies is now believed to play a key role in regional STEMI systems in which primary PCI is not applicable.

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FACILITATED PCI

The term *facilitated PCI* denotes a strategy of planned immediate PCI after an initial pharmacological regimen (ie, full-dose fibrinolysis or a platelet glycoprotein IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolytic therapy and a platelet glycoprotein IIb/IIIa inhibitor). Because of the inherent limitations of fibrinolytic therapy and primary PCI, it was suggested that combining the two therapies could provide the speed of pharmacological reperfusion with the more complete and sustained reperfusion provided by PCI. To address the merits of full-dose fibrinolytic-facilitated PCI, the ASSENT-4 trial[8] was designed to compare tenecteplase-facilitated PCI with primary PCI. The primary endpoint in this study was a composite of death, congestive heart failure, or shock within 90 days of randomization. The trial was stopped early, after enrolling 1,667 patients, because of higher in-hospital mortality in the facilitated group than in the standard PCI group. At 90 days, the primary endpoint was measured in 19% of patients assigned to facilitated PCI versus 13% of those assigned to primary PCI (P = .005). In light of these results, the updated 2007

American College of Cardiology/American Heart Association STEMI guidelines gave a class III recommendation for a full-dose fibrinolytic-facilitated PCI strategy.[9]

RESCUE PCI

Rescue PCI is defined as PCI performed for failure of fibrinolytic therapy. Accordingly, patients are reassessed 60 to 90 minutes after initiating fibrinolytic therapy to determine if reperfusion has occurred. A repeat electrocardiogram is used to assess reperfusion: a criterion of < 50% resolution in the lead with previous maximal ST-segment elevation suggests absence of reperfusion. This strategy was recently evaluated in the REACT trial.[10] The primary endpoint in this trial, a composite of death, recurrent myocardial infarction, cerebrovascular event, or severe heart failure at 6 months, was significantly less in patients treated with rescue PCI (5.3% vs 29.8.% among those treated with conservative therapy vs 31% among those treated with repeat fibrinolysis) ($P < .01$).

PHARMACOINVASIVE STRATEGY

Although primary PCI has become the treatment of choice in many urban centers where catheterization facilities are usually available, fibrinolysis remains the treatment of choice in most rural community hospitals because quick access to PCI-capable centers is not usually available. However, fibrinolysis followed by watchful waiting and noninvasive assessment is limited by incomplete reperfusion and reocclusion of the infarct-related artery.[2,11,12]

A strategy of coupling fibrinolytic therapy and early cardiac catheterization was tested several years ago during the era of balloon angioplasty.[13-15] This approach was found to be complicated by increased bleeding, with no apparent clinical benefit compared with fibrinolysis alone, and was then abandoned. Technological advances in coronary angioplasty with the introduction of stents prompted investigators to design trials to re-evaluate the merits of coupling fibrinolysis with an early invasive approach. Seven randomized trials conducted during the era of coronary stenting have reported on the outcomes of combining a pharmacological reperfusion strategy with an early invasive strategy compared to a pharmacological reperfusion strategy followed by either watchful waiting or a late invasive strategy.[16-23] Table 1 describes the pharmacological approach used for each of these trials and their respective primary outcome. The combination strategy used in these trials has led to the term *pharmacoinvasive*, which is now defined as a strategy in which full-dose fibrinolysis, or a combination of reduced-dose fibrinolytic therapy and a platelet glycoprotein IIb/IIIa inhibitor, is given for reperfusion with the intention of performing early (< 24 hours) cardiac catheterization/PCI.

It is important to understand the difference between a pharmacoinvasive strategy and a facilitated PCI strategy. The plan with facilitated PCI is to proceed immediately with intervention after the initiation of pharmacological agents, with the focus on drugs helping with the mechanical intervention. The pharmacoinvasive approach, as currently defined, does not mandate immediate intervention after the initiation of pharmacological reperfusion therapy, and the focus is on the PCI helping the outcomes of the pharmaceutical approach. Among some of the contemporary randomized trials that assessed the pharmacoinvasive approach, the time from administration of drug to catheterization or balloon inflation in the early invasive arm of the study was relatively short, and patients in these trials could be construed as having had facilitated PCI. However, the comparator arm in these trials was not primary PCI, as was the case in the ASSENT-4 trial, but was usual care or delayed intervention after administration of fibrinolytic agents.

The designs of the pharmacoinvasive trials differ. In SIAM III, all patients in the conservative arm were required to undergo coronary angiography before hospital discharge, with intention to perform PCI at that time if needed. In CAPITAL AMI, patients randomized to the pharmacoinvasive arm were taken to the catheterization laboratory immediately and had the shortest time to balloon among the trials (95 minutes). This is in contrast to GRACIA-1, in which the time to angiography was 16.7 hours. The optimal time window for early PCI after fibrinolysis remains to be determined. Also, in GRACIA-1, predischarge revascularization in the conservative group was analyzed as a secondary endpoint because only postdischarge revascularization was regarded as part of the primary endpoint. The only trial that used reduced fibrinolytic therapy plus abciximab as initial pharmacological treatment was the CARESS-in-AMI study. The protocol in TRANSFER AMI and in NORDISTEMI recommended concomitant treatment with clopidogrel at the time of fibrinolysis, which may have improved outcomes in both the pharmacoinvasive and the conservative arms of these trials. Earlier initiation of fibrinolysis could have an impact on events as well; fibrinolysis was initiated in the prehospital setting in 41% of the patients in the WEST trial and in 57% of the patients in the NORDISTEMI trial. Finally, in the NORDISTEMI study, the median transfer distance to PCI was the longest at 158 km (98 miles), and the results provide support for the application of a regional pharmacoinvasive approach for patients living at a far distance from a PCI center.

As depicted in Figure 1, most of the randomized trials evaluating the pharmacoinvasive approach found a significant benefit for patients assigned to the pharmacoinvasive strategy. In the NORDISTEMI trial, the primary endpoint did not reach statistical significance, but the composite of death, reinfarction, or stroke at 12 months was significantly

TABLE 1. CONTEMPORARY PHARMACOINVASIVE TRIALS AND THE RESPECTIVE PRIMARY OUTCOME

Study	Acronym	Recruitment Period	No. of Patients	Agent Used	Time From Fibrinolytic to Cath/PCI in Pharmacoinvasive Arm	Primary Outcome
Southwest German Interventional Study in Acute Myocardial Infarction[22]	SIAM III	1998–2003	163	RPA	3.5 ± 2.3 h[a]	Death, reinfarction, ischemic events, and target lesion revascularization at 6 months
Grupo de Análisis de la Cardiopatía Isquémica Aguda[20]	GRACIA-1	2000–2001	500	rt-PA	16.7 ± 5.6 h[a]	Death, nonfatal reinfarction, or ischemia-induced revascularization at 1 year
Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction[21]	CAPITAL AMI	2001–2004	170	TNK	95 min[b] (73, 106) Randomized to balloon	Death, recurrent myocardial infarction, recurrent unstable ischemia, or stroke at 6 months
Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction[19]	CARESS-in-AMI	2002–2007	600	Half-dose RPA + abciximab	135 min[b] (96–175)	Death, reinfarction, and refractory myocardial ischemia at 30 days
Which Early ST-Elevation Myocardial Infarction Therapy[16]	WEST	2005–2006	204	TNK	295 min	Death, reinfarction, refractory ischemia, congestive heart failure, cardiogenic shock and major ventricular arrhythmia at 30 days
Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction[18]	TRANSFER-AMI	2004–2007	1,059	TNK	2.8 h[b] (2.2–3.8) Randomized to cath	Death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days
Norwegian study on District treatment of ST-Elevation Myocardial Infarction[17]	NORDISTE-MI	2005–2008	276	TNK	130 min[b] (105, 155)	Death, reinfarction, stroke, or new myocardial ischemia at 12 months

Abbreviations: RPA, reteplase; rt-PA, recombinant tissue plasminogen activator; TNK, tenecteplase.
[a]Plus-minus values are means ± SD.
[b]Median and interquartile range.

reduced in the early invasive group compared with the conservative group (6% vs 16%; $P = .01$). Two meta-analyses that evaluated randomized pharmacoinvasive trials have reported that an early invasive strategy after fibrinolytic therapy is associated with significant reductions in mortality and reinfarction.[24,25] These two studies were published before the publication of the results of TRANSFER-AMI and CARESS-in-AMI, which also showed that the pharmacoinvasive strategy reduced ischemic events compared to a conservative approach. The risk of major bleeding was noted to

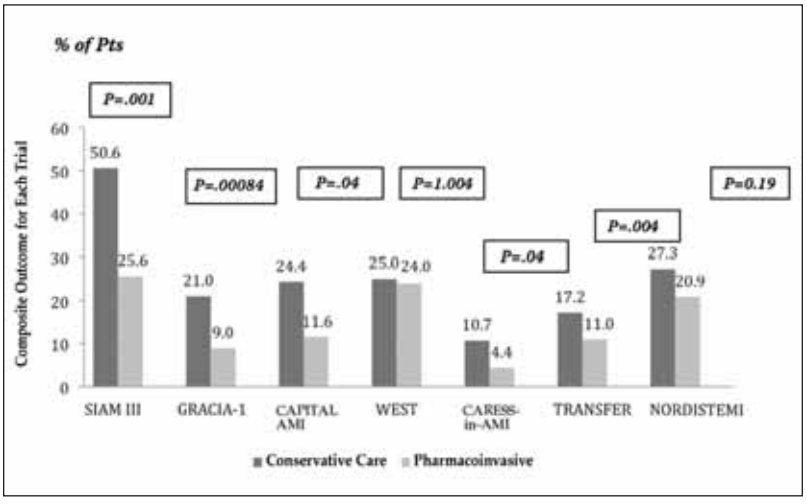

Figure 1. The results of the primary outcome from contemporary randomized trials comparing a pharmacoinvasive strategy with conservative care after initiating fibrinolytic therapy. In these trials, conservative care was defined as either an ischemia-guided or a delayed invasive approach.

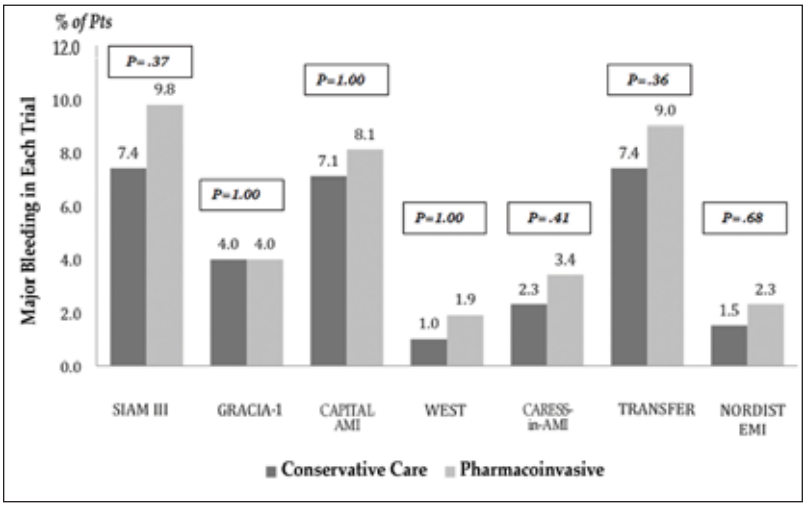

Figure 2. Rates of major bleeding reported in the pharmacoinvasive trials. The definition of major bleeding was trial specific.

be slightly higher with a pharmacoinvasive strategy in some of the trials, but this did not reach statistical significance in any of these trials (Figure 2). Pooling the data from these trials may help further define the risk of bleeding with early angiography after fibrinolytic therapy.

The 2008 European guidelines have recommended that coronary angiography be performed in patients with evidence of reperfusion within 3 to 24 hours after initiation of fibrinolytic therapy regardless of symptoms (grade IIa).[23] The 2009 focus update American College of Cardiology/American Heart Association guidelines on STEMI suggest that it is reasonable for high-risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non-PCI–capable facility to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy (grade IIa).[26] Of note, the 2009 appropriateness criteria for coronary revascularization do not recommend immediate revascularization with either fibrinolytic therapy or primary PCI in patients with STEMI presenting > 12 hours from symptom onset without ongoing symptoms of ischemia or clinical instability. [27] The results of the Occluded Artery Trial (OAT) showed that PCI performed 3 to 28 days after myocardial infarction with occlusion of the infarct-related artery did not reduce the occurrence of death, reinfarction, or heart failure in stable patients.[28] In fact, PCI was associated with a trend toward excess reinfarction during 4 years of follow-up. The results of OAT also suggest that in some patients, delays in performing coronary angiography early after initiating fibrinolytic therapy may compromise the clinical benefits associated with intervention, as demonstrated in the pharmacoinvasive trials.

THE OTTAWA STEMI SYSTEM

There has been increasing interest in developing regional systems that provide optimal reperfusion for STEMI patients. The University of Ottawa Heart Institute is the central cardiac catheterization facility that provides access for PCI for the entire Ottawa region, which has a population greater than 1.2 million. The Ottawa STEMI program has defined two strategic zones based on the likelihood of achieving a door-to-balloon time of < 90 minutes (Figure 3). Patients seen within the inner zone are treated with primary PCI, and patients seen in the outer zone are treated with the pharmacoinvasive approach. This STEMI system has been fully operational since May 2009 and continues to provide for all 16 hospitals within the region.

SUMMARY

Primary PCI is now recognized as the treatment of choice for patients presenting with STEMI when the delay to bal-

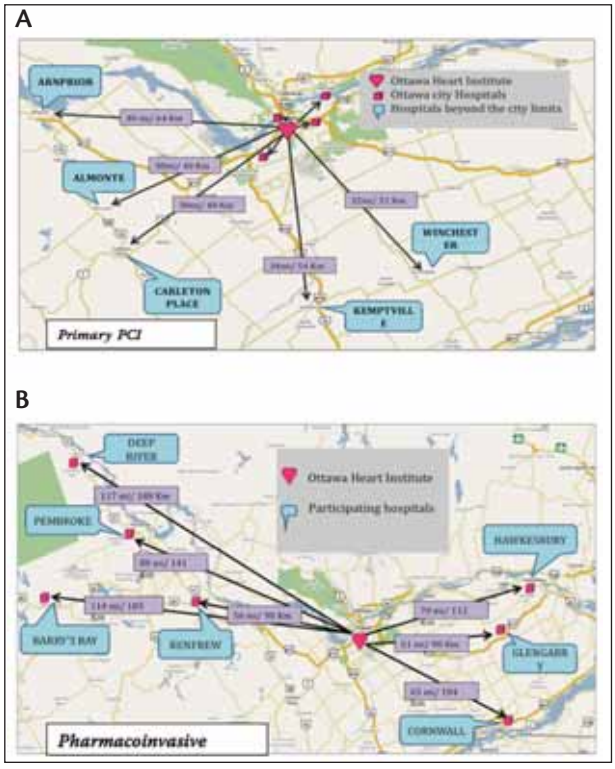

Figure 3. The University of Ottawa Heart Institute regional STEMI program uses two reperfusion strategies. Of the hospitals participating in the primary PCI pathway, the furthest hospital is located at 40 miles from the PCI center (A). Of the hospitals participating in the pharmacoinvasive pathway, the furthest hospital is located at 117 miles from the PCI center (B).

loon is < 90 minutes. When this is not possible, a pharmacoinvasive strategy allows patients to receive an initial therapy with fibrinolytic agents and ensures complete and sustained reperfusion by coupling this therapy with an early invasive approach. STEMI systems are now incorporating these two strategies into practice. ■

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