Reperfusion for ST-Segment Elevation Myocardial Infarction
An Overview of Current Treatment Options
Frans Van de Werf, MD, PhD; Donald S. Baim, MD

A 62-year-old man with no prior cardiac history presented to a local community hospital emergency room at 2 AM with 3 hours of chest pain. Initial examination showed a sinus tachycardia at 110 beats per minute, an arterial blood pressure of 100/70 mm Hg, and bibasilar rales. The ECG showed 5 mm of ST-segment elevation across the anterior precordium. Although the hospital had a diagnostic cardiac catheterization laboratory, it did not perform routine coronary angioplasty. A tertiary hospital that offers round-the-clock primary angioplasty was a 30 minute drive by ground ambulance.

The treatment of ST elevation myocardial infarction (STEMI) has undergone important and continuing evolution over the past several decades. Current practice guidelines recognize the importance of promptly restoring normal epicardial blood flow and myocardial perfusion in the infarct zone.1,2 In principle, any of several reperfusion strategies might be considered for this patient who was in the early hours of an anterior infarction with evidence of hemodynamic compromise, including pharmacological reperfusion therapy in the community hospital, primary percutaneous coronary intervention (PCI, either in the community hospital or by transport to the tertiary care hospital), or combination therapy, with initiation of reduced-dose pharmacological reperfusion therapy in the community hospital, followed by immediate transport to the tertiary care facility for PCI. Because this patient was at high risk (30 day mortality assumed to be >10% given his extensive anterior infarction and elevated Killip class on admission), the approach that gave the highest chance of achieving early and persistent reperfusion with the lowest risk of major complication should be selected. Each of the proposed therapies offers benefits compared with supportive therapy alone, but the choice among them is complex and still evolving.

Pharmacological Reperfusion Treatment
Prospective randomized trials with various thrombolytic agents have shown a clear mortality reduction compared with supportive therapy3 (Figure). The currently preferred fibrinolytic regimens are accelerated infusion of alteplase (up to 100 mg/90 minutes), bolus tenecteplase (30 to 50 mg single bolus according to body weight), or reteplase (two 10 U boluses, 30 minutes apart). They should be combined with aspirin 150 to 325 mg orally and unfractionated heparin (60 U/kg bolus [maximum of 4000 U] followed by 12 U · kg⁻¹ · h⁻¹ [maximum of 1000 U/h]). If tenecteplase is chosen, the low-molecular-weight heparin enoxaparin (30 mg IV bolus followed by 1 mg/kg subcutaneously every 12 hours, with a maximum of 100 mg for the first 2 subcutaneous injections) may be a better antithrombin agent than unfractionated heparin according to the Assessment of the Safety and Efficacy with a New Thrombolytic Regimen (ASSENT-3) results.4 In this patient, the risk of intracranial hemorrhage with any of these treatments would be low (<0.75%) given his relatively young age, the absence of a history of hypertension, and a low blood pressure on admission.

An alternative pharmacological reperfusion therapy would be a reduced (half-dose) lytic therapy in conjunction with a platelet glycoprotein IIb/IIIa antagonist, as tested in the large-scale trials Global Utilization of Streptokinase and tPA for Occluded Arteries V (GUSTO-V) (n=16 588) and ASSENT-3 (n=6095), as well as in several smaller angiographic studies.4–10 Such combination therapy may increase the speed and quality of reperfusion and reduce the incidence of recurrent ischemia (in-hospital reinfarction, recurrent or refractory ischemia, or urgent PCI), but has not been shown
Evolution of treatment strategies for acute STEMI

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Evolution of treatment strategies for acute STEMI.

to reduce mortality and may increase spontaneous bleeding complications, especially in the elderly.

**Primary PCI**

Routine immediate angioplasty does not provide an improved outcome after thrombolytic administration, although its selective use to "rescue" patients with persistent or recurrent ischemia after thrombolytic therapy is common. Emergency PCI without thrombolytic therapy (also known as "primary" PCI), however, has been shown to offer a substantial benefit over thrombolytic therapy in terms of the reliability of reperfusion (95% versus 60% restoration of TIMI 3 flow) and event-free survival. A meta-analysis of these trials showed a reduction in 30-day mortality from 6.5% to 4.4%, and a reduction in stroke from 2% to 0.7%, compared with fibrinolytic therapy. Patients with successful primary PCI and no significant hemodynamic or arrhythmic complications of acute myocardial infarction may be admitted to intermediate care units and discharged as early as 3 days post-MI, with a substantial cost saving and preserved favorable outcome. It should be acknowledged, however, that this conclusion reflects performance by highly experienced operators working in centers committed to primary PCI and delivering rapid (<120 minutes) door-to-balloon times. Expansion of primary PCI to community hospitals, with high quality results, is occurring more frequently. Additionally, it should be pointed out that most of these studies used conventional balloon angioplasty (rather than stenting) and excluded higher risk patients who were not candidates for thrombolytic therapy. To extend these findings into the broadest current practice, several issues must thus be addressed.

**Local Hospital Versus Tertiary Center**

When patients present directly to a tertiary center offering PCI, available data suggest that prompt primary angioplasty constitutes optimal therapy for STEMI within 12 hours of symptom onset. Patients presenting to local community hospitals where PCI is not performed appear to benefit from initial transport or rapid transfer to a tertiary center offering primary PCI compared with those receiving thrombolytic therapy given locally, despite the 60 to 90 minute additional treatment delay relating to organization and execution of transfer, on the basis of the results of the AIR-PAMI, Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis Study (PRAGUE), and DANAMI-2. In the 1572-patient DANAMI-2 trial, 1129 patients presenting to community hospitals were randomly assigned to on-site lytics or transfer to a tertiary hospital for PCI. Those assigned to transfer for PCI showed a comparable benefit in the primary endpoint (death, recurrent infarction, or stroke at 30 days) over those assigned to lytics, as did patients who presented directly to the tertiary hospital (8.5% versus 14.2%, \(P=0.002 \) for community hospitals; 6.7% versus 12.3%, \(P=0.048 \) for tertiary hospitals). Because of rapid movement out of the community hospital and concurrent activation of the tertiary hospital PCI team, delay times between presentation and primary PCI were only modestly prolonged (approximately 110 versus 90 minutes) in the transferred patients.

More recently, some community hospitals having cardiac catheterization facilities (but no elective PCI program) have begun to offer primary PCI for acute MI. Using skilled operators who perform elective PCI in nearby tertiary facilities, such hospitals have demonstrated results that comparable to those obtained by primary PCI in tertiary centers and thus preferable to thrombolytic therapy. The decision between local thrombolytic therapy, local primary PCI, and transfer to a primary angioplasty center therefore depends on distance, anticipated time of transfer, patient condition, local community infrastructure, and physician preference, but generally favors primary PCI when feasible.

**Stent or No Stent**

Superior acute angiographic results, procedural safety, and restenosis rates have made elective stent placement the dominant form of PCI, but it is unclear whether the same situation applies for primary intervention. In fact, some early studies raised concerns about an increased incidence of stent thrombosis, slow flow, and 1-year mortality using primary stenting rather than primary conventional balloon angioplasty. More recently, however, studies such as Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) have failed to demonstrate any increase in complication rates when stents are used, and in fact have shown a significant benefit in terms of early reocclusion and late restenosis in the infarct-related vessel. Current practice thus favors stent implantation during primary intervention.

**Adjunctive Antiplatelet, Antithrombotic, and Thrombolytic Therapy**

Because the precipitating event for acute myocardial infarction is generally thrombus formation on an ulcerated or ruptured plaque, patients undergoing primary angioplasty receive aspirin and heparin as described above. It has been suggested that incremental antiplatelet therapy (ie, glycoprotein IIb/IIIa receptor blockers) might attenuate the formation of a new platelet-rich thrombus and thereby improve the outcome of primary intervention. Trial data on this point are still inconclusive, however, with a mortality benefit of intra-
Procedural abciximab seen only with conventional balloon angioplasty. With stenting, abciximab did decrease the incidence of re-infarction, but it also increased the rate of hemorrhagic complications and provided no benefit with regard to either 1-year mortality or repeat revascularization in the stent arm of the trial.21 Thus, some operators routinely use glycoprotein IIb/IIIa receptor blockers during stenting of acute infarction, whereas other operators reserve these agents for situations in which anatomically imperfect results are obtained (distal dissection, residual thrombus, slow flow).

The issue of full-dose thrombolytic therapy before immediate PCI has been adequately addressed by earlier trials showing a lack of benefit and (in earlier studies) increased major complications. Improved revascularization procedures and sheath management and the use of more fibrin-selective lytic agents and revised antithrombotic co-therapies have reduced the risk of complications of PCI performed in the first hours after the onset of full-dose lytic therapy, but evidence for improved outcomes after thrombolytic pretreatment before PCI is still inconclusive. Several studies suggest that pretreatment does result in a greater incidence of infarct artery patency on initial angiography, but with trends toward increased bleeding complications and no conclusive improvement in PCI success or clinical outcome.22 Additional adequately-powered trials are now in development to evaluate this strategy, but pretreatment is most often used selectively when performance of primary PCI is likely to be delayed by inter-hospital transfer or local logistic considerations.

Role of Thrombus and Embolus Removal

There is no doubt that an underlying thrombus is present in the infarct-related artery in patients with STEMI. Such thrombi can be substantial in size if treatment is delayed or the vessel is of a large caliber. The AngioJet rheolytic thrombectomy catheter (Possis Medical, Minneapolis, Minn) is currently approved for thrombus removal23 and is commonly used in such cases, and other investigational catheters for thrombus removal or ultrasonic dispersion are being developed. Trials of these devices for preemptive mechanical thrombus abatement during acute MI intervention are in their early phases.

A second issue is persistent abnormal myocardial perfusion in about 70% of patients in whom normal epicardial flow is restored. Fragments of thrombus or atherosclerotic plaque may embolize distally during primary PCI and obstruct the distal microcirculation, thereby limiting the clinical benefits of primary PCI. Trials of the Guard Wire embolic protection device (PercuSurge, Sunnyvale, Calif) during saphenous vein graft intervention have shown that distal embolization is ubiquitous and use of the protective device reduces the incidence of major adverse events and improves postintervention antegrade flow.24 A similar benefit has been seen in preliminary registries of acute MI, and a randomized trial is now in progress to evaluate this indication.

The Role of Myocardial Protection

Although β-receptor blockade is an established therapy to decrease myocardial oxygen demand and/or reduce arrhythmic complications of STEMI, the main emphasis in treatment has been on the prompt restoration of myocardial perfusion. Hemodynamic support (eg, intra-aortic balloon counterpulsation) may also be beneficial in large infarctions associated with circulatory compromise, but it has not been shown that routine balloon pumping enhances myocardial protection when used in a routine fashion. In contrast, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial does suggest a survival benefit for patients undergoing coronary intervention,25 further strengthening the argument for primary angioplasty in these high risk patients.

Beyond simple reperfusion, animal data suggest that it may be possible to limit the amount of myocardial damage further during the ischemic and the early reperfusion periods. A variety of pharmacological approaches to prevention of such injury (including vasodilators, adhesion molecule blockers, and inhibitors of complement fractions) has been investigated without showing clear benefit. Recent work with intra-arterial infusion of super-saturated aqueous oxygen during the reperfusion period is of interest,26 as is the induction of moderate systemic hypothermia (33°C) via placement of a venous heat exchange catheter now under evaluation in Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction (COOL-MI) trial.27 Thus, it is likely that the next advances in myocardial recovery will derive from the combination of prompt definitive mechanical revascularization (perhaps in association with catheter thrombectomy and distal embolic protection), optimal adjunctive anticoagulant/antiplatelet therapy, and protection of the reperfused myocardium by advanced drug/reoxygenation/hypothermic intervention.

Evidence-Based Management Recommendation

In summary, available evidence suggests that the patient described above, who presented in the early hours of anterior infarction with evidence of hemodynamic compromise, should have undergone reperfusion. Although clear benefit would have been obtained by thrombolytic administration, ample data point toward a greater benefit from catheter-based intervention (primary angioplasty with stent implantation), either at a qualified community hospital or by transfer to a nearby tertiary center. Hemodynamic support with intra-aortic balloon pumping may be required but should not be performed preemptively. Treatment with platelet glycoprotein IIb/IIIa receptor blockers or partial dose thrombolitics before the primary angioplasty may be used, but definitive trial data regarding their effectiveness are pending. Still newer strategies for thrombus removal, distal embolic protection, and myocardial preservation are enticing, but should be reserved for participants in well-controlled trials.

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