Pharmacoinvasive Therapy
The Future of Treatment for ST-Elevation Myocardial Infarction
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Prompt reperfusion of ischemic myocardium is the major focus of acute treatment of patients with ST-segment elevation myocardial infarction (STEMI). Two reperfusion strategies have been developed: pharmacological and catheter based. Although these two strategies have traditionally been considered distinct and at times competing options, it is likely that care of patients with STEMI will be improved in the future if they are viewed as a single integrated effort at reperfusion.

I. Pharmacological Reperfusion: What Has Been Achieved?
Pharmacological reperfusion therapy has been a major advance in the treatment of STEMI. For almost two decades it has been the cornerstone of the acute treatment of patients presenting early to a hospital or an ambulance service (Figure 1). Although the fibrinolytic agent is the key component of the pharmacological “cocktail” administered, conjunctive antithrombotic agents are of utmost importance for maximizing and maintaining the benefit of dissolving the occlusive coronary artery thrombus.

In the early 1960s and 1970s, several trials evaluated the efficacy of intravenous streptokinase (SK), but results were not convincing because of design flaws (eg, random assignment up to 72 hours after onset of symptoms and low doses of SK infused over several hours). The intracoronary administration of SK first by Chazov et al. and later by Rentrop et al. renewed the interest in fibrinolysis. They formed, together with the angiographic finding by DeWood et al. of a thrombus in the infarct-related arteries in ≥90% of the patients with STEMI, the theoretical basis for the design of large-scale mortality trials.

Establishment of Streptokinase and Aspirin
The first of these trials was the GISSI-I trial (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico), in which 11 712 patients presenting within 12 hours after onset of symptoms were randomly assigned to 1.5 MU SK over a period of 60 minutes or conventional treatment. Of note, concomitant aspirin was given to <15% of the patients, and only ≥20% of the patients received intravenous heparin (with low-dose subcutaneous heparin given to ≥40% of the patients). At 21 days, SK was associated with an 18% reduction in mortality rate (10.7% versus 13%, \(P=0.0002\)), with a greater reduction observed in patients treated early.

In the Second International Study of Infarct Survival (ISIS)-2 study, 17 187 patients were randomized in a 2×2 factorial design, to aspirin (160 mg), SK (1.5 MU over 60 minutes), both, or neither. Each agent alone significantly reduced 35-day mortality rates, with the greatest reduction observed with the combination of SK and aspirin (8% versus 13.2% for placebo, \(P<0.001\)). Also in ISIS-2, the use of heparin was left to the discretion of the investigator and, similar to GISSI-I, ≥24% of the patients were given intravenous heparin (≥40% of the patients received subcutaneous heparin).

Ascent of Fibrin-Specific Plasminogen Activators and Intravenous Heparin
Elucidation of the biochemical mechanisms that regulate physiological fibrinolysis led to the concept of fibrin-selective agents and to the development of recombinant tissue-type plasminogen activator (rt-PA, alteplase). Coronary patency studies indicated a higher efficacy for clot lysis with rt-PA, but two subsequent mega-trials (GISSI-2/International and ISIS-3) failed to show a survival benefit over SK. The absence of early concomitant intravenous heparin and suboptimal dosing of rt-PA (over a period of 3 hours) were put forward as possible explanations for the lack of superiority over SK. The importance of concomitant heparin for maximizing the effect of rt-PA was demonstrated in an angiographic study by the Heparin and Aspirin Reperfusion Therapy (HART) investigators: At angiography performed 7 to 24 hours after rt-PA infusion, 88% of the patients who received concomitant intravenous heparin had a patent vessel versus 52% in those who received aspirin only (\(P=0.0001\)). These results together with the higher patency rates observed with accelerated, front-loaded infusion of rt-PA led to the design of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-I trial and its angiographic substudy. GUSTO-I clearly demonstrated that accelerated infusion of rt-PA with concomitant intravenous heparin is superior to SK with regard to 30-day mortality rates (6.3% versus 7.3%, \(P<0.001\)) and conclusively validated the open-
appears to be mediated by greater myocardial salvage and associated with a lower mortality rate than primary PCI that hours from the onset of symptoms, prehospital fibrinolysis is showed a 17% relative reduction in mortality rates with a greater number of lives could be saved. A meta-analysis could be started at the time of prehospital evaluation, a more specific and more potent anticoagulant and antiplatelet agents.

Convenience of Bolus Lytic Agents

Although accelerated rt-PA induced a significantly higher percentage of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow than SK at 90 minutes (54% versus 30%), brisk, early, and persistent TIMI grade 3 flow is not obtained in many patients.

In principle, there are several ways to improve the benefit of fibrinolytic therapy: earlier start of treatment (eg, prehospital administration), use of plasminogen activators with increased potency for clot lysis, and use of more specific and more potent anticoagulant and antiplatelet agents.

It seems reasonable to expect that if fibrinolytic therapy could be started at the time of prehospital evaluation, a greater number of lives could be saved. A meta-analysis showed a 17% relative reduction in mortality rates with prehospital versus in-hospital fibrinolytic therapy.

Given the importance of time from the onset of symptoms to reperfusion for minimizing infarct size, it is noteworthy that prehospital fibrinolysis may be administered 30 to 40 minutes earlier than in-hospital fibrinolysis, increases the proportion of patients who receive fibrinolysis within 30 minutes from initial contact with the medical system, and increases the number of patients who receive fibrinolysis within the first 2 hours of symptoms. When administered within the first 2 hours from the onset of symptoms, prehospital fibrinolysis is associated with a lower mortality rate than primary PCI that appears to be mediated by greater myocardial salvage and reduction in the development of cardiogenic shock. Several attempts to increase the efficacy of rt-PA and to reduce its plasma clearance (allowing bolus administration and therefore facilitating early, prehospital administration) have been undertaken. Two agents are now available for clinical use: rPA (reteplase) and TNK-tPA (tenecteplase). Both agents failed to reduce 30-day mortality rates and were associated with almost identical intracranial hemorrhage rates when compared with rt-PA in two large mortality trials, GUSTO-III and the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-2). With TNK-tPA, however, a significant reduction in noncerebral bleeding complications and a lower need for blood transfusion were observed.

Combined Use of a Reduced-Dose Fibrinolytic and GP IIb/IIIa Inhibitor

Fibrinolytic agents generate plasmin, which degrades the fibrin component of the clot and exposes the highly active, platelet-rich core. It can be hypothesized that a more potent inhibitor of platelet aggregation, such as a GP IIb/IIIa receptor inhibitor, which inhibits the final common pathway of platelet aggregation, might enhance further clot lysis and prevent additional platelet aggregation on the surface of the clot. Combined use of a GP IIb/IIIa receptor inhibitor with a reduced-dose fibrinolytic was shown to slightly enhance coronary artery patency when compared with full-dose lytic therapy. Furthermore, it can also be hypothesized that by reducing the dose of the fibrinolytic bleeding complications—including intracranial—could be reduced. In a large mortality trial with half-dose rPA (GUSTO-V) and in a moderate-sized trial with half-dose TNK-tPA (ASSENT-3), combination with abciximab failed to show any early or late survival benefit over full-dose lytic therapy. On the contrary, the incidence of major noncerebral bleeding complications increased significantly. The excess of bleeding complications was most pronounced in patients older than 75 years. A beneficial effect, consistently observed in both trials, was a reduction in in-hospital reinfarction an in the need for early PCI. This, however, did not translate into a mortality rate reduction.

Optimal Dose of Heparin and Uncertainties About New Antithrombotic Conjunctive Therapies

Aspirin and unfractionated heparin (UFH) are still the recommended antithrombotic conjunctive therapies for pharmacological reperfusion. There has been considerable debate about the timing and optimal dose of UFH. In the ASSENT-3 trial, a reduced, fully weight-adjusted dose of UFH was given (bolus of 60 U/kg with a maximum of 4000 U to be followed by an infusion of 12 U/kg per hour with a maximum of 1000 U/h) for 24 to 48 hours with early and frequent monitoring of the aPTT (target, 50 to 70 seconds).

This dose, which is now recommended in the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for management of STEMI, was associated with a reduction in major noncerebral bleeding complications when compared with a higher but less weight-adjusted dose of UFH used in the ASSENT-2 trial. Unfortunately, the rate of
intracranial hemorrhage was not reduced by this new dosing regimen.

In phase II studies, low-molecular-weight heparins have been shown to reduce the risk of reocclusion or reinfarction and to increase late patency of the infarct-related vessel.\textsuperscript{32–35} In the ASSENT-3 trial, full-dose TNK-TPA plus enoxaparin (given as an intravenous bolus of 30 mg followed by 1 mg/kg subcutaneously over a period of 12 hours) significantly reduced ischemic complications of STEMI, including reinfarction, without affecting intracranial hemorrhage rates or mortality rates.\textsuperscript{20} There was, however, a moderate increase in noncerebral bleeding complications. In view of the ease of administration and the lack of need for monitoring aPTT, the combination TNK-TPA and enoxaparin was considered to be a very attractive reperfusion strategy. However, in the subsequent ASSENT-3 Plus trial, this combination was associated with an unacceptable excess of cerebral and noncerebral bleeding complications in the elderly.\textsuperscript{20} The ongoing Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment (EXTRACT) trial is reevaluating enoxaparin with different fibrinolytic agents and with a lower dose in patients older than 75 years.

Clopidogrel given in addition to aspirin to patients with unstable angina/non–ST-elevation myocardial infarction (UA/NSTEMI) significantly reduces the risk of cardiovascular death, MI, or stroke. Little is known about the possible benefit (or harm) of clopidogrel in conjunction with fibrinolytic therapy. The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-TIMI 28 trial is currently investigating the efficacy and safety of a loading dose of 300 mg clopidogrel in addition to a fibrinolytic agent, antithrombin, and aspirin in 3000 patients.

II. Catheter-Based Reperfusion

Initial Experience With Balloon Angioplasty

The concept of catheter-based reperfusion for STEMI was introduced in 1979 when Rentrop and colleagues\textsuperscript{36} reported pilot experience with balloon angioplasty to open the occluded infarct artery in 7 patients. When compared with a nonconcurrent control group who did not receive reperfusion therapy, the angioplasty group had improved ventricular function on follow-up angiography.

The field of catheter-based reperfusion for STEMI was subsequently developed through a series of observations reported from multiple centers as well as randomized trials. In view of the evidence of mortality reduction with intravenous fibrinolytic therapy described above, randomized trials of catheter-based reperfusion did not use a placebo-controlled group but instead compared balloon angioplasty with fibrinolytic therapy.\textsuperscript{37–39} These initial trials did not demonstrate a convincing mortality benefit of balloon angioplasty but did suggest that compared with SK or a 3-hour infusion of tPA, balloon angioplasty was associated with improved patency of the infarct artery and fewer episodes of recurrent ischemia and infarction over long-term follow-up.

Several additional trials subsequently compared balloon angioplasty with a variety of fibrinolytic regimens. The collective individual patient data were pooled by the Primary Transluminal Coronary Angioplasty Trialists (PCAT) collaborators\textsuperscript{40} and showed reductions in mortality rates, the composite end point of death/reinfarction, and the rate of hemorrhagic stroke. Important lessons learned from the PCAT analysis were that the relative treatment benefit of balloon angioplasty varied across the trials, the risk profile of the patient, and the thrombolytic comparator. Longer delays to performing angioplasty were associated with a smaller treatment effect.\textsuperscript{40}

The data from trials conducted through the mid-1990s suggested that the major benefits of balloon angioplasty compared with fibrinolytic therapy were related to the higher early recanalization rates of the epicardial infarct artery, lower rates of reocclusion of initially successfully reperfused vessels, and a lower risk of hemorrhagic stroke.\textsuperscript{41} Additional benefits provided by an angiographic approach to patients with STEMI include the hemodynamic and anatomic data provided at the time of catheterization that allowed identification of a low-risk cohort of patients suitable for early discharge.\textsuperscript{42}

Advances in Catheter-Based Reperfusion

Notable advances in the field of mechanical reperfusion came with improvements in angiographic equipment, guide wires, catheters, supportive pharmacological therapy, and stents (Figure 2). No rigorous tests of these advances were undertaken in comparison with fibrinolytic therapy, but a number of trials involving patients with and without STEMI provided useful information that frame current practice as follows:

1. When UFH is used without a GP IIb/IIIa inhibitor, the target ACT is 250 to 300 seconds, but it should be reduced to 200 to 250 seconds when a GP IIb/IIIa inhibitor is administered concurrently to reduce the risk of bleeding.\textsuperscript{43–46}

2. GP IIb/IIIa inhibitors are helpful for reducing recurrent MI and urgent target vessel revascularization; the evidence for their ability to contribute to a reduction in mortality rates is less clear.\textsuperscript{47–51} Abciximab is the best-studied of the GP IIb/IIIa inhibitors; only limited angiographic data are available on the small molecule inhibitors.\textsuperscript{52} It appears helpful to administer abciximab before arrival in the catheterization laboratory so that platelet inhibition has been initiated before coronary instrumentation.\textsuperscript{46,53} Patients with cardiogenic shock appear to have the largest treatment benefit of abciximab with respect to mortality rates, reinfarction, and urgent target vessel revascularization.\textsuperscript{46,54–56}

3. Primary stent implantation is superior to balloon angioplasty alone for reducing the composite end point of death, recurrent MI, and target vessel revascularization, but this is driven entirely by the reduction in target vessel revascularization.\textsuperscript{57}

4. On the basis of a wealth of supportive data from patients with UA/NSTEMI and those undergoing elective stenting, thienopyridines are administered to patients with STEMI who undergo stent implantation.\textsuperscript{58–61}

5. Studies outside the STEMI population have established that drug-eluting stents reduce restenosis and the need for reintervention compared with bare metal stents.\textsuperscript{62} A report from the Ramipril in-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry in Rot-
terdam suggests that drug-eluting stents may be safe and effective in patients with STEMI.63

Can a Primary PCI Strategy Be Adopted in Routine Practice?

Several approaches have been taken to making a PCI strategy more generally available to patients with STEMI. The first involved comparing fibrinolytic therapy administered in a community hospital versus transfer for primary PCI.64–67 The composite end point of death, MI, or disabling stroke is reduced with primary PCI, driven almost entirely by a reduction in recurrent MI.66 Mortality rate is similar with primary PCI when compared with SK for patients presenting within 3 hours of the onset of symptoms but is lower with PCI in those presenting after 3 hours.65 Importantly, in dedicated research systems, especially in certain European countries, transportation of patients with STEMI can be accomplished expeditiously (32 to 48 minutes as in DANish trial in Acute Myocardial Infarction [DANAMI]-2 and PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis [PRAGUE]-2), with a door-to-balloon time of under 30 minutes on arrival at the PCI center. Such rapid implementation of a primary PCI strategy has not been accomplished to date in the United States, where the median time from arrival at the door of a referring hospital to balloon inflation at a PCI center after transfer is 185 minutes.68

Interpretation of studies comparing fibrinolytic therapy with transfer for PCI is complicated because of selection of patients considered safe for transportation, the different fibrinolytics used in the medical treatment comparison arm, and the possibility that the fibrinolytic arm was handicapped by using doses of UFH that are now considered too high.69,70 Also, the detection of recurrent MI is not easily accomplished within the first 24 hours after primary PCI because of elevation of biomarkers from the index event; for this reason, some studies have excluded periprocedural MI from the end point, potentially biasing the results toward primary PCI.69 In DANAMI-2, episodes of recurrent ischemia and infarction in the fibrinolytic arm were treated with repeat fibrinolysis rather than referral for PCI, a treatment strategy that is different from one used in many other centers and that may have skewed the results in favor of primary PCI.

The second approach to broadening the application of PCI for STEMI has been to extend the use of PCI to hospitals without on-site cardiac surgery.71 Observational experiences from several centers have generally reported favorable results, but the potential for case selection must be considered. The Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) trial randomly assigned patients to rt-PA or primary PCI without on-site cardiac surgery.72 At 6 months, the composite end point of death, MI, or stroke occurred in 19.9% of fibrinolytic patients versus 12.4% of patients given PCI (P<0.03); again, the majority of the difference was driven by the rate of recurrent MI, which was exceptionally high in the fibrinolytic therapy era (in-hospital recurrent MI rate, 8.8%). Of note, the majority of C-PORT patients were enrolled during routine working hours. This may have resulted in a falsely optimistic picture because PCI performed outside routine working hours is associated with a lower rate of technical success and a higher mortality rate.73

III. Pharmacoinvasive Therapy: A Tale of Two Treatments Seen as One

The logistic difficulties of implementing primary PCI in routine practice coupled with evidence of benefit of prehospital fibrinolysis (especially if administered early after the onset of symptoms) and the overarching importance of time to reperfusion regardless of strategy used serve as the foundation for developing a unified approach to management of patients with STEMI in the future.21,74–76 More than one decade ago, clinicians were discouraged from proceeding to PCI early after fibrinolysis because of lack of benefit of such a strategy and a trend toward worse outcomes in several trials.77–79 Given the advances in PCI described above and
clinical experience in contemporary practice, early referral for PCI is not only less concerning today but is scientifically appealing. The benefits of the synergy of a pharmacological approach followed by PCI have been described by Dauerman and Sobel.40 Shortening the time to reperfusion of the infarct artery by prompt initiation of pharmacological reperfusion (either before hospitalization or in the Emergency Department of any hospital) followed by early PCI to consolidate the initial reperfusion process and prevent reocclusion of the infarct artery may be the optimal reperfusion strategy for patients with STEMI in the future. Important questions that remain center around the pharmacological regimen to be given before PCI. It is likely that the choice of the regimen will be based on the risk of the STEMI and the patient’s bleeding risk. A proposal for a such a unified pharmacoinvasive approach is illustrated in Figure 3. The ongoing trials Facilitated Intervention with Enhanced reperfusion Speed to Stop Events (FINESSE) and ASSENT 4 PCI probably will provide key data to clarify the risk and benefits of the limbs shown in the figure. In FINESSE, pre-PCI treatment with half-dose recteplase plus abciximab or with abciximab alone will be compared with primary PCI plus procedural abciximab. In ASSENT 4 PCI, patients will be given full-dose tenecteplase before PCI and compared with patients undergoing standard primary PCI with the use of GP IIb/IIIa antagonists left to the discretion of the investigator. Additional research is also needed to determine if a pharmacoinvasive approach should be applied routinely or only in selected patients after fibrinolytic therapy.

Continued investigation into pharmacological and catheter-based interventions that preserve myocardial function is needed to amplify the benefits of a pharmacoinvasive strategy.81–84

References


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