Managing ST-elevation myocardial infarction

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Fibrinolytic therapy has long been an important component of the treatment of patients with ST-elevation myocardial infarction (STEMI). Several new treatment strategies are currently being developed to improve the treatment of STEMI. These strategies include the development of new fibrinolytic agents that possess longer half-lives or increased fibrin specificity as compared with streptokinase or alteplase; combining fibrinolytic therapy with recently developed antiplatelet medications; and substitution of low-molecular-weight heparins or other newer thrombin inhibitors for unfractionated heparin to improve the safety, convenience and efficacy of antithrombotic therapy.

Key Words: Antiplatelet agents, fibrinolytic drugs, low-molecular-weight heparin, myocardial infarction.

Introduction

The acute coronary syndromes of unstable angina (UA) and myocardial infarction (MI) are usually caused by the formation of a platelet-rich thrombus at the site of a ruptured or eroded atherosclerotic plaque within a coronary artery. Fibrinolytic agents, which lyse obstructing thrombus and restore blood flow to the ischaemic myocardium, reduce the likelihood of death or subsequent myocardial injury when administered soon after arterial occlusion occurs.

Despite the demonstrated effectiveness of these medications, the usefulness of fibrinolytic therapy is limited by a number of end-points. First, even when fibrinolytic therapy is rapidly initiated, treatment fails to produce adequate and durable restoration of blood flow in approximately one-half of patients. Considerable recent research has focused on identifying ways to improve the ability of fibrinolytic agents to restore blood flow as rapidly and completely as possible, and to increase the ease with which they may be used. Second, patients with MI often exhibit persistently elevated thrombin generation and activity, which is associated with a significantly increased risk for rethrombosis, which may result in reinfarction and death. Fibrinolytic drugs do not correct this hypercoagulable state, and may in fact exacerbate it by releasing thrombin and other thrombogenic materials from the dissolving thrombus. Third, these medications are associated with a substantial risk for bleeding complications. Finally, the most widely used fibrinolytic agents must be administered by continuous intravenous infusion, making them inconvenient to use.

Three potential strategies to improve the treatment of patients with MI are currently undergoing evaluation in clinical trials. The first is the development of new fibrinolytic medications that have improved fibrin specificity, thereby directing the fibrinolytic activity specifically to the obstructing thrombus and reducing systemic fibrinolytic effects and the associated risk for bleeding complications. The second approach is the development of new anticoagulants with longer half-lives, permitting bolus administration rather than continuous intravenous infusion, and improved safety and ease of use in comparison with unfractionated heparin (UFH). The third approach is the addition of antiplatelet medications to the treatment regimen. The efficacy and safety of antithrombin and antiplatelet agents for the treatment of unstable coronary artery disease have been established in clinical trials of tens of thousands of patients diagnosed with UA or non-ST-elevation myocardial infarction (NSTEMI). The role of these medications in the treatment of ST-elevation myo-
cardiac infarction (STEMI) and the best ways to combine them with fibrinolytic therapy have recently been defined in large trials, which are reviewed in the present report.

### New fibrinolytic agents

Streptokinase, a ‘first-generation’ fibrinolytic agent, was among the first clot-dissolving medications to enter clinical practice and it remains in widespread use for the treatment of MI. Streptokinase rapidly and completely catalyzes the conversion of plasminogen to plasmin throughout the body, not only dissolving obstructing blood clots but also increasing the risk for bleeding complications\(^{10,11}\). In response to this latter concern, a number of ‘second-generation’ fibrinolytic agents were developed; the most widely used of these agents is tissue-type plasminogen activator (alteplase). Despite the fact that alteplase is more fibrin specific than is streptokinase, the risk for major non-cerebral bleeding complications is higher with alteplase\(^{12}\) and the risk for intra-cranial haemorrhage or haemorrhagic stroke is also greater than that with streptokinase\(^{4,13}\).

During the past decade a large number of new ‘third-generation’ fibrinolytic agents were developed, and many of these agents have been evaluated in clinical trials of STEMI\(^{10}\). Two of these third-generation fibrinolytics are currently available for the treatment of MI. Retepase has a half-life that is 3–3.5 times longer than that of alteplase, with a comparable degree of fibrin specificity; intravenous bolus treatment regimens using repeteplase are currently being evaluated in clinical trials. A second agent, tenecteplase, is a variant of alteplase that was designed to have a long half-life, increased fibrin specificity and increased resistance to inactivation by plasminogen activator inhibitor-I. The double-blind, randomized Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-2 trial\(^{14}\) compared a rapid infusion of alteplase versus a weight-adjusted, single bolus injection of tenecteplase in STEMI patients within 6 h of symptom onset. The results showed that 30-day mortality was similar between the two groups. Intracranial haemorrhage rates were also similar between the two groups, but the tenecteplase group had fewer non-cerebral bleeding complications and less need for transfusion.

Two new fibrinolytic agents are also being evaluated in phase II pilot studies. The first is amediplase, a ‘fusion protein’ that consists of components of the tissue-type plasminogen activator molecule and components of another fibrinolytic molecule, single-chain urokinase plasminogen activator\(^{15}\). Amediplase, which is somewhat more fibrin specific than alteplase, is being evaluated in the 3K2 clinical trial, in which 200 patients with MI will be randomly assigned to treatment with one of two doses of amediplase (1-0 or 1-2 mg . kg\(^{-1}\)). The second of these new fibrinolitics is a variant of staphylokinase, a fibrinolytic substance that is derived from staphylococcus bacteria. This variant of staphylokinase has been conjugated with polyethylene glycol in a process referred to as pegylation. Pegylation reduces the rate at which a drug is removed from the circulation, prolonging the half-life and increasing the suitability of the agent for bolus (rather than continuous intravenous) administration. The Collaborative Angiographic Patency Trial of Recombinant Staphylokinase (CAPTORS)-2 trial is currently comparing single-bolus administration of peglated staphylokinase (either 0-0025 or 0-0375 mg . kg\(^{-1}\)) with alteplase. The planned enrollment of this study is 400 patients. The primary endpoint for both the 3K2 trial and the CAPTORS-2 trial is angiographically measured blood flow through the target vessel 60 min after treatment.

### Antiplatelet therapy

Activation and aggregation of platelets following the disruption of an atherosclerotic plaque is central to the pathogenesis of acute coronary artery disease, including acute MI. Platelet aggregation is completely dependent on the cross-linking of fibrinogen strands between fibrinogen receptors (the glycoprotein [GP]IIb/IIa receptor) on the platelet surface\(^{16}\). Even when fibrinolytic therapy re-establishes blood flow through the occluded artery, reocclusion of the target vessel develops soon after treatment in a substantial number of patients\(^{4}\). Several large clinical trials have found that GPIIb/IIa receptor antagonists significantly reduce the incidence of death or subsequent ischaemic events in patients with acute coronary syndromes. In an overview of clinical trials that together enrolled more than 32,000 patients with UA/STEmI\(^{17}\), the likelihood of death or repeat MI within 30 days was significantly reduced by GPIIb/IIa antagonists (9-0% of patients who received GPIIb/IIa antagonists versus 11-1% of patients who received standard therapy or placebo; \(P < 0-001\)).

The Thrombolysis in Myocardial Infarction (TIMI)-14 trial\(^{18}\) demonstrated that treatment with a GPIIb/IIa antagonist could improve long-term arterial perfusion following fibrinolytic therapy. After an initial dose-finding phase, in which abciximab was evaluated in 14 different reperfusion regimens in combination with both streptokinase and alteplase, 211 patients were randomly assigned to one of three treatment groups in a dose-certification phase. Patients in the control group received accelerated alteplase (100 mg) plus UFH (70 U . kg\(^{-1}\) bolus, 15 U . kg\(^{-1}\) per h infusion). Patients in the two experimental groups received both reduced-dose alteplase (15 mg initial bolus followed by 35 mg infused over 35 min) and abciximab (0-25 mg . kg\(^{-1}\) bolus followed by an infusion of 0-125 µg . kg\(^{-1}\) per min for 12 h), and were randomly assigned to treatment with either low-dose UFH (60 U . kg\(^{-1}\) bolus followed by infusion of 7 U . kg\(^{-1}\) per h) or very-low-dose UFH (30 U . kg\(^{-1}\) bolus followed by infusion of 4 U . kg\(^{-1}\) per h). All patients received aspirin 150–325 mg orally or 250–500 mg intravenously. Angiographic observations were made 60 and 90 min after treatment.

For the control group and the low-dose UFH group, the investigators combined the results from the dose-finding and dose-certification phases of the study; the results are
Figure 1 Abciximab increases the rate and extent of thrombolysis. The percentage of patients with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at 60 and 90 min is shown for a control group administered 100 mg accelerated-dose alteplase, and groups administered a 50-mg regimen of alteplase in combination with abciximab and either low-dose heparin or very-low-dose heparin. Pooled data (dose-finding plus dose-confirmation phases of the study) revealed that the combination of 50 mg alteplase and abciximab produced a higher percentage of patients with TIMI grade 3 flow than did 100 mg accelerated-dose alteplase. *Bolus 15 mg; infusion 35 mg over 60 min. †P = 0.0009 and ‡P = 0.01 versus control.

summarized in Fig. 1. Accelerated alteplase and standard-dose UFH produced TIMI grade 3 flow in 43% of patients at 60 min and in 62% of patients at 90 min. A reperfusion regimen of low-dose alteplase, abciximab and low-dose heparin significantly increased the proportion of patients exhibiting TIMI grade 3 flow at 90 min. The reperfusion regimen of low-dose alteplase, abciximab and very-low-dose UFH tended to produce an increase in the proportion of patients with TIMI grade 3 flow, especially at 60 min, although the differences between this treatment regimen and the control regimen were not statistically significant. In the dose-finding phase, the combination of abciximab and streptokinase was associated with major haemorrhage that correlated with increasing streptokinase dose. Among the treatment regimens examined in the dose-confirmation phase, no differences were noted in the incidence of bleeding complications or other adverse events.

The Strategies for Patency Enhancement in the Emergency Department (SPEED) trial (Global Utilization of Streptokinase and t-PA for Occcluded Coronary Arteries [GUSTO]-IV pilot trial) examined the utility of early percutaneous coronary intervention (PCI) in STEMI patients who had received thrombolytic and GPIIb/IIIa receptor antagonist agents. The researchers used the term ‘facilitated PCI’ to describe early, planned PCI after use of pharmacological agents intended to open the infarct-related artery. That study included 323 patients who underwent PCI with planned initial angiography, at a median 63 min after reperfusion therapy began. Ischaemic events, bleeding, angiographic results and clinical outcomes were compared between the intervention group and 162 patients who did not receive early PCI. The SPEED study showed that the combination strategy of platelet inhibition using abciximab and reduced-dose thrombolysis (reteplase) improved infarct-related artery patency at 60–90 min, as compared with abciximab alone or full-dose reteplase. The TIMI-14 study arrived at a similar conclusion using alteplase. SPEED also suggested that early PCI was safe and effective in this setting.

Two large phase III trials, GUSTO-V and ASSENT-3, examined GPIIb/IIIa receptor blockade in combination with reduced-dose fibrinolytic therapy.

The multicentre, international, open-label ASSENT-3 trial enrolled 6095 patients with symptoms of acute MI of less than 6 h duration. Patients were randomly assigned to one of three regimens: full-dose tenecteplase and enoxaparin; full-dose tenecteplase with weight-adjusted UFH; and half-dose tenecteplase with low-dose UFH and a 12-h infusion of abciximab. The composite end-point of the trial was 30-day mortality, in-hospital reinfarction and in-hospital refractory ischaemia, as well as major bleeding complications, including intra-cranial haemorrhage.

Analysis of the ASSENT-3 data revealed a reduction in the frequency of ischaemic complications for the tenecteplase/enoxaparin and tenecteplase/abciximab regimens. Specifically, much greater reductions in ischaemic complications of acute MI were observed in the enoxaparin and abciximab groups than were expected. The Kaplan–Meier curves for the primary efficacy and safety end-points are shown in Figs 2 and 3. Early after treatment, the curves for the enoxaparin and abciximab groups started to separate from the UFH curve.

Figure 2  Kaplan–Meier curves for primary efficacy end-point: Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial[21]. MI= myocardial infarction.

Figure 3  Kaplan–Meier curves for primary efficacy plus safety end-point: Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial[21]. ICH=intra-cranial haemorrhage; MI=myocardial infarction.

Overall, significantly fewer efficacy end-points were identified in the enoxaparin group than in the UFH group (11.4% versus 15.4%; relative risk 0.74, 95% confidence interval [CI] 0.63–0.87; P = 0.0002). Similarly, fewer efficacy end-points were identified in the abciximab group than in the UFH group (11.1% versus 15.4%; relative risk 0.72, 95% CI 0.61–0.84; P < 0.0001). The same was true for the efficacy plus safety end-point: for enoxaparin 13.7% versus 17.0% (relative risk 0.81, 95% CI 0.70–0.93; P = 0.0037) and for abciximab 14.2% versus 17.0% (relative risk 0.84, 95% CI 0.72–0.96; P = 0.01416). The ASSENT-3 investigators concluded that, given its efficacy, safety, ease of administration and lack of need for monitoring, the tenecteplase/enoxaparin combination is an attractive, alternative reperfusion strategy that merits additional study.

The GUSTO-V trial[30] was designed to detect a mortality difference between standard fibrinolytic therapy and the combination of reduced-dose fibrinolytic and a GPIIb/IIIa receptor antagonist. That randomized, multicentre, international, open-label trial enrolled 16,588 patients in the first 6 h of evolving STEMI. Patients were randomly assigned to standard-dose reteplase, or half-dose reteplase and full-dose abciximab. The primary end-point of the trial was 30-day mortality, with various complications of MI as secondary end-points. The all-case mortality rate at 30 days was 5.9% in the reteplase group versus 5.6% in the
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Figure 4 30-day mortality and activated partial thromboplastin time (aPTT) 12 h after heparin treatment.

combined reteplase and abciximab groups (odds ratio 0.95, 95% CI 0.84–1.08; P = 0.43). There were fewer deaths or non-fatal reinfarctions in patients receiving combination therapy than in the reteplase alone group, and the combination group also had fewer major non-fatal ischaemic complications of acute MI and lesser need for urgent revascularization. However, the combination group had a higher rate of non-intra-cranial bleeding complications. The GUSTO-V investigators concluded that the combination of a reduced dose of a plasminogen activator and a GPIIb/IIIa inhibitor offers 30-day survival outcomes similar to those seen with standard plasminogen activator therapy, and suggested that the results of a 1-year follow-up study may help to identify both those patients who gain particular benefit and those who are at increased risk with the use of such combination therapy.

Antithrombin therapy

In addition to activation of platelets, disruption of an atherosclerotic plaque also stimulates the production of thrombin. Thrombin generation is essential in the formation and maintenance of the obstructing thrombus in MI, and adequate anticoagulation is an important component of the standard of care for acute coronary artery disease. Although UFH has long been used as an anticoagulant, a number of new anticoagulant medications have recently become available or are expected to enter clinical practice in the near future.

Unfractionated heparin

Despite the fact that tens of thousands of patients have received UFH in clinical trials of acute coronary syndromes, the optimal heparin dose in this setting is not known. Excessive anticoagulation with UFH is associated with an increased risk for death; as shown in Fig. 4, the likelihood of death at 30 days among patients who were receiving UFH increased with increasing activated partial thromboplastin time (aPTT) measured shortly after the initiation of heparin treatment. According to treatment guidelines developed by the American Heart Association and the American College of Cardiology, UFH should be administered as an initial intravenous bolus of 60 U. kg⁻¹ followed by a maintenance infusion of 12 U. kg⁻¹ per h, with the infusion rate adjusted to maintain the aPTT between 50 and 70 s. For patients who weigh more than 70 kg, the maximum bolus dose should not exceed 4000 U and the maximum infused dose should not exceed 1000 U. h⁻¹.

UFH given subcutaneously did not provide any benefit in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-2 and International Study of Infarct Survival (ISIS)-3 trials. Data from the GUSTO-I clinical trial, in which patients with MI received UFH in combination with either streptokinase or alteplase, or both, suggested that UFH only partially inhibits thrombin generation when administered in combination with fibrinolytic therapy. Those investigators suggested that other antithrombotic agents, perhaps with more effect on earlier stages of the coagulation cascade, such as factor Xa or factor VIIa, might provide a more profound antithrombin effect. In GUSTO-I, subcutaneous UFH was not different from intravenous UFH in patients receiving streptokinase. This resulted in a recommendation in the European Society of Cardiology guidelines that UFH is not needed in patients receiving streptokinase.

The use of UFH also requires frequent anticoagulation monitoring and dose adjustment, but even with this monitoring anticoagulation is often outside the desired range. Data from the more than 10,000 patients enrolled in the GUSTO-I trial indicated that even with frequent dosage
adjustments the aPTT was outside the target range in about half of all patients[27]. In addition, despite the effectiveness of anticoagulation with UFH in the treatment of UA/NSTEMI, the role of UFH in combination with thrombolytic therapy is less well established. Clinical trials of UFH as an adjunct to streptokinase have not demonstrated that this treatment regimen is superior to the use of streptokinase without UFH, and current American College of Cardiology/American Heart Association[22] and European Society of Cardiology treatment guidelines do not recommend the use of UFH in this setting.

Low-molecular-weight heparins

Standard heparin is a heterogeneous mixture of molecules of highly variable molecular weights. Low-molecular-weight heparins (LMWHs), which are derived by the depolymerization of UFH, possess several important advantages in comparison with standard heparin[26]. These agents are more specific than UFH for factor Xa, rather than thrombin, and thereby have a relatively greater effect on thrombin generation. They also have better bioavailability following subcutaneous administration, longer half-lives, and they may be administered by subcutaneous administration without the need for continuous intravenous infusion or anticoagulation monitoring and dosage adjustment. LMWHs have been extensively evaluated for the treatment of UA/STEMI. For example, in two large, randomized, double-blind clinical trials of patients with UA or angiia at rest, the LMWH enoxaparin produced significantly greater reductions than did UFH in the occurrence of recurrent ischaemic events such as death, MI, or the need for revascularization procedures, and the results were maintained at 1 year follow-up[27-29].

The role of LMWH as an adjunct to fibrinolytic therapy for AMI has also been evaluated in several clinical trials. In one early study[30], 103 patients who received streptokinase and UFH for the acute treatment of STEMI were randomly assigned to continued anticoagulation therapy with open-label enoxaparin (40 mg once per day) for 25 days or to no additional treatment. At 6-month follow-up, reinfarction or angina had occurred in 43% of the untreated patients, as compared with 14% of those who received enoxaparin. These findings suggested that long-term treatment with LMWH could be a valuable adjunct to fibrinolytic therapy for the treatment of acute MI.

More recently, the Fraxiparin Anticoagulant Therapy in Myocardial Infarction Study Amsterdam (FATIMA) study[31] was designed to provide an initial assessment of the safety and efficacy of the LWMH nadroparin in combination with fibrinolytic therapy. A total of 30 patients diagnosed with acute MI underwent fibrinolytic treatment with alteplase followed by treatment with weight-adjusted subcutaneous nadroparin administered both before and after the initiation of fibrinolysis. Coronary angiography performed 5 days after treatment demonstrated a patent infarct-related artery in 24 out of the 30 patients. Treatment appeared well tolerated and no major bleeding complications were noted. In a second pilot study[32], the addition of dalteparin to fibrinolysis with streptokinase tended to produce a higher rate of TIMI grade 3 flow in the infarct-related artery than did placebo, although the difference between treatments was not statistically significant. Dalteparin treatment significantly reduced the number of ischaemic events between 6 and 24 h after treatment (16% versus 38% for dalteparin versus placebo; P = 0.04).

A number of trials have examined the effects of adding LMWHs to fibrinolytic therapy on angiographic measures of cardiac perfusion, or are currently underway to address this issue. In the Heparin and Aspirin Reperfusion Therapy (HART)-II study[33], patients with acute MI were treated with accelerated alteplase and aspirin, and were then randomly assigned to treatment with either UFH or enoxaparin. At angiographic evaluation 90 min after treatment, TIMI grade 2 or 3 flow in the target vessel was observed in 75.1% of patients who received UFH and in 80.1% of patients who received enoxaparin (not statistically significant). At a follow-up angiographic evaluation performed 1 week later, patients who had received enoxaparin were somewhat less likely than those who received UFH to have developed reocclusion, although the difference between the two groups was again not statistically significant (Fig. 5). No significant differences were observed between the two groups in terms of bleeding complications, and mortality rates, both in-hospital and after 30 days, were comparable. Thus, treatment with Twice-daily subcutaneous enoxaparin was at least as effective and safe as continuous intravenous treatment with UFH as an adjunct to fibrinolytic therapy.

In the Acute Myocardial Infarction – Streptokinase (AMI-SK) trial[34], 496 patients who had STEMI within the previous 12 h were treated with aspirin and streptokinase and were then randomly assigned to receive either enoxaparin (30 mg intravenously followed by 1 mg . kg⁻¹ subcutaneously every 12 h) or placebo. Enoxaparin or placebo were continued for 3–8 days during hospitalization. The primary end-point was TIMI grade 3 blood flow at day 8, and additional clinical follow-up was performed after 30 days. Patients who received enoxaparin were significantly more likely to exhibit evidence of ST-segment resolution on ECG 90 and 180 min after treatment (Fig. 6). Enoxaparin also significantly increased the number of patients with TIMI grade 3 flow after 8 days, from 57.8% with placebo to 70.3% with enoxaparin (P = 0.01). At 30-day follow-up the incidence of a composite end-point of death, MI, or angina was 13.4% for the enoxaparin group and 21.0% with UFH. Patients in the enoxaparin group tended to experience more bleeding complications (4.8% versus 2.5% for the enoxaparin and placebo groups, respectively), although this difference was not statistically significant (P = 0.2). No enoxaparin-treated patients developed intra-cranial haemorrhage or stroke during the follow-up period.

The addition of LMWH dalteparin to fibrinolytic therapy was evaluated in the ASSENT-PLUS trial[35], a phase II, open-label study in which 439 patients with STEMI were treated with alteplase and were randomized to receive either UFH or dalteparin. Dalteparin was administered as an initial dose of 120 IU antifactor Xa activity, one-quarter of which...
was given as an intravenous bolus at the time of alteplase treatment and the remainder was rapidly administered by subcutaneous injection. The patients then received additional subcutaneous dalteparin for 5–7 days. The primary end-point in that study was angiographically determined flow rate in the occluded vessel. As in the HART-II study described above, treatment with LMWH produced a trend toward greater TIMI grade 2 or 3 flow at 4–7 days, although the difference between the UFH and dalteparin groups was not statistically significant (75.6% versus 86.6% for the UFH and dalteparin groups, respectively). At day 7, the incidence of major bleeding complications was similar for the two treatment groups. Of note, the reinfarction rate was 5.2% with UFH, as compared with 0.9% with dalteparin; furthermore, the combined end-point of death and reinfarction occurred in 8.5% of patients who received UFH and in 4.1% of those who received LMWH.

The ASSENT-3 PLUS study (currently underway) will help to clarify the role of LWMHS in the treatment of MI, and the optimal timing of the initiation of reperfusion therapy. The trial features pre-hospital administration of tenecteplase in the ambulance, followed by randomization to either UFH or enoxaparin (approximately 800 patients per group).

Finally, the Enoxaparin and TNK with or without GP IIb/IIIa inhibitor as Reperfusion Strategy in STEMI (ENTIRE)-TIMI-23 study, is comparing the effects of different dosing regimens of tenecteplase, enoxaparin and abciximab in approximately 600 patients with STEMI. In that trial, patients with ST-segment elevation within the previous 6 h received aspirin and were then randomly assigned to one of four treatment groups. Patients in the first two groups received a standard reperfusion regimen with full-dose weight-adjusted tenecteplase (minimum dose for patients <60 kg in weight is 30 mg, increasing to a maximum of 50 mg for patients >90 kg), and in addition received either UFH (bolus dose of 60 U. kg⁻¹ followed by infusion of 12 U. kg⁻¹ per h for 36 h) or enoxaparin (1 mg . kg⁻¹ per day for 8 days). The group of patients who received enoxaparin was further divided into two subgroups; one of these groups received an initial intravenous bolus dose of enoxaparin (30 mg), whereas the other did not. The other two groups were treated with a combination reperfusion strategy of reduced-dose tenecteplase (with the dose ranging from 15 mg for patients <60 kg in weight to a maximum of 25 mg for patients >90 kg) and abciximab (administered as an intravenous bolus dose of 0.25 mg . kg⁻¹ followed by infusion of 0.125 mg . kg⁻¹ per h for 12 h), and were randomized to receive anticoagulation treatment with either enoxaparin or UFH (40 U. kg⁻¹ initial bolus, 5 U. kg⁻¹ per h infusion for 36 h).

The primary efficacy end-point is TIMI grade 3 blood flow at 60 min, and the primary safety end-point is TIMI major haemorrhage at 30 days. Several other secondary outcomes are being evaluated, including ST-segment resolution at 60 min and at 180 min. Clinical outcomes (death, MI, or recurrent ischaemia) at 36 h and 30 days after treatment, and need for PCI or bypass surgery within 30 days are also being assessed. Safety end-points include bleeding complications, thrombocytopenia, stroke and cardiac-related adverse events.

**Synthetic pentasaccharide**

Another recently developed antithrombotic agent is a synthetic pentasaccharide, fondaparinux, that enhances the
Direct thrombin inhibitors

Direct thrombin inhibitors bind to and block the regions of the thrombin molecule that allow it to interact with its substrates. Unlike heparin, direct thrombin inhibitors are active against both circulating and clot-bound thrombin, and they provide a more predictable antithrombin effect than does UFH[38]. The most extensively studied of these agents is hirudin. In the GUSTO-IIib trial[39], hirudin was not significantly better than UFH for the primary end-point of death or non-fatal MI, although it did significantly reduce the occurrence of a secondary end-point of death or any MI, fatal or non-fatal (1.3% versus 2.1% for the hirudin and UFH groups, respectively; $P = 0.001$). Two large trials of recombinant hirudin that included patients with STEMI[40,41] were discontinued prematurely because of an excess bleeding risk.

A new direct thrombin inhibitor, bivalrudin, is undergoing evaluation in the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial. Patients who have had STEMI within the previous 6 h will receive streptokinase (1.5 MU infused over 30–60 min), and will then be randomized to single-blind treatment with either UFH (dosage adjusted to maintain an aPTT between 50 and 75 s) or bivalrudin. The primary end-point will be all-cause mortality within 30 days of the initial hospitalization, and the planned enrollment for the trial is 17,000 patients.

### References


