Pharmacologic Reperfusion Strategies for the Treatment of ST-Segment Elevation Myocardial Infarction

John J. Young, MD, Dean J. Kereiakes, MD, FACC

The Lindner Center for Research & Education, Ohio Heart Health Center, Cincinnati, OH

The primary goal of therapy for acute ST-segment elevation myocardial infarction (STEMI) is rapid, complete, and sustained restoration of infarct-related artery (IRA) blood flow. Both pharmacologic and mechanical restoration of antegrade coronary blood flow in patients with STEMI have been demonstrated to improve left ventricular function, to reduce infarct size, and to reduce mortality. The benefits of myocardial reperfusion, including prevention of infarct expansion, reduction of ventricular remodeling, and improvement of electrical stability, are amplified when IRA patency can be achieved quickly after the onset of symptoms, particularly in the first 2 hours—a time window that is particularly challenging for mechanical methods of reperfusion, even at high-volume percutaneous coronary intervention centers. Despite this demonstrated clinical benefit of reperfusion therapy, substantial challenges exist in identifying the precise combination of therapeutic agents and strategies that will maximize patient outcomes. This review focuses on the evolving pharmacologic treatment strategies for STEMI.
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The success of reperfusion therapy in patients with acute myocardial infarction (MI) depends on the ability to achieve complete and timely restoration of antegrade blood flow in the infarct-related artery (IRA). Various pharmacologic and mechanical reperfusion options are available that may differ in their efficacy depending on the time from the onset of symptoms to the initiation of treatment. Reperfusion therapy with fibrinolytics or primary

percutaneous coronary intervention (PCI) has advanced the treatment of ST-segment elevation myocardial infarction (STEMI). A 25% reduction in mortality has been attributed to fibrinolytic therapy.[1] Primary PCI is considered an alternative strategy to fibrinolysis for the treatment of STEMI according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of acute myocardial infarction.[2]

Numerous randomized clinical trials have demonstrated a greater reduction in mortality, recurrent MI, stroke, and intracranial hemorrhage with PCI than with fibrinolysis.[3] The caveat to this conclusion is that these results were obtained in the setting of clinical trials with experienced interventionists at high-volume centers where the cardiac catheterization laboratory is available 24 hours a day.[4-7] Only recently have the time-dependent efficacies for both mechanical and pharmacologic reperfusion strategies been closely scrutinized and relative differences between these treatment modalities become evident. The time from the onset of infarct symptoms to the initiation of reperfusion, particularly with fibrinolysis, is a critical determinant for successful recanalization of the IRA as well as for survival. Remarkably, few patients receive PCI within 2 hours of the onset of symptoms, as recommended by the ACC/AHA guidelines, even in highly experienced centers.[8] Because the vast majority of hospitals lack tertiary, invasive cardiac facilities, most therapeutic strategies for acute MI have focused on evolving pharmacologic reperfusion strategies either alone or in combination with PCI.

Despite the demonstrated clinical benefit of early coronary artery reperfusion with fibrinolytic therapy, there is still great variation in the approach to reperfusion, and a large portion of STEMI patients who are eligible for reperfusion strategies do not receive them. For example, the National Registry of Myocardial Infarction (NRMI) reported that of more than 300,000 patients enrolled into the registry between 1990–1993, only a third received reperfusion therapy, even though one half to two thirds of these patients were eligible for treatment.[9] Similar findings were reported in a 1994–1998 study of 772,531 STEMI patients in which a quarter of those eligible for reperfusion therapy did not receive it.[10] Data collected in the multinational, prospective Global Registry of Acute Coronary Events (GRACE) demonstrated that out of 9251 patients enrolled, 1763 were eligible for reperfusion therapy and, of these, 30% did not receive any type of reperfusion treatment.[11] Despite pharmacologic advances, the proportion of patients with STEMI who receive reperfusion therapy has remained constant at 70% since 1994.[12]

The reasons for the underuse of pharmacologic reperfusion strategies in patients who might benefit from therapy have included undiagnosed/misdiagnosed STEMI and the clinicians' perceptions of contraindications to treatment. Most early clinical trials of chemical reperfusion therapy excluded women and patients older than 70 or 75 years. Women have higher in-hospital death rates than men do, and elderly patients generally have more extensive underlying coronary disease, other preexisting medical conditions, and greater comorbidity than do younger patients. The fear of treatment-related complications with pharmacologic agents has been the overriding reason patients are not prescribed pharmacologic reperfusion therapy.[11] Thus, there is still an opportunity to provide reperfusion therapy to a greater proportion of patients with STEMI and to improve care and clinical outcomes.

Pharmacologic Targets

During the last two decades, fibrinolytic therapy has become the gold standard for the pharmacologic treatment of STEMI. Large, randomized clinical trials have consistently demonstrated a reduction in mortality rates for patients with STEMI who were treated with fibrinolytic therapy. Nevertheless, current fibrinolytic regimens have a number of shortcomings, including the failure to induce early and sustained reperfusion in as many as 40%–50% of patients and the inability to prevent reocclusion in another 10%–20%. Most efforts to improve the clinical results from fibrinolysis have focused on the development of new medications (newer fibrinolytics, anticoagulants, and antiplatelet therapies) to improve early and sustained reperfusion. An increased understanding of the complexity of the vascular biologic process underlying STEMI has contributed to changes in the pharmacologic approach to patients with STEMI.

The process of endothelial disruption that ultimately culminates in thrombotic occlusion of the vessel is a complex interplay between the intrinsic and extrinsic coagulation pathways, thrombin and fibrin generation, platelet activation and aggregation, components of the complement cascade, and intrinsic regulatory factors (such as antithrombin III, heparin, protein-C, protein-S, and α-2 antiplasmin) that all influence the final biological outcome (Figure 1).[13] This complex, triggered, vascular biologic cascade affects the entire coronary vascular bed (epicardial vessels and microvasculature), including non-IRA vessels.

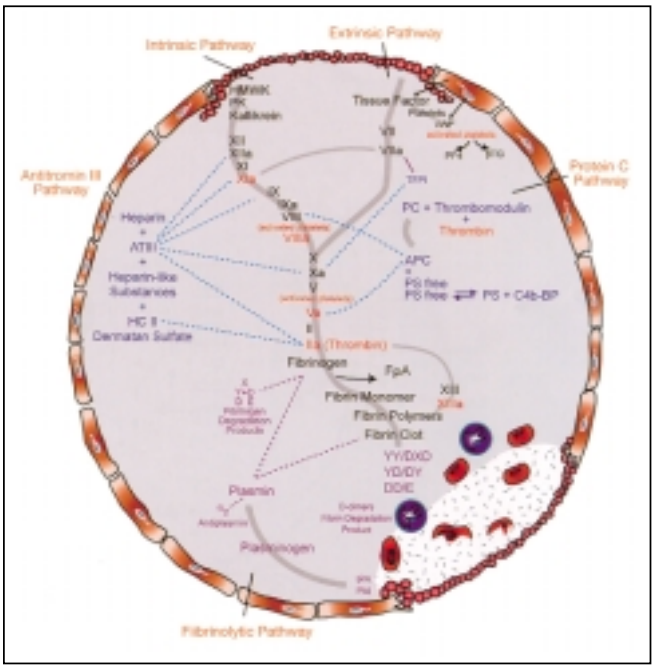


Figure 1. *A schematic diagram of the coagulation cascade as it works within an artery. The lower right part of the drawing depicts the generation of a fibrin clot. HMWK, high molecular-weight kallikrein; PK, proteinase K; vWF, von Willebrand factor; PF4, platelet factor 4; ßTG, beta thromboglobulin; PC, protein C; TFPI, tissue factor proteinase inhibitor; APC, activated protein C; ATIII, antithrombin III; HC, heparin cofactor; PS, protein S; C4b-BP, complement factor 4 binding protein; FpA, fibrinopeptide A; tPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor; YY/DD, YD/DY, DD/E, fibrin degradation products. Reproduced with permission from Callahan et al.*[13]

With the primacy of platelets and thrombin in this cascade of events, newer sites of potential pharmacologic intervention have been targeted (Figure 2).

Fibrinolytic Therapy

The initial description of fibrinolytic therapy for STEMI involved intracoronary administration of streptokinase (SK). SK is a nonenzymatic protein produced by group C β-hemolytic streptococci that induces fibrinolysis through the formation of an activator complex with plasminogen. Thus, SK acts indirectly through this complex to cleave plasminogen, with the resultant formation of plasmin that consequently degrades fibrin and fibrinogen as well as procoagulant factors V and VIII.[14] The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial and the Second International Study on Infarct Survival (ISIS)-2 demonstrated that the intravenous administration of SK for evolving MI reduced mortality when compared to standard (no SK) therapy.[15,16] The next generation fibrinolytic agents were designed to have a more rapid onset of action to establish earlier patency, as well as a longer half-life to facilitate bolus administration, and greater fibrin-specificity to minimize bleeding complications.

Clinical Trials of the Newer Fibrinolytic Agents

The potential for improved survival with the newer fibrinolytic agents was suggested by the first Thrombolysis in Myocardial Infarction (TIMI) trial, which demonstrated a 60% IRA patency rate in patients randomly allocated to receive alteplase compared with a 35% rate in those allocated to receive SK.[17] The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial randomly allocated 41,021 patients with STEMI to either front-loaded alteplase (15 mg bolus, followed by infusion of 0.75 mg/kg for 30 minutes, then 0.5 mg/kg for 60 minutes); SK (1.5 million U, with either intravenous or subcutaneous heparin); or alteplase (1.0 mg/kg infusion for 60 minutes) plus SK (1.0 million U).[18] In addition to demonstrating a greater reduction in mortality with front-loaded alteplase than with SK or the combination of SK and alteplase, this study provided further insights into the importance of time-to-treatment and the link between IRA patency, preservation of ventricular function, and reduction in mortality. Patients treated within the first 2 hours of the onset of symptoms experienced a lower 30-day mortality rate (5.5%) compared with those treated after 4 hours (9.0%).[18] In a post hoc analysis, this difference

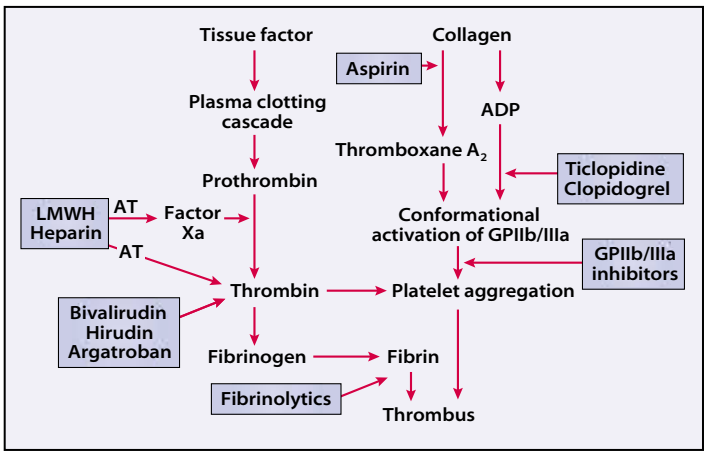


Figure 2. *Simplified coagulation cascade, fibrin generation, platelet aggregation, and ultimate thrombus formation along with sites of antithrombotic and antiplatelet drug action. ADP, adenosine diphosphate; LMWH, low molecular weight heparin; AT, antithrombin; GP IIb/IIIa, glycoprotein IIb/IIIa.*

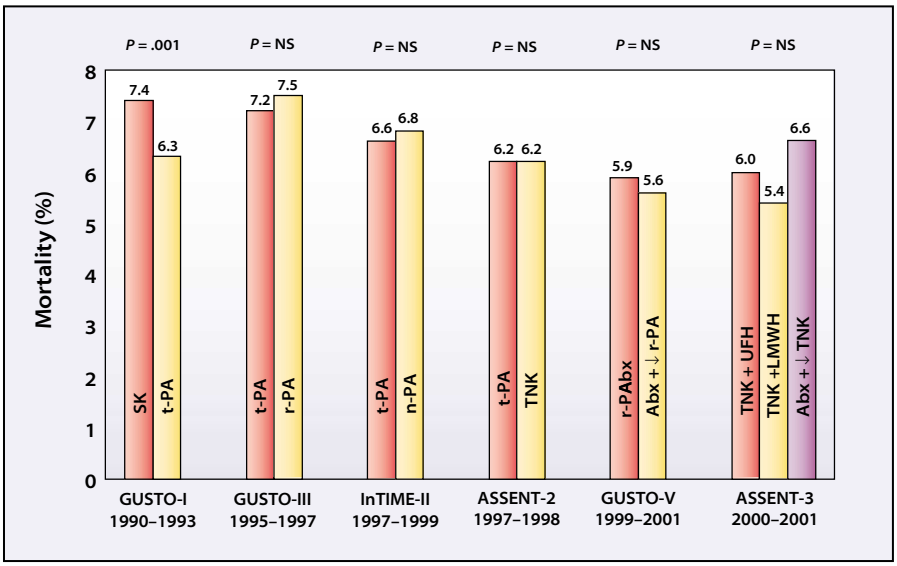


Figure 3. *Rates of 30-day mortality in the major trials of fibrinolytic therapy in patients with ST-segment myocardial infarction (STEMI). NS, not significant; SK, streptokinase; t-PA, alteplase; r-PA, reteplase; n-PA, lanoteplase; TNK, tenecteplase; Abx, abciximab; UFH, unfractionated heparin; LMWH, low molecular weight heparin; GUSTO-I, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GUSTO-III and V, Global Use of Strategies to Open Occluded Coronary Arteries; InTIME-II, Intravenous n-PA for the Treatment of Infarcting Myocardium Early; ASSENT-2 and 3, Assessment of the Safety and Efficacy of a New Thrombolytic. Data from GUSTO Investigators,[18] GUSTO III Investigators,[23] InTIME-II Investigators,[24] ASSENT-2 Investigators,[25] Topol and The GUSTO V Investigators,[43] and ASSENT-3 Investigators.[45]*

equated to a 1.0% increase in mortality with each additional hour of delay between the onset of symptoms and initiation of treatment. This association was confirmed by a meta-analysis that demonstrated that the greatest reduction in mortality was associated with treatment within the first hour after the onset of symptoms.[1] Furthermore, as demonstrated in the angiographic substudy of GUSTO-1, the reduction in mortality was dependent on early restoration of IRA patency, and 90-minute TIMI coronary flow grades were correlated with 30-day mortality. Those patients who achieved TIMI 3 (normal) epicardial flow at 90 minutes had a mortality of only 4.0% compared to patients who had TIMI 2 (diminished/delayed contrast enhancement) or TIMI 0–1 (no contrast enhancement) flow grades (7.9% and 9.2%, respectively; $P = .007$).[19] These important observations have driven the development of novel fibrinolytic agents aimed at enabling administration of bolus doses to facilitate therapy and achieve a greater rate of successful IRA reperfusion.

Modifications of Fibrinolytic Agents

Molecular modification of the recombinant tissue plasminogen activator (rt-PA) has provided agents such as reteplase and tenecteplase with characteristics that include longer plasma half-lives, regimens of single- or double-bolus dosing, and variable levels of fibrin specificity. For example, a lower fibrin affinity is thought to provide reteplase with greater clot penetration and to simplify administration (versus alteplase) because a weight adjustment is not required. Three point mutations in the alteplase molecule led to the development of tenecteplase, which has a 14-fold greater fibrin specificity and an increase in plasminogen activator inhibitor (PAI)-1 resistance. However, the theoretical advantage of improved safety with more fibrin-specific agents resulting from a lesser degree of systemic fibrinolysis has not been borne out by large clinical trials. New data suggest that bleeding associated with fibrin-specific plasminogen activators may reflect a novel mechanism by which these agents generate systemic plasmin.[20-22] Each fibrinolytic agent generates a unique profile of fibrin-degradation products that can generate systemic plasmin or contribute to the destabilization of normal hemostatic plugs in the circulation, rendering them susceptible to lysis.[20-22] Thus, the ideal fibrinolytic agent would be fibrin-specific, with a relatively short half-life to minimize the generation of fibrin-degradation products that persist in the circulation and have the potential to cause systemic bleeding. These concepts may help explain the apparent paradox of fewer bleeding complications being observed with less–fibrin-specific agents in comparison to more–fibrin-specific fibrinolytics with longer half-lives.

In the GUSTO-I trial, patients treated within the first 2 hours of the onset of symptoms experienced a lower 30-day mortality rate (5.5%) compared with those treated after 4 hours (9.0%). In a post hoc analysis, this difference equated to a 1.0% increase in mortality with each additional hour of delay between the onset of symptoms and initiation of treatment.

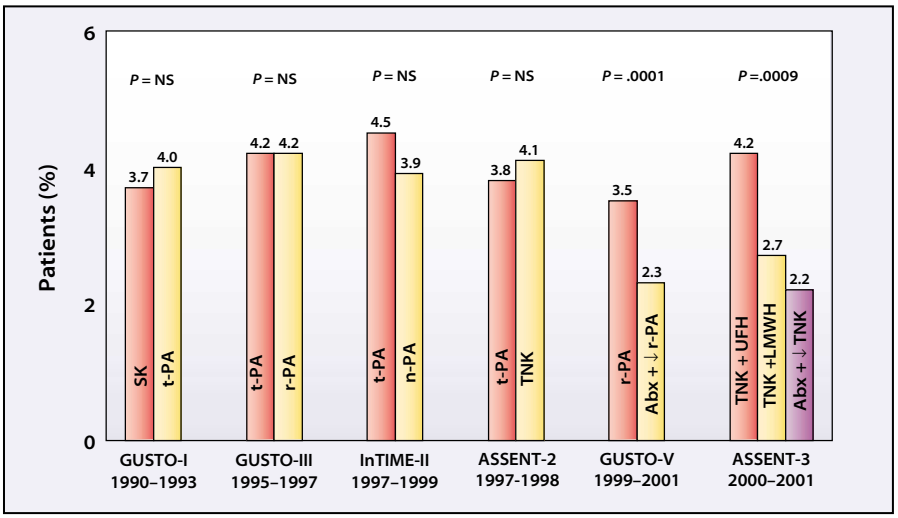


Figure 4. *Rates of in-hospital reinfarction in the major trials of fibrinolytic therapy in patients with ST-segment myocardial infarction (STEMI). NS, not significant; SK, streptokinase; t-PA, alteplase; r-PA, reteplase; n-PA, lanoteplase; TNK, tenecteplase; Abx, abciximab; UFH, unfractionated heparin; LMWH, low molecular weight heparin; GUSTO-I, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GUSTO-III and V, Global Use of Strategies to Open Occluded Coronary Arteries; InTIME-II, Intravenous n-PA for the Treatment of Infarcting Myocardium Early; ASSENT-2 and 3, Assessment of the Safety and Efficacy of a New Thrombolytic. Data from GUSTO Investigators,[18] GUSTO III Investigators,[23] InTIME-II Investigators,[24] ASSENT-2 Investigators,[25] Topol and The GUSTO V Investigators,[43] and ASSENT-3 Investigators.[45]*

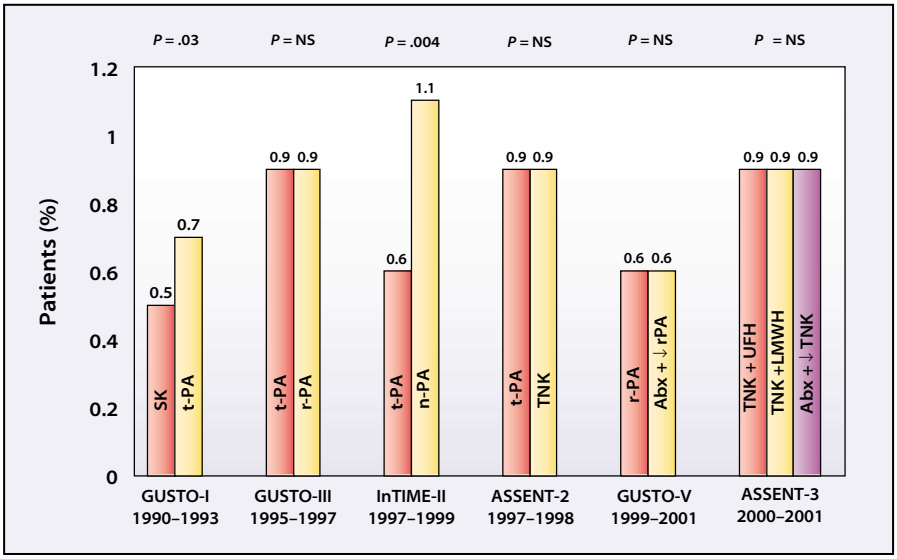
Results of Clinical Trials of Modified Fibrinolytic Agents

Although the bioengineering of fibrinolytic agents led to more favorable pharmacologic characteristics, improvements in 30-day mortality rates have not been observed in phase-III clinical trials (Figure 3). The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-III study was designed to test the superiority of reteplase over accelerated alteplase. This randomized comparison of double-bolus reteplase (10 U plus 10 U after 30 minutes) and accelerated alteplase (15 mg bolus, followed by infusion of 0.75 mg/kg over 30 minutes, then an infusion of 0.5 mg/kg over the next 60 minutes) among 15,059 patients demonstrated no improvement in 30-day mortality (reteplase, 7.47%; alteplase, 7.24%; P = .54) or in 1-year mortality (11.21% vs 11.0%, respectively).[23] The rates of intracranial hemorrhage (ICH), bleeding, and reinfarction were all similar between the reteplase and alteplase groups (see Figure 4 and Figure 5).

The Intravenous n-PA for the Treatment of Infarcting Myocardium Early (InTIME)-II trial enrolled 15,078 patients randomized to lanoteplase 120 U/kg single bolus or front-loaded alteplase in a study designed to test the equivalence of these treatments.[24] At 30 days, the mortality rate was similar (lanoteplase, 6.75%; alteplase, 6.61%) although a significant increase in ICH was observed with lanoteplase (1.12% vs alteplase, 0.64%; P = .004).

The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-2 trial evaluated 16,949 patients presenting with STEMI of less than 6 hours duration and compared a single-bolus injection of tenecteplase (30 mg–50 mg according to body weight) with accelerated alteplase. Similar rates of 30-day mortality (tenecteplase, 6.18%; alteplase, 6.15%) and ICH (tenecteplase, 0.93%; alteplase, 0.94%) were observed between the two treatment groups.[25] Thus, the cumulative results of the GUSTO-III, InTIME-II, and ASSENT-2 trials demonstrated a "therapeutic

Figure 5. *Rates of intracranial hemorrhage (ICH) in the major trials of fibrinolytic therapy in patients with ST-segment myocardial infarction (STEMI). NS, not significant; SK, streptokinase; t-PA, alteplase; r-PA, reteplase; n-PA, lanoteplase; TNK, tenecteplase; Abx, abciximab; UFH, unfractionated heparin; LMWH, low molecular weight heparin; GUSTO-I, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GUSTO-III and V, Global Use of Strategies to Open Occluded Coronary Arteries; InTIME-II, Intravenous n-PA for the Treatment of Infarcting Myocardium Early; ASSENT-2 and 3, Assessment of the Safety and Efficacy of a New Thrombolytic. Data from GUSTO Investigators,[18] GUSTO III Investigators,[23] InTIME-II Investigators,[24] ASSENT-2 Investigators,[25] Topol and The GUSTO V Investigators,[43] and ASSENT-3 Investigators.[45]*



ceiling" for survival benefit to be derived from fibrinolytic monotherapy and set the stage for continued evolution in other adjunctive anticoagulant and antiplatelet reperfusion strategies for STEMI.

Combination Therapy

Limitations of Fibrinolytic Monotherapy

The goals of any coronary reperfusion strategy are to restore flow in the epicardial vessel and to return effective oxygen delivery to the cardiac myocytes, which are ultimately supplied by the coronary microvasculature. Unfortunately, with fibrinolysis as monotherapy, the goal of rapid, complete, and sustained restoration of infarct vessel patency with adequate tissue level perfusion is achieved in only a small number of patients. Several aspects of fibrinolytic therapy are known to compromise its efficacy. First, it is known from phase II angiographic studies that even newer fibrinolytic regimens are unable to provide complete restoration of normal epicardial flow (TIMI 3) in up to 30% to 50% of treated patients.[26] Furthermore, among patients achieving normal TIMI grade 3 flow in the epicardial IRA, myocardial contrast echocardiography studies have documented abnormal myocardial perfusion in 16% to 30% of patients that correlates with a subsequent reduction in myocardial recovery and ejection fraction as well as an increase in adverse clinical events.[27,28] Factors that contribute to abnormal microvascular perfusion include distal embolization of atherothrombotic debris from the upstream epicardial lesion and local responses to cellular ischemia, including endothelial-cell swelling and leukocyte accumulation leading to reperfusion injury.

TIMI Myocardial Perfusion Grade

The TIMI study group reported the inverse relationship between epicardial coronary flow grade and mortality following administration of fibrinolytic therapy and demonstrated the lowest mortality for those patients with normal (TIMI 3) flow.[17,18,29] In addition, a newer angiographic method for grading myocardial reperfusion, the TIMI myocardial perfusion grade (TMPG), has been demonstrated to correlate more closely with mortality after fibrinolytic therapy.[30] The TMPG assesses filling and clearance of contrast in the myocardium as a marker of tissue-level perfusion in the distribution of the IRA. TMPG grade 0 is defined as no myocardial blush; TMPG 1 indicates the presence of myocardial blush, but no clearance from the microvasculature; in TMPG 2, the myocardial blush clears slowly; and in TMPG 3, the normal clearing of myocardial blush occurs. Both epicardial flow grade (TIMI flow) and tissue-level perfusion (TMPG) at 90 minutes after fibrinolytic administration are directly and independently associated with improved 2-year survival, suggesting complementary mechanisms of action.[31]

In a recent cohort of patients undergoing PCI within 24 hours of the onset of an acute MI, abnormal myocardial perfusion, as assessed by TMPG, was present in 72.1% of the patients following PCI, even though TIMI 3 IRA flow had been restored in 94.2% of the patients.[32] Further, despite the fact that normal TIMI 3 IRA flow had been restored, subsequent survival was strongly correlated with the associated TMPG (1-year mortality of 6.8% in patients with TMPG 3 vs 18.3% in those with TMPG 0; $P = .004$).[32] Thus, even though brisk antegrade epicardial IRA flow had been restored by mechanical reperfusion in patients with an evolving MI, angiographic evidence of normal tissue-level perfusion was achieved in only a minority of patients; additional therapeutic strategies appear needed to improve overall reperfusion.

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The Role of Platelet Aggregation in STEMI

The recognition of the pivotal role of platelets in the pathophysiology of STEMI has further improved our understanding of the limitations of fibrinolytic monotherapy. Proposed mechanisms for fibrinolytic resistance include incomplete clot dissolution resulting from the action of fibrinolytic agents on only one component of the clot; release of PAI-1 and α-2 antiplasmin; vasoconstriction resulting from platelet-derived thromboxane A_2; enhanced fibrin activation by exposure of clot-bound thrombin; and the direct platelet-activating effect of fibrinolytics.[33] The glycoprotein (GP) IIb/IIIa receptor is the final common pathway for platelet aggregation, regardless of the agonist responsible for initiating platelet activation. Agents that specifically antagonize fibrinogen binding by the GP IIb/IIIa receptor have been developed in an effort to improve the efficacy of treatment options in patients with acute coronary syndromes (ACS) and to reduce acute complications associated with

PCI.[34] The rationale for combining fibrinolytic therapy with potent platelet receptor inhibition by GP IIb/IIIa antagonists derives from interest in targeting other clot components including fibrin, thrombin, and activated platelets. By blocking the final common pathway of platelet aggregation, GP IIb/IIIa receptor inhibition may contribute to disaggregation of platelet-rich thrombus and may limit platelet-leukocyte interactions in the distal microvasculature. Thus, by targeting separate components of the arterial thrombosis process (fibrin, thrombin formation, and platelet aggregation) a combined pharmacologic reperfusion strategy may prove synergistic, thus enabling more rapid restoration of epicardial blood flow, reducing recurrent thrombosis and distal embolization, and providing a more favorable microenvironment for early PCI.

GP IIb/IIIa Receptor Inhibition as Adjunctive Pharmacotherapy

Several studies of patients with STEMI have examined the role of GP IIb/IIIa receptor inhibition as adjunctive pharmacotherapy for primary PCI.[35-37] Abciximab has demonstrated a consistent reduction in the composite end point of death, recurrent MI, or urgent target-vessel revascularization compared to placebo, and stenting with abciximab has been associated with improved recovery of microvascular function.[38] Three small angiographic studies have assessed the effect of abciximab alone on restoration of IRA patency during STEMI. In the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) trial, TIMI 3 IRA flow was achieved in 18% of the patients 45 minutes following the administration of abciximab.[39] Similar observations were made in the abciximab-only treatment arms of both the Strategies for Patency Enhancement in the Emergency Department (SPEED) trial (TIMI 3 flow in 27% of the patients at 60–90 minutes) and the TIMI-14 trial (TIMI 3 flow in 32% of the patients at 90 minutes).[40,41] Interestingly, there appears to have been a time dependency for achieving TIMI 3 flow after abciximab was given in these studies (increased TIMI 3 flow rate with increasing duration of time following abciximab administration), with an overall composite TIMI 3 flow of 23%. This exceeds the 10% TIMI 3 flow rate previously observed following standard medical therapy (heparin, aspirin, nitrates, and β-blockade) in the GUSTO-IIb study.[42] The initial experience with GP IIb/IIIa antagonists suggested the potential for improved IRA patency when these agents were combined with fibrinolytic therapy. These preliminary studies set the stage for trials of a combination of reduced-dose fibrinolytics and GP IIb/IIIa inhibitor therapy.

Clinical Trials of Combination Therapy

The SPEED trial. In the SPEED trial, the combination of standard-dose abciximab (a 0.25 mg/kg bolus and 0.125 mg/kg infusion) with half-dose reteplase (5 U plus 5 U 30 minutes later) was compared with standard-dose reteplase (10 U plus 10 U 30 minutes later) in 528 patients with STEMI.[40] The utility of early PCI was evaluated in a subset of 323 patients who underwent planned initial angiography at a median of 62 minutes after the initiation of reperfusion therapy. Patients receiving the combination of abciximab and half-dose reteplase had the highest IRA TIMI 3 flow rates (54%) at 60–90 minutes. A trend toward improved 30-day clinical outcomes was observed in the patients who received combination therapy.

The TIMI-14 trial. The TIMI-14 study randomized a total of 888 patients who presented with STEMI to either 100 mg of accelerated-dose alteplase alone (control), standard-dose abciximab alone, or seven escalating doses of alteplase (20 mg–65 mg) or streptokinase (500,000 U –1.5 million U) combined with abciximab.[41] A greater TIMI 3 flow rate was observed in the abciximab plus reduced-dose alteplase group compared with the alteplase-only (control) group at both 60 minutes (72% vs 43%, respectively; $P = .0009$) and 90 minutes (77% vs 62%, respectively; $P = .02$).[41] The overall rate of ICH was 1.1% in the abciximab plus reduced-dose alteplase with low-dose heparin group.

The GUSTO-V trial. Subsequently, two phase III trials were completed that evaluated the safety and efficacy of combination therapy. These trials were designed to determine whether the addition of a platelet GP IIb/IIIa inhibitor would reduce mortality more than fibrinolytic monotherapy would in patients with STEMI. The GUSTO-V trial was an international, randomized, open-label study that examined mortality in patients with STEMI who were randomly allocated to receive either conventional-dose reteplase and weight-adjusted heparin or a combination of half-dose reteplase plus standard-dose abciximab and reduced-dose heparin.[43] This trial enrolled 16,588 patients within 6 hours of evolving STEMI and had a primary end point of all-cause mortality to 30 days. Secondary end points included clinical and safety events to 30 days, composite 30-day mortality and nonfatal stroke, reinfarction, complications of MI, and mortality at 1 year. Patients received either half-dose reteplase (a 5 U bolus plus a 5 U bolus 30 minutes later) combined with standard-dose abciximab or standard-dose reteplase

(a 10 U bolus plus a 10 U bolus 30 minutes later). Patients who were randomized to half-dose reteplase plus abciximab received a reduced-dose regimen of heparin (a 60 U/kg bolus and infusion of 7 U/kg/h), whereas patients receiving standard-dose reteplase received a 5000 U bolus of heparin followed by a weight-based infusion (1000 U/h for ≥80 kg; 800 U/h for <80 kg).

As shown in Figure 3, at 30 days, all-cause mortality was 5.9% for the reteplase group compared with 5.6% for the combined reteplase and abciximab group (P = .43).[43] Thus, with respect to the primary endpoint of mortality, combination therapy was not superior to conventional fibrinolytic therapy. However, the non-inferiority of this combination strategy was established by prespecified criteria. Combination therapy did significantly reduce ischemic complications of STEMI, showing lower rates of reinfarction at 7 days (3.5% vs 2.3%; P = .0001) (see Figure 4), less need for early (<6 hours) PCI (8.6% vs 5.6%; P = .0001), and less need for urgent PCI within 7 days (14.0% vs 10.4%; P <.001) compared with fibrinolytic monotherapy, respectively.[43] Patients in the combination of abciximab plus reteplase group experienced more nonintracranial bleeding complications than did those who received reteplase alone (13.7% vs 24.6%; P <.001), whereas rates of ICH, nonfatal strokes, and total strokes were similar between the two treatment groups (see Figure 5). At the 1-year follow-up, all-cause mortality was identical (8.38%) in the group given reteplase only and in the group receiving the combination of half-dose reteplase plus abciximab.[44]

The ASSENT-3 trial. The ASSENT-3 trial was a multicenter, randomized study of 6095 patients with STEMI who were randomly assigned to one of three treatment regimens: full-dose tenecteplase and enoxaparin, half-dose tenecteplase plus standard-dose abciximab in combination with weight-adjusted low-dose unfractionated heparin (UFH), or full-dose tenecteplase with weight-adjusted UFH.[45] The primary end points were the composite occurrence of mortality, in-hospital reinfarction, or in-hospital refractory ischemia (efficacy end point), as well as the combination of this efficacy end point plus in-hospital ICH or major bleeding complications (efficacy plus safety end point) to 30 days. Patients received either a body weight-adjusted single bolus of tenecteplase (35 mg–50 mg) with enoxaparin (a 30 mg IV bolus, then 1 mg/kg q 12 h subcutaneously), or half-dose tenecteplase (15 mg–25 mg) with standard-dose abciximab plus low-dose UFH (a 40 U/kg bolus and 7 U/kg/h infusion), or a single bolus of tenecteplase plus weight-adjusted UFH (a 60 U/kg bolus and 12 U/kg/h infusion).

The patients treated with full-dose tenecteplase plus UFH had a significantly higher composite occurrence of mortality, in-hospital reinfarction, or refractory ischemia to 30 days (15.4%) compared with patients treated with tenecteplase plus enoxaparin (11.4%; P = .0002) or tenecteplase plus abciximab (11.1%; P <.0001).[45] A similar magnitude of benefit in favor of combination therapy was observed for the composite end point of efficacy plus safety: 17.0% in tenecteplase/UFH patients versus 13.7% in tenecteplase/enoxaparin patients (P = .0037) versus 14.2% in tenecteplase/abciximab patients (P = .014).[45] The occurrence of in-hospital ICH was comparable for the three treatment arms. Similar to the GUSTO-V trial, there was a reduction in ischemic adverse outcomes in both the tenecteplase plus enoxaparin and abciximab groups (see Figures 3–5). These studies illustrate the potential clinical benefit for low molecular weight heparin (LMWH) when it is employed as adjunctive pharmacotherapy with fibrinolysis for the treatment of acute MI.

The ENTIRE-TIMI 23 trial. LMWHs offer multiple therapeutic advantages over UFH and have been demonstrated equivalence or superiority to UFH in the treatment of ACS.[46] The relative ease of administration and lack of obligatory monitoring make LMWHs an attractive alternative anticoagulant to use in combination with fibrinolytic therapy. The ASSENT-3 trial demonstrated the safety and efficacy of combining a fibrinolytic agent with enoxaparin versus UFH. The Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation MI (ENTIRE-TIMI)-23 trial evaluated enoxaparin in combination with standard-dose tenecteplase compared with half-dose tenecteplase in combination with abciximab in 483 patients with STEMI.[47] Patients were randomly assigned to standard-dose tenecteplase in combination with either UFH (a 60 U/kg bolus and 12 U/kg/h infusion) or enoxaparin (a 30 mg IV bolus and 1.0 mg/kg q 12 h subcutaneously), or half-dose tenecteplase in combination with standard-dose abciximab and either UFH (a 40 U/kg bolus and 7 U/kg/h infusion) or enoxaparin (a 30 mg IV bolus and 0.3 to 0.75 mg/kg q 12 h subcutaneously). Following the administration of full-dose tenecteplase, the TIMI 3 flow grade at 60 minutes was 52% in UFH-treated patients versus 48%–51% in enoxaparin-treated patients (Figure 6). After therapy with the combination of tenecteplase plus abciximab, the TIMI 3 flow grade at

60 minutes was 48% in UFH-treated patients and 47%–58% in enoxaparin-treated patients.

Through 30 days, the composite end point of death or MI was observed in 15.9% of the patients who received tenecteplase in combination with UFH and 4.4% of the patients who received tenecteplase in combination with enoxaparin (P = .005).[47] This benefit was largely secondary to a reduction in the rate of nonfatal reinfarction. In the group taking the combination of tenecteplase plus abciximab, the composite of death/MI occurred in 6.5% of UFH- and 5.5% of enoxaparin-treated patients. Major hemorrhage with full-dose tenecteplase was observed in 2.4% of UFH- and 1.9% of enoxaparin-treated patients. Conversely, during combined therapy with tenecteplase plus abciximab, major hemorrhage was observed in 5.2% of UFH- and 8.5% of enoxaparin-treated patients. Treatment with tenecteplase plus abciximab was associated with a trend toward more complete ST-segment resolution at 180 minutes, regardless of the concomitant antithrombin administered (see Figure 6). The results of ENTIRE-TIMI 23 and ASSENT-3 suggest that enoxaparin is a potential replacement for UFH in multiple pharmacologic reperfusion strategies for STEMI.

Regimen	TIMI 3 at 60 min	ST-segment resolution at 180 min	Death/MI at 30 d	Major bleeding
TNK + UFH	52.0%	38.0%	15.9%	2.4%
TNK + enox	48.0%–51.0%	46.0%	4.4%	1.9%
↓ TNK + abx + UFH	48.0%	52.0%	6.5%	5.2%
↓ TNK + abx	47.0%–58.0%	55.0%	5.5%	8.5%

Figure 6. *Rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, ST-segment resolution, death or myocardial infarction (MI) to 30 days, and major bleeding in the Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation MI (ENTIRE-TIMI)-23 trial (N = 483). TNK, tenecteplase; UFH, unfractionated heparin; enox, enoxaparin; abx, abciximab. Data from Antman et al.*[47]

The results of ENTIRE-TIMI 23 and ASSENT-3 suggest that enoxaparin is a potential replacement for UFH in multiple pharmacologic reperfusion strategies for STEMI.

Oral Antiplatelet Therapy

Adjunctive antiplatelet therapy reduces ischemic complications in patients with ACS. Aspirin provides effective benefit in the treatment of evolving MI by irreversibly inhibiting platelet cyclo-oxygenase activity and the generation of thromboxane A_2. Recent clinical trials utilizing the platelet adenosine diphosphate (ADP) receptor antagonist clopidogrel in combination with aspirin have demonstrated clinical benefit with dual, oral, antiplatelet therapy for both non-STEMI and PCI.[48,49] In addition, pretreatment with clopidogrel at least 6 hours before PCI provided clinical benefit in reducing the composite risk of death, MI, or urgent revascularization to 28 days. Moreover, long-term (12 months) clopidogrel therapy conferred an additional 26.9% relative reduction in the occurrence of death, MI, or stroke following PCI, compared with patients who received clopidogrel for only 30 days.[50] Based on these data, there is increasing interest in dual, oral, antiplatelet therapy for patients with STEMI.

Two ongoing studies are evaluating the role of clopidogrel in the treatment of patients with acute MI. The Second Chinese Cardiac Study of Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial is a randomized, double-blind study that plans to enroll 20,000–40,000 patients with acute MI at 1500 sites.[51] Patients will be randomly allocated to receive metoprolol or matching placebo, as well as clopidogrel or placebo in a 2 × 2 factorial design on a background of aspirin therapy over a 4-week period. Apart from the administration of the study medications, all other aspects of individual patient management are at the discretion of the treating physician. The primary endpoint of this trial is the composite of death, nonfatal MI, or stroke. In addition, the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-TIMI 28 trial[52] is a multicenter, double-blind, placebo-controlled trial in patients with STEMI treated with fibrinolytic therapy and aspirin, with patients randomly assigned to receive either clopidogrel or placebo for 30 days. This study plans to enroll 2200 patients from 220 sites with the primary endpoint being TIMI 0 or 1 flow at predischarge angiography or the composite occurrence of death or MI to 30 days. Secondary angiographic and clinical endpoints will also be evaluated. These trials should provide significant information on the use of clopidogrel and dual, oral, antiplatelet therapy in the treatment of patients with STEMI.

Future Targets

In an effort to further improve the clinical outcomes of patients with STEMI, newer strategies are being investigated that capitalize on our increased understanding of the underlying vascular biologic process that culminates in acute MI. Newer fibrinolytic agents that have higher fibrin specificity and shorter half-lives may allow adequate fibrinolysis but a decrease in bleeding complications secondary to less systemic plasmin activation. The development of newer oral and intravenous antiplatelet agents that utilize the purinergic signaling pathway (P2Y12 receptor antagonists) as well as newer anticoagulants (direct thrombin inhibitors, synthetic factor Xa inhibitors, and recombinant tissue factor pathway inhibitors) may provide more effective treatment strategies. Furthermore, although reperfusion therapy reduces mortality and infarct size in patients with MI, reperfusion itself may paradoxically create additional myocardial damage by reperfusion injury.[53] A number of mechanisms have been proposed as etiologic in the reperfusion injury process, including the release of oxygen free radicals, inflammation with increased cytokine release and neutrophil accumulation in the infarct zone, plugging of small arterioles and capillaries with atherothrombotic or inflammatory debris, postcapillary venule leukocyte plugging, tissue hypoxemia, and lipid peroxidation. Numerous strategies to reduce reperfusion injury are under investigation and focus on limiting the amount of myocyte damage and promoting myocardial healing. Even more recently, the discovery of circulating endothelial progenitor cells (EPCs), which can be incorporated into sites of neovascularization, affords the possibility of recruiting these cells to promote vascular and myocardial healing.[54] Similarly, bone marrow-derived stem-cell implants may enhance infarct-zone recovery of contractile function.[55] Finally, pharmacogenomics, which takes into account certain genetic polymorphisms and their gene products, may ultimately tailor our therapeutic approaches to individual patients based on their genetics.[56]

Summary

Pharmacologic reperfusion strategies utilized in the management of patients with STEMI continue to evolve. Fibrinolytic monotherapy with currently available agents has reached a therapeutic plateau for mortality reduction. Newer anticoagulants, such as LMWH or direct antithrombins, offer potential advantages over UFH, and their role in combination with fibrinolytic therapy needs further evaluation. Although combination therapy with platelet GP IIb/IIIa inhibitors and fibrinolysis does not appear to reduce mortality from STEMI compared to fibrinolytic therapy alone, both a reduction in

Main Points

- The goals of coronary reperfusion strategies are to restore flow in the epicardial vessel and microvasculature to return effective oxygen delivery to the cardiac myocytes. A significant portion of patients with ST-segment elevation myocardial infarction (STEMI) do not receive reperfusion therapy.
- The cumulative results of major clinical trials demonstrate a "therapeutic ceiling" for survival derived from fibrinolytic monotherapy for the treatment of STEMI.
- Current fibrinolytic regimens have a number of shortcomings, including the failure to induce early and sustained reperfusion in as many as 40%–50% of patients and the inability to prevent reocclusion in another 10%–20%.
- Combination therapy significantly reduces ischemic complications of STEMI, showing lower rates of reinfarction at 7 days, less need for early (< 6 hours) PCI, and less need for urgent PCI within 7 days, when compared with fibrinolytic monotherapy.
- Newer anticoagulants, such as low molecular weight heparin (LMWH) or direct antithrombins, offer potential advantages over unfractionated heparin (UFH); their role in combination with fibrinolytic therapy awaits the results of ongoing studies.
- Oral antiplatelet therapy with clopidogrel reduces ischemic events for both acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI), and this benefit appears additive to that which accompanies the GP IIb/IIIa receptor blockade.
- Future treatment of STEMI may involve earlier implementation of effective reperfusion strategies, before arrival at the hospital or in the emergency department, adjunctive myocardial protective or anti-inflammatory agents to limit reperfusion injury, and devices that prevent atheroembolization following PCI.

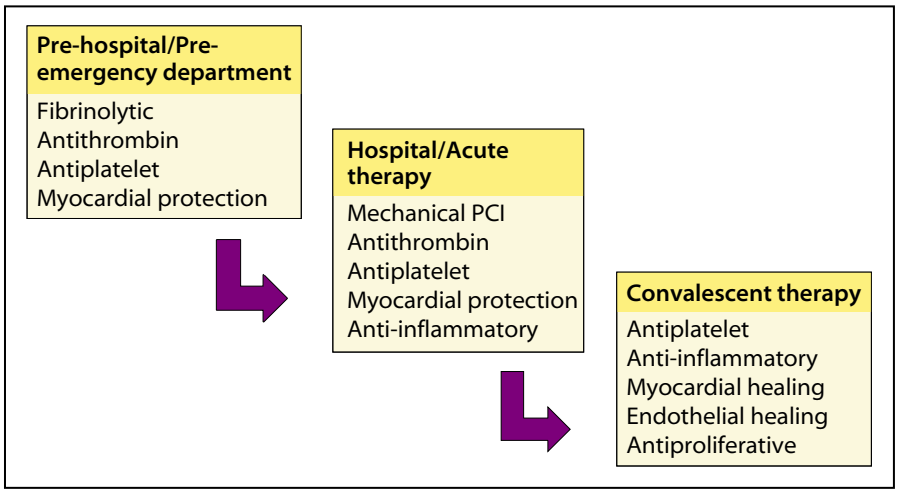

Figure 7. *Components of therapeutic strategies in the longitudinal treatment of patients with ST-segment myocardial infarction (STEMI). PCI, percutaneous coronary intervention.*

recurrent ischemic complications and more rapid and complete restoration of epicardial and microvascular flow have been observed. Oral antiplatelet therapy with clopidogrel reduces ischemic events for both ACS and PCI, and this benefit appears additive to that which accompanies the GP IIb/IIIa receptor blockade.

Future improvements in therapeutic strategies for the treatment of STEMI may involve earlier implementation of effective reperfusion strategies, before arrival at the hospital or in the emergency department, adjunctive myocardial protective or anti-inflammatory agents to limit reperfusion injury, and devices that prevent atheroembolization following PCI (see Figure 7). Myocardial recovery may be further augmented by technologies that promote healing and minimize myocyte damage and scarring. Application of this multimodality approach to patients with STEMI may be facilitated by the regionalization of care and the development of "Centers of Excellence."[57,58] Finally, a significant portion of patients with STEMI who are eligible for reperfusion therapy do not receive it. It is hoped that programs for patient and physician education, in addition to adherence to guidelines and the implementation of critical care pathways, will in the future lead to further improvement in clinical outcomes for patients with STEMI. ■

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