Update on Strategies to Improve Thrombolysis for Acute Myocardial Infarction

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Therapy for acute myocardial infarction involves rapid restoration of blood flow through a coronary artery that has been occluded by a ruptured atherosclerotic plaque. Thrombolytic therapy, the pharmacologic standard to achieve this outcome, significantly improves survival; however, current regimens have limitations: they can fail to achieve complete reperfusion, they can cause significant bleeding events, and they can result in reocclusion. In addition, complex regimens of some agents can cause dosing errors. Accordingly, newer compounds were developed to address some of these issues, and alternative strategies are being implemented. The combination of platelet glycoprotein IIb-IIIa receptor inhibitors plus thrombolytic agents produced promising results in clinical trials, including faster clot lysis and greater flow rates than either therapy alone. The addition of unfractionated heparin or low-molecular-weight heparin to thrombolytic-antiplatelet therapy is being evaluated, as is administration of thrombolytic-antiplatelet before percutaneous coronary intervention.
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OUTLINE

The etiology of acute myocardial infarction is a ruptured atherosclerotic plaque with thrombotic occlusion of the coronary artery.[1] The theory that rapid and complete restoration of blood flow in the occluded artery is directly related to reduced mortality is widely accepted, and success is evaluated in terms of achieving Thrombolysis in Myocardial Infarction (TIMI) flow grades (Table 1).[2] Significant reductions in morbidity and mortality are associated with restoration of high TIMI flow grade.[2–5] In the first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary

Table 1. Classification of TIMI Flow Grade[2]

TIMI Grade	Description
0	Absent antegrade flow
1	Partial contrast penetration, incomplete distal filling
2	Patent with opacifications of the entire distal artery; delayed contrast filling or washout
3	Normal flow

TIMI = thrombolysis in myocardial infarction.

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Table 2. Functional Regions of Thrombolytic Molecules

Function	Region of Molecule
High-affinity fibrin binding	Fibronectin finger
Receptor binding (liver)	EGF
Receptor binding	Kringle-1
Low-affinity fibrin binding, stimulates conversion of plasminogen to plasmin	Kringle-2
Lysis of plasminogen to plasmin, PAI-1 binding site	Protease domain
Mediators of plasma clearance	Carbohydrate side chains

EGF = epidermal growth factor; PAI-1 = plasminogen activator inhibitor type 1.
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Arteries (GUSTO I) study, the mortality rate in patients with TIMI 3 flow at 90 minutes was less than half that in patients with grade 0 or 1 flow (4.4% and 8.9%, respectively). Patients with grade 2 flow had an intermediate mortality rate of 7.4%.[4] The survival advantage may be seen up to 5 years after myocardial infarction.

Although thrombolytics enhance survival and preserve left ventricular function after myocardial infarction,[6, 7] current reperfusion strategies have significant limitations.[7] The drugs can fail to achieve TIMI 3 flow, may result in reocclusion, and are ineffective in patients with non-ST segment elevation.[8] The explanation for their limitations may lie in the composition of the thrombus, which is made up of fibrin, thrombin, and activated platelets. Thrombolytics lyse the fibrin component, which results in exposure of thrombin, one of the most potent platelet proaggretory substances.[9, 10] Bleeding events, including intracranial hemorrhage (ICH), are associated with these agents. Thrombolytics are less effective in patients who are not treated within 6 hours of symptom onset. In those treated within 6 hours, mortality decreases to 30/1000 patients. After 6 hours, the mortality benefit begins to decline.[11] Accordingly, newer strategies to achieve rapid, sustained reperfusion focus on administering thrombolytic agents in conjunction with glycoprotein (GP) IIb-IIIa receptor antagonists and unfractionated (UFH) or low-molecular-weight heparins (LMWH). Complementary measures, including critical pathways and revised evaluation to reduce delays in treatment and time to reperfusion, as well as combined pharmacologic and mechanical intervention, offer additional promising avenues for improving outcomes.

Pharmacology of New Plasminogen Activators

The ideal thrombolytic agent converts clot-bound plasminogen to plasmin rapidly, has high clot penetrance, is resistant to inactivation by plasminogen activator inhibitor type 1 (PAI-1), has a sufficiently long half-life to permit bolus dosing, and has an acceptable bleeding risk. Certain regions of thrombolytic molecules are associated with various functions, including fibrin binding, receptor binding clearance, resistance to inactivation from PAI-1, and lysing plasminogen to plasmin (Table 2).[12] The protease domain is common to all agents. Deletion or substitution of regions from wild-type tissue plasminogen activator (tPA) changes the molecule's properties (Table 3).[13] The pharmacology of new thrombolytics is typically compared with that of alteplase, the recombinant form of wild-type tPA, which was approved by the Food and Drug Administration (FDA) in 1986. Alteplase must be administered by continuous intravenous infusion because it has a short half-life of approximately 3–6 minutes.[14] In addition, this agent has a complex administration protocol.[15] Thus investigators attempted to modify the alteplase molecule to achieve improved thrombolytic properties.[12]

Reteplase (rPA) is a deletion mutant of alteplase. The finger, epidermal growth factor (EGF), and kringle-1 regions of the alteplase molecule are deleted, whereas the kringle-2 region and protease domain are preserved.[16] Reteplase is produced from *Escherichia coli* and does not contain carbohydrate side chains.[14, 16] It was associated with higher clot penetrance than alteplase in an ex vivo animal model, and may be associated with more efficient thrombolysis. Since alteplase binds more tightly to fibrin and the clot surface, its penetrance into the clot is decreased. Therefore, an increase in time to clot lysis occurs with increasing doses of alteplase, whereas a linear inverse relationship between dose and time to clot lysis is observed with reteplase.[16] Reteplase is approximately 5.7 times

Table 3. Characteristics of Newer Thrombolytic Agents

Characteristic	Alteplase (rtPA)	Reteplase (rPA)	Tenecteplase (TNK-tPA)	Lanoteplase
Immunogenicity	None	None	None	None
Plasminogen activation	Direct	Direct	Direct	Direct
Fibrin specificity	++	+	+++	+
Plasma half-life (min)	4–6	18	20	37
Dosage	15-mg bolus followed by 0.75 mg/kg i.v. over 30 min (max 50 mg) followed by 0.5 mg/kg i.v. (max 35 mg) over 60 min	2 x 10-MU boluses administered 30 min apart	< 60 kg, 30 mg; 60–69.9 kg, 35 mg; 70–79.9 kg, 40 mg; 80–89.9 kg, 45 mg; > 90 kg, 50 mg; administered as single bolus dose	Single 120-KU/kg bolus
PAI-1 resistance	None	Unknown	+	+
Genetic alteration to native tPA	No; recombinant version	Yes; finger, EGF, and kringle-1 regions deleted	Yes; mutation of threonine 103 to asparagine 103, asparagine 117 to glutamine 117, and Lys-His-Arg-Arg 296–299 on protease region to 4 alanines	Yes; finger and EGF regions deleted, mutation of asparagine to glutamine on position on kringle-1

EGF = epidermal growth factor.
Adapted from reference 13 with permission.

more potent than alteplase and is cleared from plasma significantly more slowly.[14, 16] Its prolonged half-life permits administration as two boluses separated by 30 minutes.[13]

The design of tenecteplase (TNK-tPA) involves multiple point mutations of the alteplase molecule. Asparagine 103 is substituted for threonine 103, glutamine 117 is substituted for asparagine 117, and the sequence Lys 296-His 297-Arg 298-Arg 299 on the protease region is replaced by four alanines.[17, 18] Tenecteplase has improved resistance to PAI-1,[19, 20] increased area under the curve (AUC),[19] decreased clearance,[19] longer half-life,[20] and increased fibrin specificity[17–20] compared with alteplase. Its thrombolytic potency is 6–13.5 times greater than that of alteplase.[17–20] Tenecteplase is administered as a single bolus injection.

Lanoteplase, also called nPA, is a deletion and point mutation of the alteplase molecule. The finger and EGF regions are deleted and Asn 117 is replaced with Gln 117.[21] These alterations result in decreased fibrin specificity, which improves clot penetration and lysis of established clots,[16, 22, 23] and plasma clearance that is decreased by approximately 20-fold compared with alteplase.[21] This agent's long half-life (~ 49 min) allows for bolus intravenous administration. Lanoteplase is approximately 8.6 times more potent than alteplase.[21] Although pharmacologic differences among alteplase, reteplase, tenecteplase, and lanoteplase result in specific dosing regimens, the clinical significance of additional differences can be observed only by direct comparisons.

Thrombolytic drugs in early stages of development for myocardial infarction include recombinant prourokinase, saruplase, staphylokinase, recombinant thrombin activated plasminogen, a recombinant vampire bat saliva analog, and hementin, a recombinant derivative from the saliva of an Amazon leech.[24]

Reducing Delays in Administering Thrombolytics

A significant source of delay in utilizing reperfusion strategies occurs when patients fail to seek medical care promptly.[25–27] At least 250,000 Americans die each year of myocardial infarction within 1 hour after onset of symptoms.[28] Mean and median prehospital delay times in 1997 were 5.5 and 2.1 hours, respectively, similar to those reported in 1994,[26] and educational efforts to improve them have not been successful to date.[29, 30] A marginal decrease in median time from symptom onset to hospital arrival was seen between 1990 and 1999 (2.2 vs 2.0 hrs, p=0.0001).[31] Therefore, efforts are centered on

more rapid administration of thrombolytic therapy. The update of the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for management of patients with acute myocardial infarction recommends that patients with ischemic chest pain symptoms undergo a targeted clinical examination and a 12-lead electrocardiogram (ECG) that is interpreted within 10 minutes of arrival at hospital. In addition, "door-to-needle" time, the time from arrival at hospital to thrombolytic administration, should not exceed 30 minutes.[32] Door-to-needle times have improved but still average approximately 50 minutes.[27]

Studies of thrombolytic therapy administered before hospital arrival, or in the field, reported reduction in mortality of approximately 18% (1.7% absolute reduction) associated with a gain of 61 minutes in time to treatment compared with conventionally administered thrombolytics.[33] The ACC-AHA guidelines recommend that prehospital administration of thrombolytics be considered only when transport to a medical facility would exceed 90 minutes.[32] One limitation of older thrombolytics, such as streptokinase (SK) and alteplase, is that they require a continuous infusion, which makes administration during transport difficult. Newer thrombolytics, such as reteplase and tenecteplase, which may be administered as a rapid bolus, make prehospital administration more feasible. In the ongoing Prehospital Administration of rPA in ST Segment Elevation Myocardial Infarction (ER TIMI 19) trial,[34] reteplase is administered before hospital arrival. Emergency medical technicians transmit the 12-lead ECG by telephone, and the decision regarding thrombolytic eligibility is made with the emergency department physician. The first 10-U bolus of reteplase is administered in the ambulance, and a second 10-U bolus is administered 30 minutes later either in the ambulance, if transport time is longer than 30 minutes, or in the emergency room.[34] Studies suggested that this practice would likely save 30–60 minutes in time from onset of symptoms to drug administration.[35]

Another way to expedite administration of thrombolytics is to improve methods of identifying eligible patients. The National Registry of Myocardial Infarction (NRMI) 2 study reported that of 84,663 patients with myocardial infarction eligible to receive reperfusion therapy, only 76% were so treated.[36] Reperfusion therapy was defined as intravenous thrombolytics, primary percutaneous coronary intervention (PCI), immediate coronary artery bypass graft (CABG) surgery, or intracoronary thrombolytics. Of these patients, 87.3% received intravenous thrombolytics. In particular, older patients, women, those with inferior wall myocardial infarction, and those with no symptoms were eligible but less likely to receive reperfusion therapy.[36] Analysis of NRMI 1, 2, and 3 showed a significant decline in administration of intravenous thrombolytic agents between 1990 and 1999 (34.3% and 20.8%, p=0.0001). During the same time period there was a significant increase in primary PCI (2.4% and 7.3%, p=0.0001).[31]

Recent Clinical Trials

New Drugs

Several new drugs were evaluated in clinical trials.

Reteplase

The International Joint Efficacy Comparison of Thrombolytics[37] (INJECT) was a randomized, multicenter, double-blind clinical trial. It attempted to determine the equivalence of reteplase and SK in 6010 patients with ST segment elevation myocardial infarction within 12 hours of symptom onset. Patients were randomized to receive either two 10-U boluses of reteplase separated by 30 minutes, or a 60-minute infusion of SK 1.5 MU, each with corresponding placebo control. Patients received an initial dose of aspirin 250–320 mg, followed by 75–150 mg/day. Unfractionated heparin was administered to all patients as a 5000-U bolus followed by an infusion of 1000 U/hour, with infusion rates adjusted to maintain an activated partial thromboplastin time (aPTT) 1.5–2.0 times control. Any other treatments or interventions were given at the physician's discretion. The primary end point, 35-day mortality, was 9.02% in the reteplase group and 9.53% in the SK group (difference of -0.51%, 90% confidence interval [CI] -1.74–0.73%). Mortality rates at 6 months were 11.02% and 12.05%, respectively (difference of -1.03%, 95% CI -2.65–0.59%). The ICH rate in the reteplase group was twice that in the SK group, although the difference was not statistically significant.

The two groups had similar rates of bleeding events. Greater frequency of bleeding events and

the need for transfusions were seen in patients with body weight of 65 kg or less regardless of treatment. At 48 hours, the mean decrease in hemoglobin was significantly lower in the SK group than in the reteplase group (1.14 vs 1.00 g/dl, p=0.0001). Allergic reactions occurred in fewer patients treated with reteplase than in those treated with SK (3 vs 15, p<0.05). When stroke rates were analyzed according to five subgroups—age, gender, weight, systolic blood pressure, and history of hypertension—no significant differences were noted. The investigators concluded that reteplase is clinically safe and is at least equivalent to SK.

The Reteplase versus Alteplase in Acute Myocardial Infarction (RAPID I)[38] and the Reteplase versus Alteplase in Acute Myocardial Infarction II (RAPID II)[39] trials were open-label, multicenter, randomized studies comparing reteplase and alteplase rates of TIMI grade 2 and 3 flow in patients with ST segment elevation myocardial infarction treated within 6 hours of symptom onset. In RAPID I, reteplase was administered as a single 15-U bolus, a 10-U bolus followed by a 5-U bolus 30 minutes later, or a 10-U bolus followed by a 10-U bolus 30 minutes later. Alteplase was administered as a bolus of 6–10 mg followed by 60 mg/hour for 1 hour and 20 mg/hour for 2 hours (total dose 100 mg). In RAPID II, patients received reteplase as either two 10-U boluses separated by 30 minutes, or accelerated alteplase as a 15-mg bolus, followed by 0.75 mg/kg (up to 50 mg) over 30 minutes, followed by 0.5 mg/kg (up to 35 mg) over 60 minutes. All patients received aspirin 160–325 mg before starting thrombolytic therapy and continued once/day at least through discharge. They also received UFH 5000-U bolus followed by 1000 U/hour, with dosages adjusted to maintain aPTT 1.5–2.0 times control value. In both trials, the primary end point was assessed by coronary angiography performed 90 minutes after starting thrombolysis; left ventriculography was performed at the same time. Angiograms were performed at 30 and 60 minutes if possible. Angiograms were assessed by a central core laboratory in a blinded fashion in RAPID II. In RAPID I, no mechanical or medical interventions were made in the presence of TIMI grade 2 or 3 flow unless there was evidence of continuing ischemia; but in RAPID II, mechanical intervention was performed at the discretion of the cardiologist if flow rates were grade 2 or lower. Coronary angiography and left ventriculography were repeated before discharge, at a median of 8 days in RAPID I and 5 days in RAPID II. The samples in RAPID I and II were 606 and 324 patients, respectively.

RAPID I found no significant difference in combined TIMI grade 2 or 3 flow between reteplase (10 U plus 10 U) and alteplase at 90 minutes (85% and 78%, respectively, p=0.084). However, patients receiving reteplase had a significantly higher rate of grade 3 flow than those given alteplase at 60 minutes (51% and 33%, p=0.009), 90 minutes (63% and 49%, p=0.019), and hospital discharge (88% and 71%, p<0.001). The 60-minute grade 3 flow rate in the reteplase group was similar to the 90-minute 3 flow in the alteplase group.

More patients in RAPID II receiving reteplase achieved TIMI grade 3 flow at 90 minutes compared with alteplase (59.9% and 45.2%, p=0.011). They also had significantly higher rates of 90-minute total patency (TIMI grade 2 or 3 flow, 83.4% and 73.3%, p=0.031). At 60 minutes, total patency was 81.8% in reteplase-treated patients and 66.1% in alteplase-treated patients (p=0.032), and grade 3 flow was 51.2% and 37.4%, respectively (p=0.006). There was no significant difference in patency at 30 minutes. In RAPID I, late total patency and TIMI grade 3 flow were similar between groups (89.1% and 75.0% reteplase, 90.3% and 77.0% alteplase). In both trials, ventricular function was improved with reteplase (10 U plus 10 U) compared with alteplase. Bleeding risks were similar for both agents. Significantly fewer strokes were observed in reteplase recipients than in alteplase recipients in RAPID I (p=0.03), and in RAPID II the frequency was similar between groups. These trials established the dose of reteplase as two 10-U boluses separated by 30 minutes, and suggested that complete patency, TIMI 3 flow, was achieved at a superior rate and more rapidly with reteplase than with alteplase. Mortality rates reported in RAPID II, 4.1% for reteplase and 8.4% for alteplase (NS), were used to calculate the sample size for another large comparative clinical trial.

The GUSTO III[40] was a multicenter, randomized, open-label trial comparing reteplase with alteplase for myocardial infarction. Patients with at least 30 minutes of continuous ischemia seen within 6 hours of symptom onset having ST segment elevation or left bundle branch block were eligible to participate. Fifteen thousand fifty-nine patients were randomized in a 2:1 fashion to receive either reteplase as two 10-U bolus doses administered 30 minutes apart, or

alteplase 15-mg bolus, followed by a 30-minute infusion of 0.75 mg/kg (maximum 50 mg), followed by a 60-minute infusion of 0.50 mg/kg over 60 minutes (maximum 35 mg). Aspirin 160 mg was administered to each patient at study entry, followed by 160–325 mg/day thereafter. Unfractionated heparin 5000-U bolus was followed by 1000 U/hour for patients weighing 80 kg or more and 800 U/hour for those less than 80 kg. All UFH dosages were adjusted to maintain an aPTT of 50–70 seconds. No angiographic substudy was conducted. Mortality at 30 days, the primary end point, was 7.47% and 7.24% in reteplase- and alteplase-treated patients, respectively (p=0.61 unadjusted, p=0.54 covariate-adjusted, 95% CI -1.11–0.66%). Weight was not associated with reteplase mortality, suggesting that the dose does not require adjustment based on weight; however, whether or not lower weight was associated with increased bleeding risk was not reported.

Similar rates of stroke and ICH were observed in the two groups (1.64% reteplase, 1.79% alteplase). Death or disabling stroke occurred in 7.89% and 7.91% (NS), serious bleeding events in 0.95% and 1.20% (NS), and moderate bleeding in 6.9% and 6.8% (NS) of patients, respectively. Blood transfusions were necessary in 5.9% of reteplase- and 6.2% of alteplase-treated patients (NS). The two groups were similar in rates of reinfarction, new-onset congestive heart failure, and cardiac arrhythmias. They did not differ significantly in rates of angiography, percutaneous transluminal coronary angioplasty (PTCA), CABG surgery, or other major procedures. Of interest, mortality rates in GUSTO III were higher than those in GUSTO I, which was suggested to be secondary to increased enrollment of patients older than 75 years and women, who generally have higher myocardial infarction mortality than men.[40]

Whether or not mortality is similar between reteplase and accelerated alteplase is a subject of continued debate.[41] The GUSTO III hypothesis was that mortality was lower with reteplase than with alteplase. The sample of 15,000 patients was designed to detect a 20% difference in mortality with 85% power.[40] The null hypothesis was that there was no difference in mortality. Because statistical significance was not reached, the null hypothesis could not be rejected. Some believe that, because the CI surrounding mortality rate with reteplase suggests that mortality with the agent may be more than 1.0% higher than with alteplase, the two drugs are not equivalent.[40, 42] The significance of choosing 1.0% stems from results of GUSTO I that established the superiority of accelerated alteplase over SK, with either subcutaneous or intravenous UFH, with a statistically significant mortality difference of 1.0%. Also, the angiographic substudy of GUSTO was responsible for establishing the open artery hypothesis whereby mortality was directly linked to 90-minute coronary artery patency, especially TIMI 3 flow.[4] Since the lower 95% CI was 1.11%, meaning reteplase mortality could be 1.11% higher, the 1% absolute mortality difference criterion of equivalency was not met. Speculative reasons why mortality with reteplase was not lower than with alteplase in GUSTO III include the fact that the open artery hypothesis was flawed. Perhaps 90-minute coronary artery patency is not the most appropriate time frame for assessment, considering the 30-minute patency in RAPID II was similar between agents.[41] Also, the sample of RAPID I and II combined was much smaller than that of the GUSTO I angiographic substudy, so perhaps TIMI flow rates were not accurate. The sample of GUSTO III was much smaller than that of GUSTO I, thereby increasing the chance of a type II error.

Others argued that the results show that the two agents are clinically similar because 15,000 patients is an adequate sample to assess clinically important differences in mortality, and that further comparative clinical trials would not assist clinical decision making as the drugs are essentially equal in cost.[40, 43] Some consider that the results of GUSTO III plus ease of administrating reteplase make reteplase a more attractive choice since more patients may be treated and treatment may be given sooner. Bolus administration may make adoption of critical pathways for treating myocardial infarction in the emergency room more attractive. Results of a multicenter, retrospective chart review of 250 patients treated with alteplase and 250 with reteplase suggest that reteplase was administered, on average, 17 minutes sooner than alteplase.[44]

Tenecteplase

Tenecteplase (TNK-tPA) was approved by the FDA based on results of four clinical trials.[45–48] The TIMI 10A[45] study was an open-label, phase I, ascending-dose trial of tenecteplase 5, 7.5, 10, 15, 20, 30, 40, and 50 mg administered as a bolus over 5–10 seconds. Subjects were 113 patients seeking treatment for myocardial infarction

within 12 hours of symptom onset. Study end points were pharmacokinetics, coagulation parameters, TIMI grade 3 flow at 90 minutes, serious bleeding, and anaphylaxis. All patients received a 5000-U bolus of intravenous UFH followed by an infusion of 1000 U/hour, adjusted to achieve an aPTT of 55–85 seconds. Aspirin 150–325 mg/day was administered to all patients. Pharmacokinetic values that were evaluated included plasma clearance and elimination half-life. Tenecteplase plasma clearance ranged from 125 ± 25–216 ± 98 ml/minute with doses of 5–50 mg. Elimination half-life ranged from 11 ± 5–20 ± 6 minutes across doses. Drug clearance was delayed and half-life prolonged compared with values reported for wild-type tPA (572 ± 132 ml/min and 3.5 ± 1.4 min, respectively).

Coagulation factors were evaluated for all doses at 1 and 3 hours. At 1 hour, an increase in consumption of α_2-antiplasmin was seen with increasing doses of tenecteplase. A dose-dependent increase in systemic plasmin generation was indicated by an increase in plasmin–α_2-antiplasmin complexes. Reductions were seen in fibrinogen and plasminogen of 3% and 13%, respectively, with all doses. Coagulation parameters at 3 hours were similar to those at 1 hour; however, no details were given. The TIMI grade 3 flow at 90 minutes was higher with 50 mg than with lower doses (p=0.032). Grade 3 flow was achieved at a rate of 59% and 64% with 30 and 50 mg, respectively. Grade 2 or 3 flow was achieved in 85% of patients overall, and was not dose related; it was achieved after 60 minutes in 79% and 82% of patients receiving 50 and 30 mg, respectively. Rescue PCI was performed in 16 of 17 patients who had TIMI grade 0–1 flow on 90-minute angiogram. Thirty-day mortality with all doses combined was 35%. Reinfarction occurred in 4.4% of patients. No strokes or ICHs occurred during the study. Major bleeding occurred in 6.2% of all patients and was distributed across all doses. Antibodies to tenecteplase were not detected in any patient at 30 days. Because tenecteplase has a longer half-life, it can be given as a single intravenous bolus. Since rates of TIMI 3 flow were not considered dose dependent, further investigation of tenecteplase dosing was warranted.

TIMI 10B[46] was a dose-finding angiographic trial in which 886 patients with myocardial infarction evaluated within 12 hours of symptom onset were randomized to receive a single bolus of tenecteplase 30 or 50 mg, or accelerated alteplase infusion 15-mg bolus followed by a 30-minute infusion of 0.75 mg/kg (up to 50 mg), followed by a 60-minute infusion of 0.50 mg/kg (up to 35 mg) in a 1:1:1 ratio. The TIMI grade 3 flow on 90-minute angiogram was the primary end point. The investigators noticed an increased risk of ICH and suspended the 50-mg dose of tenecteplase; a protocol amendment was made to add a 40-mg dose. Patients were then randomized to tenecteplase 40 or 30 mg or alteplase in a 4:1:1 ratio. All patients received aspirin 150–325 mg/day. At first, intravenous UFH was administered at the treating physician's discretion. Secondary to increased risk, the protocol was revised to include weight-based UFH dosing: patients weighing more than 67 kg received a 5000-U bolus followed by an infusion of 1000 U/hour; those weighing 67 kg or less received a bolus of 4000 U followed by an infusion of 800 U/hour. Adjustments were made according to a nomogram to achieve an aPTT of 55–80 seconds. Pharmacokinetic values were measured in 159 patients. Across tenecteplase doses of 30, 40, and 50 mg, plasma clearance ranged from 98.4 ± 42–119.0 ± 49 ml/minute and elimination half-life ranged from 5.5 ± 5.5–21.5 ± 8.2 minutes. Plasma clearance for alteplase was 453 ± 170 ml/minute with elimination half-life 3.5 ± 1.4 minutes. Over the first 6 hours, fibrinogen dropped by 5–10% across 30-, 40-, and 50-mg doses of tenecteplase, compared with 40% with alteplase. Plasminogen fell by 10–15% after tenecteplase compared with 50% with alteplase. α_2-Antiplasmin consumption with subsequent increase in plasmin–α_2-antiplasmin complexes was 4–5 times greater with alteplase than with any dose of tenecteplase.

No difference was seen between tenecteplase 40 mg and alteplase in rate of TIMI grade 3 flow at 90 minutes (62.8% and 62.7%, NS). Grade 3 flow was significantly lower in patients who received tenecteplase 30 mg than in those who received alteplase (54.3% and 62.7%, p=0.035). Grade 3 flow was achieved in 65.8% of patients receiving tenecteplase 50 mg, which was not significantly different from alteplase. A significant dose-response relationship was observed with tenecteplase for both TIMI 3 (p=0.03) and combined TIMI 2 and 3 flow (p=0.04). There was no significant difference among treatments in rate of 60-minute grade 3 flow. In each treatment arm, grade 3 or grade 2 or 3 flow was similar in patients seen within 6 hours of symptom onset compared with those evaluated more than 6 hours after onset. No

difference in TIMI flow rates were seen in those randomized before institution of weight-based UFH dosing compared with those randomized after. Dosages for each patient were weight corrected to determine a mg/kg dose. Patients receiving tenecteplase doses approximately 0.5 mg/kg and higher had grade 3 flow at a rate of 62–63%, compared with 51–54% at lower doses ($p=0.028$ across quintiles).

Intracranial hemorrhages occurred in 1.0%, 1.9%, and 3.8% of patients receiving tenecteplase 30, 40, and 50 mg, respectively, compared with 1.9% for alteplase. Serious bleeding occurred in 1.9%, 5.2%, and 11.5% of patients, respectively, compared with 8.5% for alteplase ($p<0.001$ across tenecteplase doses, $p<0.001$ for tenecteplase 30 mg vs alteplase, $p<0.001$ for tenecteplase 30 mg vs 50 mg). Weight-corrected doses greater than 0.55 mg/kg were associated with significantly more serious bleeding episodes ($p=0.001$) and ICHs ($p=0.033$). Significantly more bleeding ($p=0.002$) and ICHs ($p=0.014$) were also observed at higher corrected doses, even after the UFH weight-adjusted protocol was implemented. After implementation of that protocol, rates of both serious bleeding and ICH fell significantly in both tenecteplase- and alteplase-treated patients. Overall, 30-day mortality was 4.9% and reinfarction occurred in 5.4% of patients, with no significant differences between tenecteplase and alteplase. One (0.3%) of 364 patients had antibodies to tenecteplase at 30 days, but at 90 days antibodies no longer were detected.

This trial established that weight adjustment of both tenecteplase and UFH was important for improving the efficacy and safety profile of tenecteplase.[46]

The first Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT 1) trial[47] was a randomized, multicenter trial of 3235 patients who had myocardial infarction. The primary objective was to evaluate the safety of several doses of tenecteplase with the goal of identifying an optimal dose for use in a large phase III mortality study. The study was conducted in conjunction with TIMI 10B. Patients in ASSENT 1 were initially randomized to receive either tenecteplase 30 or 50 mg; however, because of ICH rates observed in TIMI 10B, a 40-mg dose replaced the 50-mg dose. All patients received tenecteplase as a single bolus of 30, 40, or 50 mg over 5–10 seconds. Immediately on entering the study patients received oral or intravenous aspirin 150–325 mg. Unfractionated heparin infusions were started as soon as possible and were initially dosed at the discretion of the treating physician. As with TIMI 10B, the protocol was amended to include weight-based UFH dosing, in which patients weighing more than 67 kg received a 5000-U bolus followed by an infusion of 1000 U/hour, and those weighing 67 kg or less received a 4000-U bolus followed by an infusion of 800 U/hour. All heparin dosages were adjusted to maintain an aPTT of 55–80 seconds. Patients received other agents and invasive procedures at the discretion of the investigating physician. The primary end point was the rate of ICH at 30 days with different doses of tenecteplase. Secondary end points were rates of major clinical events at hospital discharge and at 30 days.

Of the 3235 patients, 1705 received tenecteplase 30 mg, 1457 received 40 mg, and 73 received 50 mg. At 30 days the rate of total stroke was 1.5%, with ICH occurring in 25 patients (0.77%), 11 (44%) of whom died. Those treated within 6 hours of onset of symptoms had a lower rate of ICH than those treated between 6 and 12 hours (0.56% vs 1.19%, no p value given). Similarly, those treated after implementation of UFH weight-adjusted dosing had lower rates of ICH compared with those treated before implementation (0.72% vs 1.25%, no p value given).

Rates of major clinical outcomes—death, recurrent myocardial infarction, total stroke, cardiac revascularization, pulmonary edema, cardiogenic shock, anaphylaxis, and death or nonfatal stroke—were similar between groups with the exception of recurrent myocardial infarction and revascularization procedures. The frequency of reinfarction with tenecteplase 30, 40, and 50 mg was 8.2%, 5.9%, and 5.5%, respectively (no p value given). Revascularization procedures were performed in 29.5%, 28.0%, and 37.0% of patients, respectively (no p value given). Severe bleeding events occurred in 1.8%, 1.4%, and 2.7%, respectively, and moderate bleeding in 0.7%, 1.2%, and 1.4%, respectively. Red blood cell transfusions were necessary in 4.2% of patients receiving 40 mg and in 5.5% of those given 50 mg. Based on results of ASSENT 1 and TIMI 10B, a single bolus dose of 0.5–0.55 mg/kg of tenecteplase was selected for phase III trials.

The ASSENT 2 was a multicenter, double-blind, randomized trial designed to assess the equivalence of tenecteplase and alteplase in patients with myocardial infarction who were

Table 4. Weight-Adjusted Doses of Tenecteplase[48]

Weight (kg)	Tenecteplase Dose (mg)
< 60	30
60–69.9	35
70–79.9	40
80–89.9	45
≥ 90	50

treated within 6 hours of symptom onset.[48] A sample of approximately 16,500 was selected for this equivalence or noninferiority trial, based on the null hypothesis (perhaps more correctly termed a "directional" hypothesis) that 30-day mortality of tenecteplase would exceed that of alteplase by more than 1%, or that the relative risk of 30-day mortality of tenecteplase would exceed that of alteplase by more than 14%, whichever difference was smaller. A total of 16,949 patients were randomized to receive either a single weight-based bolus dose of tenecteplase (Table 4) or accelerated alteplase. In patients weighing 67 kg or less, an intravenous bolus of UHF 4000 U was administered, followed by infusion of 800 U/hour; for patients weighing more than 67 kg an intravenous 5000-U bolus was followed by an infusion of 1000 U/hour. Dosages of UHF were adjusted to maintain an aPTT of 50–75 seconds. At 30 days, the groups did not differ in total mortality (6.179% tenecteplase, 6.151% alteplase).

There was no difference in 30-day mortality in any subgroup analyzed, except in those treated more than 4 hours after onset of symptoms. In that subgroup, those receiving tenecteplase had significantly lower mortality than patients receiving alteplase (7.0% and 9.2%, p=0.018). Rates of total, hemorrhagic, and ischemic strokes were similar. Rates of total stroke were 1.78% with tenecteplase and 1.66% with alteplase (p=0.555) and hemorrhagic stroke 0.93% and 0.94%, respectively. Death or nonfatal stroke occurred in 7.11% and 7.04%, respectively. Patients given tenecteplase had fewer bleeding complications (26.1% vs 28.4%, p<0.0003) and less need for blood transfusions (4.3% vs 5.5%, p=0.0002). The investigators concluded that a weight-adjusted, single bolus of tenecteplase is equivalent to front-loaded accelerated alteplase in terms of all-cause mortality at 30 days. Since rates of ICH were similar and bleeding complications were lower with tenecteplase, they suggest that that drug is safer than front-loaded alteplase.

Tenecteplase was approved by the FDA in June 2000. No economic study quantified dollars saved based on safety profile. Tenecteplase has similar ICH and less bleeding compared with alteplase. Alteplase has data to support its use in stroke and pulmonary embolism. Tenecteplase is dosed based on weight, whereas reteplase does not require weight-based dosing.

Lanoteplase

Two small and two large myocardial infarction clinical trials were performed with lanoteplase (nPA).[49-54] In one trial,[49] time to recanalization was significantly shorter with lanoteplase than with urokinase (31.8 ± 12.7 vs 56.5 ± 6.3 min, p<0.01), but 1-month reocclusion rates were higher (20% lanoteplase, 3.9% urokinase, p<0.05). In another study,[50] recanalization times were significantly faster in patients who received lanoteplase compared with those who received alteplase (16.1 ± 3.9 vs 39.6 ± 4.8 min, p<0.01).

The first Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME I) trial[51] was a multicenter, randomized, double-blind, dose-ranging angiographic trial comparing TIMI 3 flow at 60 minutes between accelerated alteplase and four doses of lanoteplase in patients with suspected myocardial infarction evaluated within 6 hours of onset of symptoms. Secondary end points were 90-minute TIMI grade 3 and 2 or 3 flow and reocclusion as seen by angiography on days 3–5 after start of therapy. All patients received aspirin 150–325 mg/day and a bolus of UFH 5000 U followed by an infusion of 1000 U/hour adjusted to an aPTT of 60–85 seconds. Six hundred two patients were randomized in a 1:1:1:1:1 ratio to receive one of five thrombolytic regimens consisting of one of four doses of lanoteplase or accelerated alteplase. Lanoteplase was administered as 15, 30, 60, and 120 KU/kg (maximum 12,000 KU) as a single bolus dose.

Dose-related increases in 60-minute TIMI 3 flow were 23.6%, 29.5%, 44%, and 47.1% for 15, 30, 60, and 120 KU/kg, respectively (p<0.001). In the alteplase group, 37.4% of patients achieved grade 3 flow at 60 minutes, which was not statistically different from the rate achieved with lanoteplase 120 KU/kg. There was a significant increase in the proportion of patients with grade 3 flow at 90 minutes as the dose of lanoteplase increased (26.1%, 31.7%, 47.5%, and 57.1% for 15, 30, 60, and 120 KU/kg, respectively, p<0.001). In the alteplase group, 46.4% of patients achieved grade 3 flow at 90 minutes, which was not significantly different from the

lanoteplase group. At 90 minutes after starting lanoteplase, 54.1% of patients receiving 15 KU/kg and 83.0% of those receiving 120 KU/kg had achieved TIMI grade 2 or 3 flow ($p<0.001$). Lanoteplase 120 KU/kg was superior to alteplase, with 83.0% and 71.4% of patients achieving grade 2 or 3 flow at 90 minutes, respectively (difference 11.6%, 95% CI 0.7–22.5%).

Composite clinical outcomes, defined as death, reinfarction, major bleeding, or heart failure within 30 days, occurred in 12.3%, 6.5%, 12.3%, 9.0%, and 21.8% of patients given lanoteplase 15, 30, 60, and 120 KU/kg, and alteplase, respectively. No significant differences in adverse events were noted among groups. Major bleeding occurred in 7 (1.5%) of 479 patients who received any dose of lanoteplase and 7 (5.6%) of 124 who received alteplase. Bleeding events were reported in 40.7% of patients receiving lanoteplase and 50.4% of patients given alteplase. Two strokes occurred in the alteplase group, one hemorrhagic and one thromboembolic. No strokes occurred in the lanoteplase group. Thirty-day mortality was 3.1% in lanoteplase- and 6.5% in alteplase-treated patients. This study established the lanoteplase dose of 120 KU/kg, which was studied in InTIME II (also called TIMI 17).

The InTIME II study,[52, 53] which has not yet been published, was a randomized trial that investigated the equivalence of lanoteplase and alteplase in 15,078 patients with acute myocardial infarction. Patients were randomized in a 2:1 fashion to receive lanoteplase 120 KU/kg as a single bolus, or front-loaded accelerated alteplase. In addition, all patients received aspirin and UFH, adjusted to maintain aPTT 1.5–2 times control. Primary end points of this equivalence trial were 30-day mortality and safety. Preliminary results showed no significant difference in rates of death at 30 days between groups (6.6% alteplase, 6.77% lanoteplase). However, patients treated with lanoteplase had a higher rate of ICH compared with those receiving alteplase (1.13% vs 0.62%, $p=0.003$). The overall stroke rate was similar: 1.52% with alteplase and 1.89% with lanoteplase. Significantly more mild bleeding complications occurred in lanoteplase recipients than in alteplase recipients (19.6% vs 14.7%, $p<0.001$), but no difference was seen in the frequency of major or moderate bleeding.

In a 6-month follow-up that was conducted in patients who participated in InTIME II,[54] mortality was similar in those who received lanoteplase and alteplase (8.85% and 9.15%, $p=0.71$). A substudy, InTIME IIB, found that omission of the UFH bolus led to a nonsignificant 0.25% absolute reduction in the rate of ICH.[55] Because InTIME II showed equivalency of agents but a greater risk of ICH with lanoteplase, Bristol-Myers Squibb, sponsor of the InTIME trials, withdrew its investigational new drug application and relinquished compound development to Biogen. Thus, it is unlikely that lanoteplase will be marketed for treatment of myocardial infarction.

Rescue PCI for Failed Thrombolysis

Major limitations of thrombolytics include failure to achieve reperfusion, and reocclusion or reinfarction of the infarcted artery.[56] Complete antegrade perfusion of the artery within 90 minutes occurs in only 29–32% of patients given SK[4] and approximately 50% of those given alteplase [4, 39, 57] or reteplase,[39, 57] with up to one-fourth of these patients experiencing reocclusion.[58] Several proposed mechanisms for lack of efficacy include failure to achieve a lytic state in the area of occlusion, persistent mechanical obstruction, and the presence of platelet microthrombi.[59] Lysis of fibrin within a coronary thrombus exposes clot-bound thrombin,[60] which leads to increased platelet activation[61, 62] and GP IIb-IIIa receptor expression,[62] resulting in the paradoxic prothrombotic effect of thrombolytics.[60, 61] "No reflow," or failure of microcirculatory reperfusion secondary to platelet microthrombi resistant to thrombolysis, may lead to cell edema and injury or necrosis.[59] Thrombolytic failure also is associated with increased plaque complexity, plaque hemorrhage, and delay in thrombolysis.[59]

Patients with failed thrombolysis may be identified when the 12-lead ECG does not show resolution of ST segment elevation within 90 minutes after start of therapy.[63] Failure of ST segment resolution is highly predictive of high mortality after thrombolytic administration.[59, 64] A patient who fails thrombolysis also may have continued ischemic chest discomfort.

A strategy of immediate angiography and either PTCA (traditional balloon angioplasty) or PCI (including intracoronary stenting) in all patients receiving full-dosage thrombolytics to ensure achievement of TIMI 3 flow was abandoned secondary to results of TIMI IIA. That study showed no benefit and increased bleeding risk in patients undergoing these routine procedures compared with patients undergoing intervention during hospitalization only if they experienced

ischemic symptoms at rest or during low-level exercise stress tests.[65] Early results of clinical trials evaluating rescue angioplasty or PTCA only in patients who did not achieve successful reperfusion with thrombolysis alone were favorable. Five Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials reported the same short- and long-term mortality in patients who underwent PTCA after having TIMI grade 0 or 1 flow 90 minutes after thrombolytic administration. However, failure of PTCA in rescue angioplasty was associated with very high 30-day mortality of 39% in the TAMI studies[66] and 24–30% reocclusion rate in TIMI IIA.[67] This was confirmed by more recent data from a small subgroup of the GUSTO I angiographic substudy who underwent rescue PTCA. Thirty-day mortality was high in patients who were classified as rescue failures (30.4%), whereas it was similar in those who achieved TIMI grade 2 or 3 flow (8.6%) as in those achieving successful reperfusion with thrombolysis alone (5.2%). In this GUSTO I subgroup, only 67% of rescue PTCA attempts resulted in restoration of grade 3 flow, and bleeding rates were slightly higher than in patients undergoing protocol-driven angiography alone (8.6% vs 6.8%, p value not specified).

The Cohort of Rescue Angioplasty in Myocardial Infarction (CORAMI) study was an unrandomized trial that evaluated 299 patients who received thrombolytic therapy and underwent emergency angiography 90 minutes later.[56] Eighty-seven patients (29%) were considered thrombolytic failures and underwent rescue PTCA; the procedure was successful in 90%. Although the results of this trial appear promising, few randomized trials specifically evaluated rescue PTCA or PCI.

The first report randomized 28 patients more than 3 hours after the onset of myocardial infarction to rescue angioplasty or conservative therapy. The trend was toward lower mortality with rescue angioplasty (6.3% vs 33.3%, p=0.13).[68] The RESCUE I trial randomized 150 patients with anterior wall myocardial infarction and occluded left anterior descending arteries after thrombolytic therapy to rescue PTCA versus conservative management.[69] No differences were seen in resting ejection fraction (p=0.49), death (p=0.11), or severe heart failure (p=0.18) between groups. Compared with conservative therapy, the group receiving PTCA had a significantly higher exercise ejection fraction (43% vs 38%, p=0.04), as well as a significant reduction in the combined end point of death and severe heart failure (6% vs 17%, p=0.05). Analysis of data from 1456 patients enrolled in nine randomized trials, including those cited, reported a reduction in early heart failure and improved 1-year survival in patients randomized to rescue PTCA versus usual medical care.[70] These reports suggest that rescue PTCA has higher mortality and complication rates compared with primary PTCA (without thrombolytics) for treating myocardial infarction.

Although not definitely proven to reduce early or late mortality, rescue PTCA or PCI is widely performed. Many such interventions include intracoronary stent placement and adjunctive GP IIb-IIIa receptor blocker therapy, which may improve outcomes. Whereas intracoronary stents decrease procedural complications and reduce restenosis and the need for target vessel revascularization compared with primary PCI (without thrombolytic therapy) in myocardial infarction,[71] published experience with the combination of full-dosage thrombolytics and GP IIb-IIIa receptor blockers in the rescue setting is lacking. One small study,[72] a retrospective analysis of GUSTO III, reported results of administering abciximab during PCI in 83 patients for failed thrombolysis with either reteplase or alteplase, compared with 309 patients who did not receive abciximab. Eighty patients who did and 308 who did not receive abciximab received intracoronary stents. The trend was toward lower mortality in patients receiving abciximab, 3.6% versus 9.7% (p=0.076). Rates of nonfatal stroke were similar in both groups (1.3%). However, patients treated with abciximab had a greater frequency of severe bleeds (3.6% vs 1.0%, p=0.08) and more bleeding overall (72% vs 50%, p=0.007). Although not a randomized comparison, this small study is the first to suggest that rescue PCI with intracoronary stenting and abciximab can improve benefits in patients with myocardial infarction.

A larger retrospective study evaluated the safety and efficacy of abciximab during rescue angioplasty.[73] Two hundred fourteen patients who failed thrombolytic therapy were identified from Duke University and Mayo Clinic databases, as well as from GUSTO III and Strategy for Patency Enhancement in the Emergency Department (SPEED) trials. All patients received full-dosage thrombolytic therapy and abciximab within 12 hours of failed thrombolysis, and PCI was performed immediately in 203 patients.

Major bleeding (ICH or retroperitoneal bleeding, > 5-g/dl drop in hemoglobin, need for transfusion) was the primary end point. Stroke, death, reinfarction, and need for revascularization (CABG surgery, repeat PCI) were secondary end points. The median time to abciximab administration was 4.6 hours (range 3.3–7.4 hrs). Fifty patients (23%) experienced major bleeding (95% CI 18–30%). Three patients (1.4%) had an ICH (95% CI 0.3–4%), 34 (16%) required transfusions (95% CI 11–22%), and 15 (7%) had a hemoglobin drop of more than 5 g/dl. Seventeen patients required revascularization; of these, nine required CABG surgery and eight underwent repeat PCI. Three hemorrhagic and two nonhemorrhagic strokes occurred during the study. Six patients had reinfarction and 16 died during hospitalization. Three independent predictors of major hemorrhage were identified by multivariate analysis: time to abciximab administration (odds ratio [OR] 0.91/hr, 95% CI 0.83–0.99, p=0.03), intraaortic balloon pump (IABP) insertion (OR 4.42, 95% CI 2.00–9.72, p=0.0002), and age (OR 1.53/yr, 95% CI 1.05–2.21, p=0.03). Female gender, lower body weight, and higher activated clotting times (ACTs) during PCI were factors associated with higher bleeding rates on univariate analysis. However, on multivariate analysis, these characteristics were not identified as independent predictors of major bleeding. The investigators concluded that 20–25% of patients will experience major bleeding when abciximab is administered within 24 hours after full-dosage thrombolytic therapy, with increasing age, IABP insertion, and shorter time from thrombolytic therapy to abciximab administration being independent predictors of such events.

Although rescue PCI is one option for failed thrombolysis, additional information is required, particularly evaluating bleeding risk with concomitant GP IIb-IIIa receptor blockers. Also, not all centers have interventional cardiologists and catheterization facilities to perform rescue PCI, and transfer to such facilities increases time to complete restoration of blood flow to the myocardium, limiting applicability of this procedure. In fact, even with primary PCI, the time from onset of symptoms to first balloon inflation is directly associated with increased mortality.[74] Therefore, primary thrombolysis remains the preferred initial treatment for most medical centers, and consideration should be given to repeat administration of a thrombolytic if therapy fails, also called rescue thrombolysis.

Rescue Thrombolysis

A small, placebo-controlled, randomized study of 37 patients evaluating alteplase administration (19 patients) for failed lysis with SK reported improved ejection fraction with alteplase versus placebo (44% vs 34%, p=0.04). No ICHs occurred, and only one patient, randomized to placebo, required a transfusion.[75]

The efficacy of rescue thrombolysis was evaluated in 90 patients.[76] Patients admitted with myocardial infarction who were eligible to receive thrombolytic therapy were treated with accelerated-dosage alteplase 10-mg intravenous bolus followed by a 60-minute infusion of 40 mg. Patients with persistent pain and ST segment elevation 120 minutes after start of alteplase therapy were randomized in a double-blind manner to receive a second dose of alteplase or placebo (45 patients each). The groups did not differ in baseline characteristics. In alteplase-treated patients, 77.7% experienced decreased pain and resolution of ST segment elevation within 50 minutes of starting the second dose of alteplase. Most of them (73.4%) had signs of reperfusion within 20 minutes of beginning the second dose. The patients receiving placebo had a significantly lower rate of reperfusion, 26.6% within 35–85 minutes (mean 55 min, p=0.0001). Comparison of peak creatine kinase and creatine kinase myocardial band revealed earlier and lower peaks in alteplase-treated patients compared with placebo (p=0.002 and 0.009, respectively). Angiography was performed in 39 patients receiving alteplase and 31 receiving placebo. In those with signs of reperfusion, TIMI 2 or 3 flow was seen during angiography.

In-hospital mortality was not significantly different between groups, 28.8% for placebo and 6.6% for alteplase (p=0.41). Recurrent angina and nonfatal myocardial infarction were more common in patients who received a second dose of alteplase than in those receiving placebo (40% vs 6.6%, p=0.006 and 15.5% vs 0%, p=0.014, respectively). No significant difference in major bleeding was observed between groups (2.2% alteplase, 0% placebo, NS). One alteplace-treated patient had a nonfatal stroke, which was the only major bleed in the trial. However, significantly more minor bleeds occurred in the alteplase group than in the placebo group (44.4% vs 15.5%, p=0.047). The authors concluded that administering a second dose of a thrombolytic agent to patients with persistent ischemia is a reasonable option, since the benefits of limiting

Table 5. Dose-Ranging Trials of Combination Thrombolytic and Glycoprotein IIb-IIIa Inhibitor Therapy for Acute Myocardial Infarction

Trial	Thrombolytic	GP IIb-IIIa Receptor Inhibitor
TAMI 8[81]	Alteplase	Abciximab
IMPACT-AMI[82]	Alteplase	Eptifibatide
Streptokinase-eptifibatide[83]	Streptokinase	Eptifibatide
PARADIGM[84]	Alteplase, streptokinase	Lamifiban
TIMI 14[85]	Alteplase	Abciximab
SPEED[86]	Reteplase	Abciximab
INTRO-AMI[87]	Alteplase	Eptifibatide

TAMI-8 = Thrombolysis and Angioplasty in Myocardial Infarction 8 pilot study; IMPACT-AMI = Integrelin to Manage Platelet Aggregation to Combat Thrombosis after Acute Myocardial Infarction; PARADIGM = Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction; TIMI 14 = Thrombolysis in Myocardial Infarction 14 trial; SPEED = Strategy for Patency Enhancement in the Emergency Department; INTRO-AMI = Integrilin and Reduced Dose of Thrombolytics in Acute Myocardial Infarction study.

the area of infarct outweigh the risks of bleeding.

These results must be viewed with caution for two major reasons. The number of patients was small. In addition, the group that received a second dose of alteplase had significantly higher ischemic complications than the group receiving placebo.[76] Comparisons between rescue PCI and rescue thrombolysis are warranted.

Adjunctive Therapy with GP IIb-IIIa Receptor Blockers

Primary PCI has the distinct advantage over thrombolytic therapy in that it is associated with lower rates of bleeding, particularly ICH, and in clinical trials resulted in higher rates of TIMI 3 flow of 73%[77] to 91.6%.[78] Adjunctive therapies, such as aspirin and UFH, have been used to balance the prothrombotic effect of thrombolytic agents.[10, 78] Clinical trials are investigating GP IIb-IIIa inhibitors and LMWHs as adjunctive therapy to thrombolytics in myocardial infarction. When platelets become activated, they express the GP IIb-IIIa receptor, also called the $\alpha_{IIb}\beta_3$ receptor, on their surface.[78, 79] The GP IIb-IIIa receptor is available to bind fibrinogen and von Willebrand factor, which allow platelets to crosslink, creating a growing platelet aggregate. The GP IIb-IIIa inhibitors achieve platelet aggregation inhibition superior to aspirin, ticlopidine, and clopidogrel. Abciximab, the first of these agents, is a murine monoclonal antibody directed at the GP IIb-IIIa receptors. It nonspecifically binds to these receptors in addition to other surface receptors, including vitronectin ($\alpha_v\beta_3$) and Mac-1 ($\alpha_M\beta_2$ or CD11b/CD18), on platelets and leukocytes.[80] Peptide and peptidomimetic GP IIb-IIIa inhibitors, such as eptifibatide, tirofiban, and lamifiban, compete with fibrinogen for binding to the GP IIb-IIIa receptors.[78, 79] These agents accomplish competitive inhibition by mimicking an amino acid sequence found on the α-chain of fibrinogen.[78] Inhibition of the final common pathway of platelet aggregation is the rationale for adjunctive therapy with GP IIb-IIIa inhibitors in patients with myocardial infarction who are treated with thrombolysis.[9, 10, 78, 79] The correct combination of dosages and effects on mortality with or without PCI in myocardial infarction are being studied.

Trials of Thrombolytics plus Glycoprotein IIb-IIIa Inhibitors

Results of seven dose-ranging trials combining SK, alteplase or reteplase with either abciximab or eptifibatide in ST segment elevation myocardial infarction have been reported to date (Table 5).[81–87] If lower dosages of thrombolytics could be administered, perhaps lower rates of ICH could be achieved while maintaining mortality reductions and decreasing cost. If TIMI 3 flow could be enhanced, perhaps mortality could be reduced. These phase II trials explored 90-minute TIMI 3 flow rates. The first, TAMI 8,[81] enrolled 70 patients with myocardial infarction evaluated within 6 hours of symptoms; 60 received standard alteplase administered over 3 hours plus an abciximab bolus dose of 0.1–0.25 mg/kg at 3, 6, or 15 hours after alteplase; 10 patients receiving alteplase alone served as controls. Patency (TIMI grade 2 or 3 flow) occurred in 92% of those given combined

Table 6. Treatment Groups for Integrilin to Manage Platelet Aggregation to Combat Thrombosis after Acute Myocardial Infarction[82]

Group	No. of Pts (placebo/eptifibatide)	Eptifibatide Bolus (µg/kg)	Eptifibatide Infusion (µg/kg/min)	UFH Dose Bolus (U/kg)/Infusion (U/kg/hr)[a]
1a	6/18	36	0.2	40/15
1b	8/14	72	0.4	40/15
1c	6/12	108	0.6	None/15[b]
1d	6/15	135	0.75	None/15[b]
1e	9/15	135	0.75	40/15
1f	7/16	180	0.75	40/15
2	16/32	180	0.75	40/15

UFH = unfractionated heparin.
[a]Adjusted to maintain activated partial thromboplastin time of 2–2.5 times control.
[b]To begin 60 minutes after alteplase initiation, eptifibatide arm only. patients randomized to placebo received an UFH bolus of 40 U/kg before the infusion.

therapy versus 56% of controls in 43 patients undergoing elective angiography. The percentage of patients undergoing PCI after abciximab was not reported. Recurrent ischemia occurred in 13% of the combined therapy group versus 20% of controls, with major bleeding occurring in similar numbers of patients. Abciximab was administered in the hours after thrombolysis because of concern about safety.[82] Because GP IIb-IIIa receptor inhibition proved safe, subsequent trials administered one of the agents simultaneously with thrombolysis.

Integrelin to Manage Platelet Aggregation to Combat Thrombosis after Acute Myocardial Infarction (IMPACT-AMI)[82] was a randomized, placebo-controlled, dose-ranging study investigating administration of alteplase with eptifibatide as a 24-hour infusion in ST segment elevation myocardial infarction treated within 6 hours of symptom onset. A TIMI grade 3 flow at 90 minutes was the primary end point. Secondary end points were occurrence of a composite of clinical events (death, reinfarction, need for revascularization, stroke, new-onset heart failure, pulmonary edema) and bleeding. Patients were randomized into one of seven groups (Table 6).[82] The first six groups (1a–1f) consisted of a sequential, dose-escalation phase comparing open-label eptifibatide with placebo. Investigators progressed to a higher dose once safety analyses were done for the previous dose. Patients in the last group (group 2) were randomly assigned, in a double-blind fashion, to the highest dose of eptifibatide in the dose-escalation part of the study. In addition to eptifibatide or placebo, all patients received accelerated alteplase 15-mg bolus, followed by 0.75 mg/kg (maximum 50 mg) over 30 minutes, followed by 0.5 mg/kg (maximum 35 mg) over 60 minutes. All patients also received aspirin 325 mg/day starting before study drug administration, and continuous intravenous UFH infusions.[82] One hundred seventy patients had angiograms that could be evaluated at 90 minutes.

Pooled data from phases 1 and 2 in patients treated with the highest dosage of eptifibatide (180-µg/kg bolus, followed by 0.75 µg/kg/min infusion) had higher TIMI grade 3 flow than those treated with placebo (66% vs 39%, p=0.006). The frequency of death or reinfarction was 8.0%, 7.8%, and 7.3% in all patients randomized to eptifibatide, those receiving the highest dosage of eptifibatide, and those receiving placebo, respectively. Composite outcomes occurred in 41.8%, 44.8%, and 43.1% of placebo-treated patients, all eptifibatide-treated patients, and those treated with the highest dosage of eptifibatide, respectively. Most bleeding that occurred was mild and related to the access site. Three patients in the placebo group and five patients randomized to eptifibatide developed severe thrombocytopenia, defined as platelet count less than 50,000 (no p value given). One ICH occurred in a patient receiving the highest dosage of eptifibatide (no p value given). The investigators concluded that a potent glycoprotein IIb-IIIa inhibitor in combination with alteplase, aspirin, and heparin enhances the speed and frequency of reperfusion in acute myocardial infarction.

A double-blind, placebo-controlled, pilot trial compared SK plus eptifibatide to SK plus placebo.[83] All patients received standard-dosage SK 1.5 MU administered over 60 minutes and were randomized to receive either eptifibatide 180-µg/kg bolus followed by an infusion of 0.75, 1.33, or 2.0 µg/kg/minute in an escalating

manner, or placebo. Preliminary results showed a modest increase in TIMI grade 3 flow at 90 minutes in patients who received SK plus eptifibatide (53% receiving lowest dosage of eptifibatide) compared with those who received SK plus placebo (38%). There was, however, an increase in bleeding with the combination, especially in patients receiving higher dosages of eptifibatide. The investigators recommend avoiding full-dosage SK in combination with higher dosages of eptifibatide. This may have implications in other areas if eptifibatide is administered during rescue PCI for failed SK thrombolysis.

The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) study[84] assessed the safety, pharmacokinetics, pharmacodynamics, and effects on reperfusion of lamifiban given with thrombolytic therapy to patients with ST segment elevation myocardial infarction evaluated within 12 hours of symptom onset. The primary pharmacodynamic end point was dosage of lamifiban that would give 85% or greater adenosine diphosphate (ADP)-induced platelet aggregation inhibition, without causing increases in bleeding. The primary safety end point was bleeding during hospitalization and the primary efficacy end point was a composite outcome of angiographic, electrocardiographic, and clinical markers of reperfusion at hospital discharge or 30 days.

Patients were assigned to receive full dosages of alteplase or SK with the agent chosen at the discretion of the treating physician. All patients received aspirin 160–325 mg/day. Those who received alteplase also received UFH 5000-U bolus followed by an infusion of 1000 U/hour titrated to maintain aPTT of 60–80 seconds for at least 24 hours after thrombolytic therapy. Patients who received SK received no UFH for the first 24 hours. All patients in part A of the trial received open-label lamifiban beginning with a bolus dose of 300 µg followed by a 1-µg/minute infusion, and increasing to a second dosage based on safety and degree of platelet aggregation. Identifying a dosing strategy that could produce 85–95% ADP-induced inhibition of platelet aggregation was the goal of part A.

Part B was a double-blind comparison of a bolus of lamifiban followed by a 24-hour infusion and placebo. Patients were randomized in a 2:1 ratio to receive lamifiban or placebo. Part C was similar to part B, except the length of infusion was 48 hours. The goal was to begin lamifiban within 30 minutes of starting thrombolytic therapy.

Three hundred fifty-three patients were enrolled, with 266 receiving alteplase and 85 receiving SK. In part A, 15 patients received lamifiban 300 µg followed by infusion of 1.0 µg/minute over 24 hours, and 15 received lamifiban 400-µg bolus followed by infusion of 2.0 µg/minute over 24 hours. One hundred twelve patients in part B received lamifiban 400-µg bolus followed by a 1.5-µg/minute infusion over 24 hours, and 61 received placebo. In Part C, 94 patents received lamifiban 400-µg bolus and 2.0 µg/minute infused for 48 hours, and 56 received placebo.

For those treated with lamifiban, the median time from start of thrombolysis to administration of study drug was 0.42 hours compared with 0.48 hours for patients receiving placebo. Early termination of the study drug occurred in 17.2% and 13.7% of those receiving lamifiban and placebo, respectively. Bleeding was the most common cause of discontinuation (37.1% lamifiban, 0% placebo).

Adenosine diphosphate- and thrombin receptor agonist peptide-mediated platelet aggregation inhibition by lamifiban was dose dependent. At 60–90 minutes after the bolus, platelet aggregation inhibition was comparable among dosages. Thrombin receptor agonist protein is a more potent platelet activator than ADP, thus higher dosages of lamifiban were necessary to produce the same degree of platelet aggregation inhibition as that when ADP was the platelet activator. Patients treated with SK and lamifiban appeared to have more platelet aggregation inhibition than those treated with alteplase and lamifiban. Median inhibition with lamifiban at different dosages ranged from 80–100% for SK-treated patients compared with 48–89% for alteplase-treated patients.

Bleeding rates were higher in lamifiban-treated patients (3.0%) than placebo-treated patients (1.7%, no p value given). One patient receiving alteplase plus lamifiban and a second receiving SK plus lamifiban experienced ICH. Gastrointestinal, CABG surgery-related, and femoral access site bleeding were the main causes of intermediate and major bleeding events. Bleeding increased when alteplase or SK was given in combination with lamifiban compared with placebo.

No significant differences among treatments were observed in rate of death, reinfarction, refractory ischemia, nonelective revascular-

Table 7. TIMI 14 Results: TIMI Grade 3 Flow at 90 Minutes[85]

	Control	Abciximab Alone	Abciximab + Streptokinase			
Abciximab						
Bolus (mg/kg)	—	0.25	0.25			
Infusion (μg/kg/min x 12 hrs)	—	0.125	0.125			
Thrombolytic	Alteplase (mg)		Streptokinase (U x 10^3)			
Bolus	15	—	—	—	—	—
Infusion	≤ 50 over 30 min ≤ 35 over 60 min	—	500 over 30 min	750 over 30 min	1250 over 50 min	1500 over 30 min
Total dose (μg/kg)	≤ 100	—	500	750	1250	1500
Heparin						
Bolus (U/kg)	70	60	60	60	60	—
Infusion (U/kg/hr)	15	7	7	7	7	—
No. of patients	163	32	37	49	51	6
TIMI grade 3 flow (%)	57	32	41	34	46	80

	Abciximab + Alteplase							
Abciximab								
Bolus (mg/kg)	0.25						0.30	0.25
Infusion (μg/kg/min x 12 hrs)	0.125							
Thrombolytic	Alteplase (mg)							
Bolus	20	35	15	50	15	15	15	15
Infusion	—	—	20 over 30 min	—	35 over 30 min	35 over 60 min	35 over 60 min	50 over 60 min
Total dose (mg/kg)	20	35	35	50	50	50	50	65
Heparin								
Bolus (U/kg)	60	60	60	60	60	60	30	60
Infusion (U/kg/hr)	7	7	7	7	7	7	4	7
No. of patients	38	42	50	36	53	34	48	38
TIMI grade 3 flow (%)	53	32	61	59	63	76	74	73

TIMI = thrombolysis in myocardial infarction.

ization, persistent or recurrent ST segment elevation, or TIMI flow less than grade 3. In patients treated with lamifiban, the speed and stability of reperfusion were significantly better than in those treated with placebo. Reperfusion, as measured by time to steady-state of the ST segment, was faster with lamifiban than with placebo (88 vs 122.3 min, p=0.003). Whereas 90-minute patency as assessed by ECG was higher in lamifiban-treated patients (80.1% vs 62.5%, p=0.005) compared with placebo-treated patients, no difference between groups was observed in rate of grade 3 flow, with only 34 patients undergoing 90-minute angiography. Clinical outcomes appeared better in lamifiban-treated patients, with 29% of these patients experiencing recurrent ischemia compared with 51.4% of those receiving placebo (p=0.001). Late ischemia occurred in 12.6% and 24.4% of patients treated with lamifiban and placebo, respectively (p=0.022). Lamifiban in combination with thrombolytic therapy seems to be associated with faster and more complete reperfusion when compared with placebo, but further work is necessary to clarify dosing as bleeding was increased.

The TIMI 14 trial[85] was a complex dose-finding study of 14 reperfusion strategies of combined reduced-dosage alteplase, reduced-dosage SK, or full-dosage SK with abciximab versus standard thrombolytic therapy alone in ST segment elevation in patients with myocardial infarction treated within 12 hours of symptom onset. All patients in both dose-finding and dose-confirmation phases received aspirin 150–325 mg orally or 250–500 mg intravenously. Regimens for the dose-finding phase of the trial are summarized in Table 7. No UFH was given to those who received SK 1.5 MU to reduce the risk of bleeding. Patients were randomized to one of three groups for the dose-confirmation phase. The control group received full-dosage, accelerated alteplase. Investigational groups received standard-dosage abciximab with various combinations of thrombolytic dosages and varied dosages of UFH. In addition, a group was treated with full-dosage abciximab alone. Coronary angiography was performed within 90 minutes of starting thrombolytic therapy, with PCI performed at the discretion of the treating

physician. Patients were followed for 30 days. The TIMI grade 3 flow at 90 minutes was the primary efficacy end point. Clinical efficacy end points were all-cause mortality, recurrent myocardial infarction, recurrent ischemia, need for urgent revascularization, severe pump failure, need for rescue PCI, and CABG surgery. The primary safety end point was major hemorrhage. The development of thrombocytopenia was an additional safety end point. Eight hundred eighty-eight patients participated in both phases of the study. Secondary to unacceptable bleeding, SK 1.5 MU plus abciximab was prematurely terminated after enrolling only six patients. The TIMI grade 3 flow at 90 minutes was achieved in 57% of patients receiving full-dosage alteplase alone, 32% receiving abciximab alone, 34–46% of those receiving between 500,000 U and 1.25 MU of SK, and 38–61% of those receiving alteplase in combination with abciximab. Rates of TIMI grade 3 flow at 90 minutes were similar between full-dosage alteplase alone and regimens containing alteplase 20, 35, 50, and 65 mg in combination with abciximab. The lowest grade 3 flow was observed in patients receiving abciximab alone and reduced-dosage SK.

The regimen containing alteplase 15-mg bolus followed by 35 mg infusion over 60 minutes in combination with abciximab was the most promising. Compared with full-dosage alteplase alone, it produced substantial increase in grade 3 flow (76% vs 57%, p=0.08) and infarct-related artery patency (93% vs 78%, p=0.09) at 90 minutes. Reduced-dosage alteplase regimens containing reduced dosages of UFH performed equally as well as full-dosage alteplase plus standard UFH dosages.

Major hemorrhage occurred in 6% of patients receiving alteplase alone, 3% receiving abciximab alone, 7% in all alteplase and abciximab-containing regimens, and 10% in all SK- and abciximab-containing regimens. Overall rates of ICH, mortality, recurrent myocardial infarction, and severe pump failure were 1.1%, 4%, 3%, and 1%, respectively, with no significant differences across groups. Severe recurrent ischemia requiring revascularization occurred in 31% of patients overall and was highest in patients given abciximab alone (59%). Rescue PCI was performed in 19% of patients overall and was highest in patients treated with abciximab alone (41%). Grade 3 flow at 60 minutes with either abciximab plus alteplase 50 mg administered over 30 minutes (58%) or abciximab plus accelerated alteplase 65 mg administered over 60 minutes (63%) was similar to 90-minute grade 3 flow in patients treated with alteplase 100 mg over 90 minutes (57%). Thus abciximab, in combination with half-dosage alteplase produced early and significant increases in TIMI grade 3 flow compared with alteplase alone. No increase in the risk of major bleeding was observed with improvement in reperfusion. Streptokinase plus abciximab produced modest improvements in TIMI grade 3 flow with an increased risk of bleeding.

The primary outcome of the SPEED trial,[86] also known as the GUSTO V pilot study, was TIMI grade 3 flow at 60–90 minutes. Secondary end points were clinical composite outcomes such as death, reinfarction, or urgent revascularization, stroke or ICH, and major hemorrhage with blood transfusion. Patients were eligible to participate if they were evaluated up to 12 hours after the onset of chest pain at least 30 minutes in duration with ST segment elevation. In phase A (dose-escalation evaluation), 304 patients were randomized in a 4:1 ratio to receive standard-dosage abciximab 0.25-mg/kg bolus followed by 0.125 µg/kg/minute infusion for 12 hours, or standard-dosage abciximab plus one of five low-dosage reteplase regimens. Reteplase was given as a single bolus injection of 5, 7.5, or 10 U or as two bolus injections, the first being 5 U and the second 2.5 or 5 U. In phase B (dose confirmation), 224 patients were randomized to receive standard-dosage reteplase two 10-U boluses separated by 30 minutes or standard-dosage abciximab plus two 5-U boluses of reteplase separated by 30 minutes. All patients received aspirin 150–325 mg orally or 250–500 mg intravenously. Daily oral aspirin 80–325 mg was continued for at least 30 days. In phase A, UFH 60-U/kg bolus was administered to all patients. In phase B, patients who were randomized to abciximab plus reteplase received UFH boluses of 40 U/kg (up to 4000 U), and those randomized to reteplase alone received a 70-U/kg bolus (up to 5000 U). The UFH boluses were followed by a continuous infusion or weight-adjusted boluses during angiography and intervention to maintain an ACT of 200 seconds. Heparin was continued after the interventions at the discretion of the treating physician. If UFH was continued, dosages were adjusted to maintain an aPTT of 50–70 seconds. Since all patients underwent immediate angiography with primary PCI at the discretion of the investigator, it was considered ethical to treat patients with abciximab alone.

Table 8. Results of Strategies for Patency Enhancement in the Emergency Department (SPEED)

Event	Abciximab Alone (phase A)	Abciximab + Reteplase 5 U +5 U (phase A)	Abciximab + Any Reteplase (phase A)	Reteplase Alone (phase B)	Abciximab + Reteplase 5 U +5 U (phase B)
Death (%)	3.2	3.9	3.3	5.5	3.5
Reinfarction (%)	0	2.6	3.7	2.8	0.9
Urgent revascularization (%)	6.3	6.6	5.4	3.7	2.6
Death or reinfarction (%)	3.2	6.6	6.6	8.3	3.5
Ischemic stroke (%)	1.6	0	0.4	0.9	0
Intracranial hemorrhage (%)	0	1.3	0.8	0.9	0
Severe pump failure (%)	6.3	3.9	3.7	2.8	4.3
Bypass surgery (%)	6.3	6.6	8.7	9.2	6.1

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Table 9. Dosing of Eptifibatide and Alteplase[87]

Group	No. of Patients	Eptifibatide Bolus 1 (µg/kg)	Eptifibatide Bolus 2 (µg/kg)	Eptifibatide Infusion (µg/kg/min)	Alteplase (mg)
A	35	180	—	1.33	25
B	37	180	90	1.33	25
E	33	180	—	1.33	50
F	53	180	90	1.33	50
G	33	180	—	2.0	50
I	49	180	90	2.0	50
N	56	180	180	1.33	50
O	46	180	180	2.0	50

In phase A, at 60–90 minutes TIMI grade 3 flow was achieved in 27% of patients receiving abciximab alone, 55% receiving abciximab plus reteplase 5 U, 44% receiving abciximab plus reteplase 7.5 U, 46% receiving abciximab plus reteplase 10 U, 42% receiving abciximab plus reteplase 5 U plus 2.5 U, and 62% receiving abciximab plus reteplase 5 U plus 5 U. Abciximab plus two 5-U boluses of reteplase was significantly superior to abciximab alone at achieving grade 3 flow at 60–90 minutes (62% vs 27%, p=0.001). The overall mortality rate was 3.8%. Rates of ischemic complications and the composite outcomes did not differ significantly among groups (Table 8). Blood transfusions were required in 11.4% of patients overall. Major bleeding occurred in 3.3% of those randomized to receive abciximab alone and 9.2% in all reteplase-abciximab groups combined (p=0.11). Thrombocytopenia occurred more often in patients who received abciximab and reteplase than in those who received abciximab alone (8.3% vs 1.6%, p=0.12). Three ICHs occurred during the trial, one each in recipients of abciximab-reteplase 5 U, reteplase 10 + 10 U, and abciximab-reteplase 5 + 5 U. Two of them were fatal. The investigators concluded that combining reteplase and abciximab to treat acute myocardial infarction can increase the rate of complete reperfusion compared with reteplase alone.

Table 10. Preliminary Results of INTRO-AMI Dose-Finding Phase[a]

Group	TIMI Grade 3 Flow, 60 Minutes (%) (n=77)	TIMI Grade 3 Flow, 90 Minutes (%) (n=156)
A	48	50
B	47	39
E	59	58
F	65	78
G	59	75
I	51	63
N	60	74
O	46	55

[a]Gong SD, personal communication, May 2, 2000.

The Integrilin and Reduced Dose of Thrombolytics in Acute Myocardial Infarction (INTRO-AMI) study[87] investigated the efficacy of low-dosage alteplase in combination with escalating dosages of eptifibatide for patients seen within 6 hours of onset of acute ST segment elevation myocardial infarction (Table 9). A bolus dose of UFH 60 U/kg (maximum 4000 U)

Table 11. Continuing Randomized, Multicenter Clinical Trials of Combination Thrombolytic, Glycoprotein IIb-IIIa Inhibitor, and Anticoagulant Therapy for Acute Myocardial Infarction

Trial Name	Thrombolytic	GP IIb-IIIa Receptor Inhibitor	Anticoagulant	End Point
Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO V)	Reteplase	Abciximab	UFH, dalteparin	Mortality
Assessment of the Safety and Efficacy of New Thrombolytic (ASSENT 3), ASSENT 3 Plus	Tenecteplase	Abciximab	UFH, enoxaparin	Mortality, recurrent myocardial infarction, refractory ischemia, ICH, major bleeding
Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI [TIMI 20])	Tenecteplase	Eptifibatide	UFH	60-min TIMI 3 flow, ST segment resolution
Fibrinolytic and Aggrastat ST Elevation Resolution (FASTER [TIMI 24])	Tenecteplase	Tirofiban	UFH	60-min TIMI 3 flow, ST segment resolution
Enoxaparin and TNK-tPA with or without GP IIb-IIIa Inhibitors as Reperfusion Strategy in ST Elevation MI (ENTIRE [TIMI-23])	Tenecteplase	Abciximab	UFH, enoxaparin	60-min TIMI 3 flow, ST segment resolution
Streptokinase Acute Myocardial Infarction (SK-AMI)	Streptokinase	None	Enoxaparin	TIMI 3 flow, safety
Hirulog Early Reperfusion/ Occlusion (HERO-II)	Streptokinase	None	UFH, bivalrudin	Mortality

UFH = unfractionated heparin; ICH = intracranial hemorrhage; TIMI = thrombolysis in myocardial infarction.

was administered before the start of alteplase, followed by infusion of 7 U/kg/hour (not to exceed 800 U/hr). The primary end point was TIMI grade 3 flow at 60 minutes, which ranged from 47–60% and among groups (Table 10) (Gong SD, personal communication, May 2, 2000). Sixty percent of patients receiving eptifibatide as a double bolus of 180 µg/kg followed by 1.33 µg/kg/minute in combination with alteplase 50 mg (15-mg bolus followed by 35 mg administered over 1 hr) achieved TIMI grade 3 flow at 60 minutes, as did 74% of patients at 90 minutes. Although higher, the 180-µg/kg bolus of eptifibatide followed by an infusion of 2.0 µg/kg/minute resulted in lower grade 3 flow rates at 60 and 90 minutes. The rate of major bleeding (classified according to TIMI bleeding scale[88]) was 16.7% with the 180-µg/kg double-bolus followed by 1.33 µg/kg/minute infusion and 22.7% with 2.0 µg/kg/minute infusion in combination with alteplase 50 mg (no p value given). Two of the most promising combination regimens[87] are being tested versus accelerated alteplase alone in the dose-confirmation trial.

Whereas all of these trials suggest that reduced-dosage thrombolytic plus full-dosage GP IIb-IIIa blocker enhance efficacy compared with full-dosage thrombolytic alone, none of them was large enough to confirm safety. Table 11 summarizes continuing myocardial infarction trials that combine thrombolytics with GP IIb-IIIa inhibitors.

Adjunctive Therapy with Unfractionated Heparin

Dosing of UFH with thrombolysis is evolving. Recommendations from the ACC-AHA suggest that intravenous UFH is required with reteplase and alteplase and is optional with nonfibrin-specific SK.[32] Whereas UFH improves coronary artery patency and reduces rates of reocclusion when administered with alteplase for ST segment elevation myocardial infarction,[2, 89, 90] its routine addition to SK therapy is not substantiated.[32] Also, elevated aPTT levels after UFH and thrombolysis were associated with high rates of

30-day mortality, stroke, and bleeding.[91] Thus UFH infusion is not recommended after SK until the aPTT, checked 6 hours after starting SK, is less than 2.0 times the control (~ 70 sec). Dosages of UFH administered with reteplase and alteplase are much lower than previously recommended and are based on GUSTO and TIMI 10B studies, a 60-U/kg (maximum 4000 U) bolus dose followed by 12 U/kg/hour (maximum 1000 U/hr) titrated to an aPTT of 1.5–2.0 times control (50–70 sec).[32] However, in the combination trials with GP IIb-IIIa inhibitors, dosages of UFH were 40-U/kg bolus followed by 15 U/kg/hour, 60 U/kg followed by 7 U/kg/hour, and 30 U/kg followed by 4 U/kg/hour.[82, 86] Thus, whereas concomitant anticoagulant is required with fibrin-specific thrombolytics, the exact dosage is not known. However, the lower restoration of TIMI 3 flow seen with very-low-dosage UFH in TIMI 14 and SPEED, and selection of 60 U/kg for GUSTO V, suggest that 60 U/kg is recommended.

Adjunctive Therapy with LMWHs

Whereas UFH is the recommended anticoagulant for ST segment elevation myocardial infarction, certain features of LMWHs make them attractive alternatives. They are easier to administer, have predictable dose-response relationships, and do not require aPTT monitoring. In non-ST segment elevation acute coronary syndromes, enoxaparin proved superior to UFH in two large, randomized clinical trials.[92, 93] Pharmacologic reasons for enoxaparin's superiority include its ability to inhibit thrombin generation and activity to a greater extent than UFH in acute coronary syndromes,[94] causing less platelet activation,[95] and to suppress activity of von Willebrand factor necessary for clot adherence to endothelium.[96]

Six studies examined LMWHs administered with thrombolytics.[97–102] Small dose-finding studies of dalteparin[97, 98] and enoxaparin,[99] as well as randomized clinical trials of dalteparin[100] and enoxaparin,[101, 102] established safety. In the Biochemical Markers in Acute Coronary Syndromes (BIOMACS) II trial,[100] 101 patients with myocardial infarction were randomized to receive either dalteparin 100 IU/kg subcutaneously or placebo just before SK, with a second dose of dalteparin 120 IU/kg given to all patients 12 hours after the first dose of either placebo or dalteparin. The primary end point was TIMI flow measured 20–28 hours after study drug initiation and 8–16 hours after the last injection of study drug. The trend was toward improved TIMI 3 flow with dalteparin (68% vs 51%, p=0.10). Six bleeding events occurred, five of which were in dalteparin recipients. Of the events, two were major, both occurring in the dalteparin group. The rest were minor bleeds, most occurring at the site of puncture in the femoral artery.

A preliminary report[101] examined 300 patients randomly assigned to an enoxaparin 40-mg intravenous bolus followed by 40 mg subcutaneously every 8 hours or to UFH, after receiving thrombolytic therapy. No significant differences were found between groups in rates of death, nonfatal myocardial infarction, or readmission with ischemic chest pain. A significant difference was observed in the composite end point of death, nonfatal myocardial infarction, or readmission with ischemic chest pain in favor of the enoxaparin-treated patients (26% vs 36%, p=0.04). Fewer reinfarctions in the 48 hours after discontinuing therapy were seen in the enoxaparin group (3 vs 10 patients, p=0.05). No difference in the rate of clinically significant bleeding was observed between the two groups. Enoxaparin appears safe and effective for reducing cardiac events when used after thrombolytic therapy.

In the Heparin Aspirin Reperfusion Trial (HART) II,[102] enoxaparin 30-mg intravenous bolus followed by 1 mg/kg subcutaneously every 12 hours was compared with UFH 4000–5000-U intravenous bolus followed by a continuous infusion of 15 U/kg/hour in 400 patients receiving accelerated alteplase. The primary outcome was TIMI 3 flow measured at 90 minutes. A secondary end point was clinical outcome measured at 30 days. Similar to BIOMACS II, the results of HART II revealed a "trend" for improved TIMI 3 (52.9% vs 47.6%, p value not reported) and TIMI grade 2 or 3 flow (80.1% vs 75.1%, p value not reported). Among patients with TIMI 3 flow, fewer of those receiving enoxaparin experienced reocclusion at 1 week compared with those given UFH (5.9% vs 9.8%, p value not reported). Clinical outcomes of bleeding, death, or urgent revascularization were similar in the two groups. These preliminary results are being tested in larger clinical trials described in Table 11.

Facilitated Percutaneous Coronary Intervention after Thrombolysis

Studies of thrombolysis followed by immediate

angiography suggested high rates of thrombotic and bleeding complications.[103–105] One trial comparing full-dosage SK and immediate PCI versus PCI alone reported similar patency rates and higher bleeding rates in SK-treated patients.[106] Facilitated PCI is a term used to describe planned PCI after pharmacologic reperfusion therapy.[107] An improved pharmacologic regimen could lessen the need for PCI resulting from earlier achievement of TIMI 3 flow, and patients scheduled for early PCI may be more stable and have fewer adverse cardiac events during and after PCI.[107]

The multicenter, randomized, double-blind, placebo-controlled Plasminogen-activator Angioplasty Compatibility Trial (PACT)[108] investigated the efficacy and safety of reduced-dosage alteplase to promote early patency during the delay patients experience while waiting for PCI. Patients were eligible to participate if they had symptoms of ischemia for at least 30 minutes and ST segment elevation on ECG, and were seen within 6 hours of onset of symptoms.

Patients received UFH 5000-U bolus followed by an infusion of 1000 U/hour (1200 U/hr for those weighing > 80 kg) and oral aspirin 325 mg. They were then randomized to receive a 50-mg bolus of alteplase or placebo administered over 3 minutes. Angiography was performed as soon as possible after study drug administration. If TIMI grade 0, 1, or 2 flow was observed in the infarct related artery, PCI was performed immediately. If grade 3 flow was observed, a second dose of the study drug was administered and PCI deferred. Left ventriculograms were performed on all patients. Unfractionated heparin was continued for a minimum of 48 hours and titrated to maintain an aPTT of 60–85 seconds. Follow-up angiography was performed 5–7 days after admission. Other drugs, including GP IIb-IIIa inhibitors, and interventions were left to the discretion of the investigators.

On arrival at the catheterization laboratory, TIMI grade 2 or 3 flow was present in 61% of 302 patients who received alteplase and 34% of 304 who received placebo ($p<0.001$). Significantly more patients treated with alteplase had grade 3 flow when arriving at the catheterization laboratory (33% vs 15%, $p<0.0001$). No difference in PCI success was observed with conversion of vessels with grade 1 or 2 flow to grade 2 or 3 flow occurring in 92.8% of alteplase recipients and 94.6% of placebo recipients ($p=0.52$), and conversion to grade 3 flow occurring in 76.6% and 79.0%, respectively ($p=0.62$).

Percutaneous coronary intervention restored grade 3 flow in 82.8% of patients who received alteplase and 86.7% of those who received placebo when the initial flow was grade 2 ($p=0.59$). Reocclusion rates were similar for both groups. Balloon PTCA accounted for 74% of interventions. In each group, 26% of patients received stents and 5% received abciximab during the intervention.

Initial left ventriculograms were analyzed in 444 patients and follow-up ventriculograms in 373. There was no significant difference in ejection fraction when groups were compared by treatment assignment, without regard to time, method of patency, or final TIMI flow grade. Timing of grade 3 flow restoration influenced left ventricular function, with patients who came to the catheterization laboratory with grade 3 flow already present having an initial mean ejection fraction of 60.5% and a convalescent mean ejection fraction of 62.4%. This was compared with those who underwent PTCA who had initial mean ejection fraction of 58.7% and a convalescent mean ejection fraction of 57.9% ($p=0.26$ initial, $p=0.004$ convalescent). Those who never achieved grade 3 flow had an initial mean ejection fraction of 55.8% and convalescent mean ejection fraction of 54.7%. In 25 patients, PTCA restored grade 3 flow within 1 hour of study drug administration. These patients had a mean convalescent ejection fraction of 62.5%, which was similar to those who arrived at the catheterization laboratory with grade 3 flow. The infarct-related vessel was mechanically opened in 88% of patients longer than 1 hour after study drug administration. The convalescent ejection fraction in these patients was 57.3%, which was significantly lower than in those who were reperfused pharmacologically or by very early mechanical intervention (62.4% and 62.5%, respectively, $p<0.005$).

The frequency of adverse events did not differ significantly between groups. Major hemorrhage occurred in 12.9% and 13.5% of alteplase- and placebo-treated patients, respectively ($p=0.84$). No difference existed between groups in the need for urgent revascularization at a later date. No significant difference in 30-day mortality rates were observed among those arriving at the catheterization laboratory with an open infarct-related artery, those who achieved TIMI grade 3 flow with PTCA, and those who never achieved TIMI grade 3 flow (2.1%, 3.1%, 4.7%, respectively, $p=0.48$). Similarly, mortality rates at

1 year did not differ significantly (2.8%, 5.3%, 7.9%, respectively, p=0.18).

The investigators concluded that a regimen of low-dosage thrombolytic therapy with subsequent PCI might lead to early recanalization, which may result in preservation of left ventricular function without an increase in adverse events. A separate analysis of patients who received adjunctive abciximab was not provided.[108]

Because of success with adjunctive GP IIb-IIIa receptor antagonists in PCI to reduce adverse cardiac events in patients with non-ST segment elevation acute coronary syndromes,[109] the agents were studied in ST segment elevation myocardial infarction to minimize complications of PCI after administration of thrombolysis. In the TIMI 14 trial, 133 patients underwent early PCI after 90-minute angiogram. Patients receiving alteplase or alteplase plus abciximab had a higher rate of resolution of ST segment elevation, a marker associate with improved subendocardial blood flow and mortality in larger studies, compared with patients receiving thrombolytic therapy alone, 49% versus 8%.[110] In the SPEED trial,[87] PCI of the infarct-related artery at 60–90 minutes was performed in 81% of patients receiving abciximab alone (phase A), 75% receiving abciximab plus all low dosages of reteplase (phases A and B), and 67.5% receiving abciximab plus two 5-U bolus doses of reteplase (phases A and B). Success of PCI was 97%, 89%, and 86%, respectively.

Preliminary results were reported from the subgroup of patients undergoing PCI in SPEED.[111] The TIMI 3 flow and rates of death, myocardial infarction, or urgent revascularization were compared in 47 patients who received abciximab alone and 161 receiving abciximab plus two 5-U bolus doses of reteplase who underwent early PCI within 60–90 minutes after starting thrombolytic therapy. Angiographic results were compared in those with initial TIMI grade 0–1 flow versus those with grade 2–3 flow. Significantly more patients with initial flow of 0–1 underwent early PCI compared with those with initial flow of 2–3 (90% vs 62%, $p<0.001$). Fewer patients receiving abciximab plus half-dosage reteplase underwent PCI (65% vs 79%, $p<0.05$) compared with those receiving abciximab alone. The rate of TIMI 3 flow before PCI was higher in patients receiving abciximab plus half-dosage reteplase than in those receiving abciximab alone (47% vs 27%, $p<0.05$). After PCI, grade 3 flow was achieved in 87% and 95% of patients, respectively. At 30 days, the rate of death, myocardial infarction, or need for urgent revascularization was 6.9%. Major bleeding occurred in 4.3% of all 321 patients who underwent PCI. Thus early PCI after combination reteplase and abciximab therapy is safe, in addition to facilitating high TIMI 3 flow rates, and may improve outcomes in myocardial infarction. The investigators also concluded combination therapy with reteplase and abciximab may reduce the need for early PCI.[111]

A subgroup of 117 patients from INTRO-AMI[112] underwent PCI at the time of catheterization 60 minutes after receiving eptifibatide in combination with alteplase 25 or 50 mg for myocardial infarction. Both mortality and recurrent myocardial infarction were preliminarily reported to be 3.7%. Stroke occurred in 0.7% of patients. Major and minor bleeding events were observed in 14.7% and 29.4%, respectively.[109] Data from SPEED and preliminary data from INTRO-AMI suggest that immediate PCI in combination with low-dosage thrombolytic therapy and platelet inhibition appears to be safe and effective.

Beneficial success of combined thrombolytic and GP IIb-IIIa receptor inhibitor therapy in patients undergoing PCI in SPEED, TIMI 14, and INTRO-AMI may stem from the agents' dethrombosis properties. This phenomenon, observed first anecdotally during angiography whereby the clot would disappear after bolus injection of the GP IIb-IIIa receptor inhibitor,[113] has now been confirmed, with GP IIb-IIIa receptor inhibitor therapy alone showing rates of TIMI 3 flow higher than placebo. Lower clot burden reduced the rate of major adverse cardiac events after PCI.[114] Further investigation should be undertaken to evaluate GP IIb-IIIa inhibitors in patients who are not thrombolytic candidates secondary to selected contraindications, or primary PCI candidates because of lack of availability.

Summary

There is continued interest in thrombolysis for myocardial infarction. Development of newer agents with longer half-lives, such as reteplase and tenecteplase, may reduce delays through early administration. Studies of prehospital administration of newer agents continue. Reteplase, which does not require weight-adjusted dosing, may lead to fewer drug errors since weight is often not recorded in the emergency room. However, since thrombolysis

alone may not achieve adequate reperfusion, rescue PCI or facilitated PCI may have to be performed. Triple therapy with thrombolysis, GP IIb-IIIa inhibitor, and PCI is being investigated. Preliminary data suggest enhanced TIMI 3 flow without higher bleeding rates. Adjunctive therapy with lower dosages of UFH or dalteparin and enoxaparin are also being studied. The precise dosage of UFH that is most efficacious and not associated with increased bleeding is not known. The LMWHs offer ease of administration, with preliminary studies suggesting enhanced TIMI 3 flow. Larger studies of combined GP IIb-IIIa receptor inhibitors with LMWH and thrombolysis, which are adequately powered to determine safety and mortality, are under way. Reperfusion therapy for patients with myocardial infarction is changing rapidly, and pharmacists should keep up to date on newer antithrombotic therapies to enhance myocardial blood flow and reduce mortality.

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