Antithrombotic Therapy in Patients With Acute Coronary Syndromes

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The potential armamentarium of agents used in the treatment of acute coronary syndromes continues to expand, including such well-tested agents as aspirin, unfractionated heparin, and earlier-generation fibrinolytic agents, and newer agents such as low-molecular-weight heparins, direct thrombin inhibitors, thienopyridines, platelet glycoprotein IIb/IIIa receptor inhibitors, and bolus-administration fibrinolytic agents. Older and newer antithrombotic agents have undergone and continue to undergo intensive clinical investigation in patients with the clinical spectrum of acute coronary syndromes, which includes unstable angina, non–Q-wave (non–ST-segment elevation) myocardial infarction, and ST-segment elevation myocardial infarction. These studies, often conducted on an international scope and involving thousands of patients, provide data allowing practitioners to optimize the care of patients with acute coronary syndromes. In this article, studies of these established and newer agents in the treatment of patients with acute coronary syndromes are reviewed critically and summarized. Recommendations regarding use of antithrombotic agents in patients with acute coronary syndromes are then given.

UNDERSTANDING THE NOMENCLATURE USED IN CLINICAL TRIALS

Although older studies of antithrombotic therapy have addressed unstable angina as a distinct condition, more recent studies have recognized that unstable angina and non–Q-wave myocardial infarction (MI) are part of a continuum of coronary thrombotic disorders termed acute coronary syndromes and have assessed antithrombotic therapy in these patients as a group (and used acute coronary syndrome to refer to this group of patients). Acute coronary syndromes has also been used variably in the literature to also include those patients who present with ST-segment elevation MI. Further confusing the nomenclature is the fact that Q waves may not develop in some patients who present with ST-segment elevation (probably as a result of early spontaneous, pharmacological, or mechanical reperfusion) and are later termed to have non–Q-wave MI. Also, Q-wave MI may develop in a small proportion of patients who present without ST-segment elevation.

For the purposes of clarity in this review, in studies in which patients labeled as presenting with unstable angina or non–Q-wave MI were enrolled and studied, the term non–ST-segment elevation acute coronary syndromes will be used. The term acute coronary syndrome will be reserved only for describing the broad spectrum of patients that includes unstable angina, non–Q-wave MI, and ST-segment elevation MI.

ANTIPLATELET AGENTS

Aspirin

Aspirin has been used medicinally since antiquity. Its antithrombotic action is due to irreversible blockade of the formation of thromboxane A₂, a potent mediator of
platelet aggregation. The inhibitory effects of aspirin on platelet aggregation are rapid, with maximal effects achieved within 15 to 30 minutes of oral administration of a dose as low as 81 mg.\(^1\)

The beneficial effects of aspirin in patients with unstable angina were demonstrated in several studies conducted in the 1980s,\(^2,3\) including a study conducted at the Montreal Heart Institute.\(^4\) In that study, 479 patients with unstable angina were randomized to treatment with aspirin (325 mg twice daily), intravenous heparin sodium, both, or neither (\textbf{Figure 1}). Compared with patients who received neither therapy, those who were treated with aspirin were 71% less likely to suffer a nonfatal or fatal MI (absolute rates, approximately 12% vs 3%, respectively). In the larger Research Group on Instability in Coronary Artery Disease (RISC) study of patients with unstable angina or non-Q-wave MI, the risk for subsequent MI or death was reduced by aspirin therapy (75 mg/d) at 5-day follow-up by 57% (from 5.8% to 2.5%).\(^5\)

In the ISIS-2 (Second International Study of Infarct Survival) trial, more than 17000 patients with suspected MI were randomized to aspirin therapy (160 mg/d), streptokinase, both, or placebo. Aspirin or streptokinase therapy alone reduced vascular mortality by 23% to 25% compared with placebo therapy; treatment with both agents reduced vascular mortality by 42%.\(^6\) The study included patients with ST-segment elevation, ST-segment depression, bundle-branch block, or other electrocardiographic (ECG) abnormalities. Treatment with aspirin decreased vascular mortality by 23%, a reduction comparable to the 25% reduction achieved with streptokinase therapy. Patients in the ISIS-2 trial treated with streptokinase derived additional benefit from concomitant therapy with aspirin. In those treated with both agents, vascular mortality was decreased by 42%. The additional beneficial effect of aspirin in those receiving thrombolytic therapy is believed to be due at least in part to aspirin's decreasing the rates of vessel reocclusion and thus of myocardial infarction. The result of these treatment regimens on vascular mortality in the ISIS-2 trial are shown in \textbf{Figure 2}. These trials thus firmly established the clinically relevant beneficial effect of aspirin therapy for the broad range of patients with acute coronary syndromes.

\section*{Ticlopidine and Clopidogrel}

The thienopyridines ticlopidine hydrochloride and clopidogrel block adenosine diphosphate (ADP)–mediated platelet activation and lead to irreversible inhibition of platelet aggregation.\(^7\) The inhibitory effects of the thienopyridines on platelet aggregation may be synergistic to those achieved with aspirin therapy.\(^7\) Like aspirin, the thienopyridines are relatively weak inhibitors of platelet activation compared with the platelet glycoprotein IIb/IIIa (GpIIb-IIIa) inhibitors.

Although the thienopyridines have become an integral part of pharmacological therapy in patients undergoing coronary stent implantation, there remain only scant data on the role of these agents in patients with acute coronary syndromes. In an Italian study, 652 patients with unstable angina were treated with ticlopidine hydrochloride (Ticlid), 250 mg twice daily, plus conventional therapy or with conventional therapy alone during hospitalization, with continued therapy for approximately 6 months after discharge.\(^8\) Treatment with ticlopidine decreased the incidences of nonfatal MI and vascular death by 46%. However, the conventional therapy arm did not include aspirin or heparin, and most of the reduction in events with ticlopidine therapy occurred not during the initial hospitalization but in the months after discharge.

The relatively short onset of action (in terms of platelet inhibition) provided by a loading dose of clopidogrel (Plavix), the once-daily dosing schedule, and the moderate degree of platelet inhibition achieved might make this agent a possible alternate therapy in patients with acute coronary syndromes who have true aspirin allergies. However, such a role has not been established or, at least in terms of published studies, evaluated. Nevertheless, given the recognized importance of antiplatelet therapy in acute MI in patients with true aspirin allergies, it has been recommended that other antiplatelet agents such as clopidogrel or ticlopidine be considered as alternate therapies.\(^9\)
Platelet GpIIb-IIIa Inhibitors

Each platelet contains approximately 60,000 to 80,000 GpIIb-IIIa receptors for fibrinogen on its membrane. When platelets are activated, these GpIIb-IIIa complexes undergo a conformational change that enables them to bind fibrinogen. As illustrated in Figure 3, the binding to GpIIb-IIIa receptors located on different platelets by the same fibrinogen dimer leads to platelet aggregation. The GpIIb-IIIa inhibitor molecules bind to the GpIIb-IIIa complex and thereby block the binding of fibrinogen to its receptor, leading to complete inhibition of platelet aggregation.

There are currently 3 intravenously administered approved GpIIb-IIIa inhibitors. Abciximab (ReoPro) is the Fab fragment of a monoclonal antibody to GpIIb-IIIa that has been humanized to reduce immunogenicity.10 As the antibody fragment binds tightly to the GpIIb-IIIa receptor, the effective physiological half-life of platelet inhibition is relatively long (approximately 12 hours). Eptifibatide (Integrilin) is a synthetic cyclic heptapeptide.11 Tirofiban hydrochloride (Aggrastat) is a nonpeptide mimetic.12 Eptifibatide and tirofiban are competitive inhibitors of the GpIIb-IIIa receptor. The half-lives of the smaller molecules eptifibatide and tirofiban, which are predominantly renally cleared, are on the order of 90 to 120 minutes. Because these smaller molecules are predominantly renally cleared, the dose of these agents should be adjusted in patients with renal insufficiency.

At currently used doses, the GpIIb-IIIa receptors are able to inhibit platelet aggregation on the order of at least 80%.13 The contraindications to GpIIb-IIIa inhibitor use are primarily related to bleeding risks, and are, in general terms, comparable to those of thrombolytic therapy. Patients with platelet counts of less than 100 × 10^9/L should not be treated with these agents.

Most trials of the GpIIb-IIIa inhibitors have been performed in the setting of patients undergoing percutaneous revascularization. Several studies, however, have focused on the use of GpIIb-IIIa inhibitors as the initial or primary therapy in patients with non–ST-segment elevation acute coronary syndromes. Inclusion criteria for these trials generally consisted of the presence of (1) ischemic ST-segment depression, (2) transient and/or minor (<1 mm) ST-segment elevation, (3) ischemic T-wave inversions, or (4) elevated levels of creatine phosphokinase of muscle band (CPK-MB levels) on admission.

In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study,14 patients with non–ST-segment elevation acute coronary syndromes were initially treated with heparin alone, tirofiban alone, or tirofiban plus heparin for 48 hours before undergoing cardiac catheterization and, when appropriate, revascularization. The tirofiban-alone arm was terminated prematurely due to an excess of deaths compared with the heparin-alone arm. The primary composite end point of death, MI, or refractory ischemia at 7 days was lower in those treated with tirofiban plus heparin compared with those treated with heparin alone (12.9% vs 17.9%; P = .004). Most of this benefit was maintained at the 30-day and 6-month follow-ups.14

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study,15 almost 11,000 patients with non–ST-segment elevation acute coronary syndromes were randomized to treatment with eptifibatide (Integrilin) or placebo; heparin therapy was encouraged but not mandated. Patients could be treated medically alone, or could undergo subsequent cardiac catheterization and revascularization at the discretion of their physicians. Most patients in the study were treated solely with medical therapy. Overall, the primary composite end point of death or MI at 30 days occurred in fewer patients treated with eptifibatide than in those who received placebo (14.2% vs 15.7%; P = .04); in those patients in North America enrolled in PURSUIT, there was an approximate 22% reduction in death and MI with eptifibatide therapy (11.7% vs 15.0%). Those patients in PURSUIT who underwent percutaneous revascularization had the greatest relative reduction in adverse outcome (11.6% vs 16.7%; P = .01).15

In the Chimeric 7E3 Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study of patients with refractory unstable angina who were found during cardiac catheterization to have lesions amenable to percutaneous transluminal coronary angioplasty (PTCA) and were then subsequently treated with abciximab or placebo for 18 to 24 hours before undergoing PTCA, treatment with abciximab was asso-
associated with a lower incidence of adverse outcomes. The more general role of abciximab in the treatment of patients with non–ST-segment elevation acute coronary syndromes is being evaluated as part of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IV study.

A fourth intravenously administered GpIIb-IIIa inhibitor, lamifiban, which has been evaluated as therapy for non–ST-segment acute coronary syndromes in the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)–A and PARAGON-B trials, has not been shown to be of significant benefit, and is not approved for clinical use.

Boersma and colleagues analyzed the combined data from the PURSUIT, PRISM-PLUS, and CAPTURE studies, examining the benefits of GpIIb-IIIa therapy in patients with non–ST-segment elevation acute coronary syndromes during pharmacological therapy alone and for the first 48 hours after percutaneous coronary intervention in those patients who subsequently underwent the procedure. During the period of pharmacological therapy alone, those patients who received GpIIb-IIIa therapy had a 34% relative reduction in the incidence of death or nonfatal MI compared with those who received placebo therapy (absolute event rates, 2.5% and 3.8%, respectively; P<.001). The incidence of death or nonfatal MI during the first 48 hours after percutaneous coronary intervention in those who subsequently underwent the procedure was reduced by 41% with GpIIb-IIIa therapy (absolute rates, 4.9% and 8.0%, respectively; P<.001). These findings are illustrated in Figure 4.

Given the overall positive results of trials of intravenous GpIIb-IIIa inhibitors, and observations that a prothrombotic state may exist for weeks or even several months after acute ischemic events, it was hypothesized that postdischarge longer-term treatment with oral GpIIb-IIIa inhibitors would decrease ischemic events in patients with acute coronary syndromes. Despite initial encouraging results and high hopes for these trials, the results of phase 3 studies thus far have been disappointing. Treatment with oral GpIIb-IIIa inhibitors has been associated with increased rates of bleeding complications and/or trends toward an increased incidence of adverse ischemic events.

Although the explanation(s) for the disappointing results from these trials of oral GpIIb-IIIa inhibitors remains speculative, a partial explanation may be provided from a substudy of the ORAL GpIIb-IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes (OPUS)–Thrombin Inhibition in Myocardial Ischemia (TIMI) 16 trial, in which it was found that patients treated with the oral GpIIb-IIIa inhibitor orbofiban had a paradoxical increase in platelet reactivity (perhaps due to ligand-induced receptor activation).

ANTITHROMBIN AGENTS: UNFRACTIONATED HEPARIN, DIRECT THROMBIN INHIBITORS, AND LOW-MOLECULAR-WEIGHT HEPARINS

Unfractionated Heparin

Commercial preparations of unfractionated heparin consist of a heterogeneous mixture of glycosaminoglycans, with molecular weights ranging from approximately 3000 to 30000. Only about one third of the molecules in these products are anticoagulantly active. Heparin exerts its anticoagulant effect by interacting with antithrombin III, dramatically increasing its ability to bind to and neutralize thrombin and other activated clotting factors. Thrombin that is already fibrin bound, however, is relatively protected from inactivation by the heparin–antithrombin III complex.

In 1981, Telford and Wilson demonstrated that in patients with unstable angina, intravenous administration of unfractionated heparin reduced the rate of progression to MI from 15% to 3%, a relative reduction of 80%. In the Montreal Heart Institute trial, the incidence of nonfatal or fatal MI was reduced by treatment with intravenous heparin therapy from a rate of 12% in those treated with placebo alone to a rate of only 0.8% in those treated with heparin alone.

The role of unfractionated heparin in the treatment of MI in the modern era is still not well resolved. Individual studies of heparin in the prethrombolytic era produced inconsistent results. An overview of these studies of heparin therapy for acute MI found that patients who were not treated with aspirin had an 18% reduction in reinfarction and a 23% reduction in death; however, in those patients who were also treated with aspirin, the reductions were on the order of only 5% to 10%.

The role of adjunctive heparin therapy in patients with acute MI who are treated with thrombolytic therapy and aspirin is undergoing re-
ISIS-330 studies included arms in which patients treated with thrombolytic therapy, most of whom presented with ST-segment elevation, were randomized to adjunctive subcutaneous heparin sodium therapy (12,500 U twice daily) or no heparin therapy. When the results of both studies are combined, it appears that subcutaneous heparin therapy modestly reduces the incidence of inhospital mortality, although this benefit is no longer apparent at 5 weeks and is associated with a small increased risk for bleeding complications. In the GUSTO-I trial, in patients treated with streptokinase, there were no significant differences in 90-minute coronary artery patency or mortality between those treated with subcutaneous heparin and those treated with intravenous heparin.

Although in patients treated with tissue plasminogen-activator (tPA), intravenous heparin does not appear to improve early vessel patency when assessed angiographically 90 minutes after administration of the thrombolytic agent, it may have a role in maintaining vessel patency in the 1 to 4 days after tPA administration. An overview of randomized trials involving intravenous heparin therapy, however, did not detect any significant effects of heparin therapy on rates or recurrent ischemia, reinfarction, or mortality.

The dosing recommendations for intravenous heparin administration in patients treated with tPA has recently been revised by the American College of Cardiology–American Heart Association (ACC/AHA) Committee on Management of Acute Myocardial Infarction. These recommendations now call for even less aggressive heparin administration, with a bolus dose of 60 U/kg (maximum, 4000 U) at the initiation of tPA infusion and an initial maintenance infusion of approximately 12 U/kg per hour (maximum, 1000 U/h), subsequently adjusted as needed to a target activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times control (50-70 seconds). Although not specifically addressed in the Committee recommendations, it may be reasonable to extrapolate this heparin dosing regimen to patients treated with reteplase (r-PA) (and possibly tenecteplase [TNK-tPA]).

Direct Thrombin Inhibitors

As their name implies, the direct thrombin inhibitors can inactivate thrombin directly, without the need for antithrombin III. The prototype of the direct thrombin inhibitors is hirudin, a 65-amino acid polypeptide originally isolated from the saliva of the medicinal leech (but now produced by recombinant DNA technology). Bivalirudin (Hirulog) is a synthetic 20–amino acid polypeptide.

The introduction of direct thrombin inhibitors was accompanied by high hopes that these agents would prove superior to unfractionated heparin in the treatment of acute ischemic heart disease. Unlike unfractionated heparin, direct thrombin inhibitors do not require any cofactors, can neutralize clot-bound thrombin, and are not inactivated by plasma proteins or platelet factor 4. They also may provide a more reliable degree of anticoagulation and enhance the rate of thrombolysis with thrombolytic therapy better than unfractionated heparin. Early, generally modest-sized studies of these agents in patients who were and were not treated with thrombolytic therapy suggested that the direct thrombin inhibitors were safe, led to dose-dependent and therapeutic degrees of anticoagulation, improved angiographic findings and TIMI grade coronary arterial flow, and were associated with low rates of adverse outcomes.

Several larger trials subsequently compared hirudin with unfractionated heparin in patients with non–ST-segment elevation acute coronary syndromes. As part of the GUSTO IIb Study, more than 8000 patients were randomized to treatment with hirudin or unfractionated heparin. The primary end point of death or MI at 30 days was not notably different between treatment groups (8.3% vs 9.1%; P = .22).

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS)–1 pilot study, the combined end point of death, MI, or refractory angina occurred in 4.4% of patients treated with low-dose hirudin (0.2-mg/kg bolus, then 0.1-mg/kg per hour infusion), 3.0% of patients treated with moderate-dose hirudin (0.4-mg/kg bolus, then 0.15-mg/kg per hour infusion) and 6.5% of patients treated with unfractionated heparin. Based on these findings, in OASIS-2, more than 10,000 patients were randomized to treatment with this moderate dose regimen of hirudin or unfractionated heparin. The primary end point of death or new MI at 7 days occurred in 3.6% of those treated with hirudin and 4.2% of those treated with heparin (P = .08). The composite end point of death, myocardial infarction, or refractory angina occurred in 5.6% of those treated with hirudin and 6.7% of those treated with heparin (P = .01). These results are shown in Figure 5.
common with hirudin, although the number of life-threatening episodes and hemorrhagic strokes were similar.73 Pooled analysis of GUSTO IIb, OASIS-1, and OASIS-2 studies comparing hirudin therapy with unfractionated heparin sodium therapy in patients with acute coronary syndromes indicates relative risk. Adapted with permission from OASIS-2 Investigators.47

Several recent, generally larger, trials have also evaluated the utility of direct thrombin inhibitors as adjunctive therapy in patients with ST-segment elevation treated with thrombolytic therapy. In the TIMI 9A,48 GUSTO IIA,49 and Hirudin for Improvement of Thrombolysis–III50 trials, the use of relatively high doses of hirudin was associated with unacceptable high rates of intracranial bleeding. The TIMI and GUSTO trials were reconfigured (and were designated TIMI 9B and GUSTO IIb), and compared lower doses of hirudin and unfractionated heparin. In the TIMI 9B trial, the composite primary end point occurred in 12.9% of hirudin-treated patients and 11.9% of heparin-treated patients (P = NS).51 In the GUSTO IIb trial, death or MI at 30 days occurred in 9.9% of those treated with hirudin and 11.3% of those treated with heparin (P = .06). Taken together, the TIMI 9B and GUSTO IIb findings suggest little if any benefit of routinely using hirudin over unfractionated heparin as an adjunctive therapy in patients treated with thrombolytic therapy and aspirin.

Clinical studies of these agents have produced agent-dependent results (Table). Two studies of enoxaparin sodium (Lovenox) have determined that treatment with this LMWH may be superior to treatment with unfractionated heparin in patients with non–ST-segment elevation acute coronary syndromes. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study, the 14-day incidence of the combined end point of death, MI, or recurrent angina was lower in patients treated with subcutaneous enoxaparin sodium (1 mg/kg every 12 hours) than with intravenous unfractionated heparin sodium (16.6% vs 19.8%).62 The TIMI 11B study also found that treatment with enoxaparin sodium (30-mg intravenous bolus then 1 mg/kg subcutaneously every 12 hours) was superior to

**Figure 6.** Combined results from the Global Use of Strategies to Open Occluded Coronary Arteries IIb. Organization to Assess Strategies for Ischemic Syndromes (OASIS)-1, and OASIS-2 studies comparing hirudin therapy with unfractionated heparin sodium therapy in patients with acute coronary syndromes. RR indicates relative risk. Adapted with permission from OASIS-2 Investigators.47

**Figure 7.** The low-molecular-weight heparins (LMWH) are produced from chemical or enzymatic degradation and cleavage of unfractionated heparin. Methods of cleavage and isolation vary for different commercially produced LMWHs. Adapted with permission from Fareed et al.57

**Figure 8.** Percentage of composition of unfractionated and low-molecular-weight heparin (LMWH) in terms of molecular weight. The 3 LMWHs that have been evaluated in clinical trials of acute coronary syndromes are shown, along with their respective anti–factor Xa/anti–factor IIa activity. The LMWHs have relatively greater anti–factor Xa activity, resistance to inactivation from platelet factor 4 (PF4), less nonspecific binding, and greater inhibition of thrombin generation. Based on data from Weitz,60 Zed et al.,60 and Antman and Handin.58

Low-Molecular-Weight Heparin

Low-molecular-weight heparins are derived from enzymatic or chemical cleavage of unfractionated heparin (Figure 7). The potential advantages of low-molecular-weight heparins (LMWHs) have made them attractive subjects for study in acute coronary syndromes. Compared with unfractionated heparin, the LMWHs have less nonspecific binding, greater resistance to inactivation by platelet factor 4, greater anti–factor Xa activity (leading to greater “upstream” inhibition of the coagulation cascade), greater inhibition of thrombin generation, longer half-lives, and a more reliable anticoagulation effect (Figure 8).58,59 In addition, the LMWHs can be administered subcutaneously and require no monitoring of the aPTT.

The incidence of heparin-induced thrombocytopenia is much lower with LMWH than with unfractionated heparin.69-72 However, it should be noted that LMWH should not be administered to patients with established heparin-induced thrombocytopenia because of a high degree of cross-reactivity with the antibody associated with unfractionated heparin–induced thrombocytopenia (a direct thrombin inhibitor or danaparoid sodium should be used instead in such patients).59

Clinical studies of these agents have produced agent-dependent results (Table). Two studies of enoxaparin sodium (Lovenox) have determined that treatment with this LMWH may be superior to treatment with unfractionated heparin in patients with non–ST-segment elevation acute coronary syndromes. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study, the 14-day incidence of the combined end point of death, MI, or recurrent angina was lower in patients treated with subcutaneous enoxaparin sodium (1 mg/kg every 12 hours) than with intravenous unfractionated heparin sodium (16.6% vs 19.8%).62 The TIMI 11B study also found that treatment with enoxaparin sodium (30-mg intravenous bolus then 1 mg/kg subcutaneously every 12 hours) was superior to
treatment with intravenous heparin in reducing the 14-day composite end point of death, MI, or need for urgent revascularization (14.2% vs 16.7%). Meta-analysis of these 2 trials showed an approximate 20% reduction in death and cardiac ischemic events with enoxaparin therapy (Figure 9). An economic analysis of the ESSENCE data, shown in Figure 10, found treatment with enoxaparin to be cost-effective.

Although an earlier small study by Gurfinkel and colleagues found that treatment with nadroparin calcium (Fraxiparine) resulted in lower incidences of adverse events than treatment with placebo or intravenous unfractionated heparin, results from the larger Fraxiparine in Ischaemic Syndrome (FRAXIS) study demonstrate that outcome may be worse with nadroparin therapy when compared with intravenous unfractionated heparin therapy. In the Fraxiparine During Instability in Coronary Artery Disease (FRIC) study, treatment with dalteparin sodium (Fragmin) proved no better than that with unfractionated heparin, and in fact there were more deaths in those treated with dalteparin.

Studies of postdischarge, longer-duration LMWH therapy in patients with acute coronary syndromes have been generally discouraging. Despite the theoretical benefits of continuing antithrombin therapy for 1 to several months after discharge, no clinical trial has demonstrated a statistically significant benefit for such routine outpatient therapy in patients with non-ST-segment elevation acute coronary syndromes.

### THROMBOLYTIC (FIBRINOLYTIC) THERAPY

The thrombolytic (fibrinolytic) agents convert inactive plasminogen to active plasmin. Plasmin in turn acts to degrade fibrin, although plasmin is relatively substrate nonspecific and can degrade other proteins, including fibrinogen. The earliest thrombolytic agent tested in clinical trials, streptokinase, was not fibrin specific or clot specific, meaning that it would lead to indiscriminate systemic plasmin production, a situation that could lead to a systemic lytic state. The newer thrombolytic agents, beginning with the tPA alteplase and now including reteplase (r-PA) and tenecteplase (TNK-tPA), were designed to be more fibrin specific or clot specific, meaning that they would generate plasmin preferentially at the fibrin surface in a preformed thrombus, in the hopes that this would decrease bleeding complications (a hope that was not found to be the case). The longer half-lives of the next-generation thrombolytic agents, reteplase (r-PA) and tenecteplase (TNK-tPA), allow them to be administered as bolus therapy.

### Thrombolytic Therapy in Non–ST-Segment Elevation Acute Coronary Syndromes

Pathological, angiographic, and angioscopic studies performed during the 1980s demonstrated that intracoronary thrombus was a common finding in patients with

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**Table 1: Results of Studies Comparing LMWHs With Unfractionated Heparin in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes**

<table>
<thead>
<tr>
<th>Reference</th>
<th>LMWH</th>
<th>Dose</th>
<th>End Point</th>
<th>End Point With LMWH, %</th>
<th>End Point With Comparison Treatment, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurfinkel et al.64 1995</td>
<td>Nadroparin calcium (Fraxiparine)</td>
<td>214 U/kg SQ twice daily</td>
<td>Death, MI, recurrent angina, or major bleeding</td>
<td>22</td>
<td>63</td>
<td>.07</td>
</tr>
<tr>
<td>The FRAXIS Study Group.65 1999</td>
<td>Nadroparin calcium (Fraxiparine)</td>
<td>(1) 86 anti-factor Xa IU × 6 d</td>
<td>Death, MI, recurrent angina</td>
<td>(1) 17.8</td>
<td>15.1</td>
<td>(.05)</td>
</tr>
<tr>
<td>Klein et al.66 1997</td>
<td>Dalteparin sodium (Fragmin)</td>
<td>(2) 86 anti-factor Xa IU × 14 d</td>
<td>Death, MI, or recurrent angina</td>
<td>(2) 20.0</td>
<td>(2) .25</td>
<td></td>
</tr>
<tr>
<td>Cohen et al.67 1997</td>
<td>Enoxaparin sodium (Lovenox)</td>
<td>1 mg/kg SQ every 12 h</td>
<td>Death, MI, or recurrent angina</td>
<td>9.3</td>
<td>7.6</td>
<td>.33</td>
</tr>
<tr>
<td>Antman et al.68 1999</td>
<td>Enoxaparin sodium (Lovenox)</td>
<td>30 mg IV then 1 mg/kg SQ every 12 h</td>
<td>Death, MI, or urgent revascularization</td>
<td>16.6</td>
<td>19.8</td>
<td>.02</td>
</tr>
</tbody>
</table>

*LMWH indicates low-molecular-weight heparin; FRAXIS, Fraxiparine in Ischaemic Syndrome; SQ, subcutaneous; IV, intravenous; and MI, myocardial infarction.

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unstable angina. This finding led to the hypothesis that thrombolytic therapy would be of benefit in reducing adverse outcomes in patients with unstable angina. Early angiographic and clinical studies produced conflicting results. These trials found that MI developed in a greater percentage of patients treated with thrombolytic therapy than in those treated were treated with heparin alone.

As part of the TIMI 3B trial, 1473 patients with unstable angina or non–Q-wave MI were randomized to treatment with tPA or placebo. All patients were treated with aspirin and intravenous heparin. The composite primary end point of death, MI, or spontaneous recurrent or inducible ischemia occurred in a similar percentage of the tPA- and placebo-treated patients (54.2% and 55.5%, respectively).

The Fibrinolytics Therapy Trials’ Collaborative Group reviewed the data from all large trials of thrombolytic therapy in suspected acute MI. In patients who presented with ST-segment depression or with nonspecific ECG abnormalities, there was no benefit with thrombolytic therapy (Figure 11). If fact, those who presented with ST-segment depression actually tended to worsen if treated with thrombolytic therapy. Taken as a whole, analyses of studies in which thrombolytic therapy was administered to patients with non–ST-segment elevation acute coronary syndromes (unstable angina or non–ST-segment elevation MI) demonstrate that thrombolytic therapy leads to no net benefit and may actually increase the incidence of subsequent MI and death in such patients.

**Thrombolytic Therapy in ST-Segment Elevation MI**

The role of thrombolytic therapy in patients who present with ST-segment elevation MI has been demonstrated repeatedly and definitively. Studies comparing thrombolytic therapy with placebo have consistently shown a statistically and clinically significant reduction (usually on the order of 25%-33%) in mortality with thrombolytic therapy. Although initial studies relied on intracoronary administration of the thrombolytic agent, later studies demonstrated that the more practical intravenous administration of these agents was also efficacious. Thrombolytic agents that have been shown in placebo-controlled landmark studies to be efficacious include streptokinase (GISSI-1, Intravenous Streptokinase in Acute Myocardial Infarction [ISAM]), and ISIS-2), anistreplase (APSAC [anisoylated plasminogen streptokinase activator complex] Intervention Mortality Study [AIMS]), and tPA (Anglo-Scandinavian Study of Early Thrombolysis [ASSET], Estudio Multicentrico Estreptoquinasa Republicas de America del Sur [EMERAS], and Late Assessment of Thrombolytic Efficacy [LATE]).

The relative benefit of thrombolytic treatment in terms of lives saved per 1000 patients treated based on time to treatment from chest pain onset and initial ECG findings are shown in Figure 11. Patients who are treated within several hours of chest pain onset derive the greatest benefit.

As most earlier trials of thrombolytic therapy had enrolled patients who could be treated within 6 hours of chest pain onset, 2 trials addressed whether treatment of patients who presented later than 6 hours after chest pain onset could also derive benefit. In the EMERAS trial, which compared streptokinase with placebo, there was a trend toward decreased mortality in those treated 7 to 12 hours after symptom onset (11.7% vs 13.2%). In the LATE study, which compared tPA with placebo, there was a statistically
cally significant 25.6% reduction in mortality in those who were treated 6 to 12 hours after chest pain onset.57 These 2 trials, 86,87 as well as another analysis,85 provided data that extended the therapeutic window for thrombolytic therapy to 12 hours.

Among patients with ECG findings of ST-segment elevation, those with ST-segment elevation in the anterior leads derive the greatest benefit. Those with inferior ST-segment elevation derive a more modest but still clinically important reduction in mortality.85 Selected patients who present with symptoms highly suggestive of acute MI and ECG findings demonstrating bundle-branch block obscuring ST-segment analysis also derive significant benefit from thrombolytic therapy.85,88 In particular, those found to have a left bundle-branch block that is known or presumed to be new derive great benefit from thrombolytic therapy. The benefits of thrombolytic therapy based on time to treatment and on ECG findings are shown in Figure 11.

Several large trials have been performed comparing the relative efficacy of different thrombolytic agents. In the GISSI-280 and ISIS-339 trials, no significant differences in efficacy were found between streptokinase and tPA. However, proponents of tPA have noted that in these trials, heparin was administered subcutaneously (not intravenously) and was only started 4 to 12 hours after thrombolytic administration. In the first GUSTO trial, there was a statistically significant lower mortality rate in those treated with tPA and intravenous heparin therapy (started at the time of thrombolytic therapy) compared with those treated with streptokinase and intravenous or subcutaneous heparin (6.3% with tPA vs 7.3% with streptokinase; \( P = .001 \)).32 In these trials, tPA was associated with a small increased risk for intracranial hemorrhage compared with treatment with streptokinase.

The GUSTO-III trial compared tPA with the newer recombinant plasminogen activator (reteplase [r-PA]), which is administered in two 10-mg boluses given 30 minutes apart. There were no statistically significant differences in 30-day mortality, overall stroke rates, or combined end points between agents.80 In the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT–2) trial including almost 17,000 patients with acute MI, tPA therapy was compared with another newer plasminogen activator, tenecteplase (TNK-tPA), a modified form of tPA that can be administered as a single bolus (30-50 mg, based on weight). Compared with tPA, tenecteplase (TNK-tPA) has slower plasma clearance, better fibrin specificity, and higher resistance to plasminogen-activator inhibitor-1. The 30-day mortality rate and the rate of intracranial hemorrhage, however, were similar with tPA and tenecteplase (TNK-tPA).91

Decisions about whether to use tPA or streptokinase can be based to some extent on such factors as relative mortality reductions, intracranial hemorrhage risk, and cost (tPA is approximately 10 times more expensive than streptokinase). It has been proposed that tPA be preferentially considered in patients who present early after symptom onset with a large area of myocardium in jeopardy (eg, large anterior MI) and low risk for intracranial hemorrhage, whereas streptokinase be considered in those with less potential for mortality benefit and greater risk for intracranial hemorrhage.88 The newer thrombolytic agents reteplase (r-PA) and tenecteplase (TNK-tPA) appear to have similar overall efficacy compared with tPA; however, these newer agents are more easily administered and present the potential to treat selected patients with ST-segment elevation myocardial infarction before arrival in the emergency department.

**COMBINATION ANTITHROMBOTIC THERAPY**

The demonstrated efficacy of newer antithrombotic agents has led investigators to begin exploring the use of these newer agents in combination with thrombolytic therapy. As LMWHs and platelet GpIIb-IIIa inhibitors have been shown to be of benefit in patients with non-ST-segment elevation MI, investigators have begun to explore using these medications in combination. Recent preliminary observational data, presented by James J. Ferguson III, MD, at the European Society of Cardiology,92 suggested that the combination of the LMWH enoxaparin and a platelet GpIIb-IIIa inhibitor was safe and associated with a very low incidence of major adverse cardiac events (James J. Ferguson III, MD, written communication, November 1, 2000).

Preliminary studies in patients with ST-segment elevation MI suggest that the combination of GpIIb-IIIa receptor inhibition with modified doses of thrombolytic agents can lead to a greater incidence of normal coronary blood flow (TIMI 3 flow) as assessed using 60- to 90-minute angiograms than with that achieved with thrombolytic therapy alone.93-95 Normal coronary blood flow in the culprit coronary artery, as assessed using 90-minute angiography, is restored with thrombolytic therapy alone in approximately 50% to 55% of treated patients, whereas these preliminary results have found that combining GpIIb-IIIa therapy with half-dose thrombolytic therapy can result in restoration of normal blood flow in approximately 70% to 75% of treated patients.95,96-97 In general, results of combination therapy have been better with tPA or reteplase (r-PA) than with streptokinase, as therapy with streptokinase has resulted in lower rates of normal coronary blood flow and a greater incidence of bleeding complications.93-95,97 The results of larger trials of combination GpIIb-IIIa and thrombolytic therapy, including GUSTO IV–Acute Myocardial Infarction (AMI) (abciximab + half-dose reteplase [r-PA], Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI)–TIMI 20 (epifibatide + half-dose tenecteplase [TNK-tPA]), and Fibrinolytic and Aggrastat ST Elevation Resolution (FASTER)–TIMI 24 (tirofiban + half-dose tenecteplase [TNK-tPA]), should become available shortly, and could have a significant impact on our understanding of optimal treatment of patients with acute MI (Herbert B. Lee, PhD, written communication, March 3, 2000).

Preliminary data presented at the 2000 Meeting of the American College of Cardiology from the
Heparin Aspirin Reperfusion Trial (HART)—II study assessing the utility of enoxaparin as antithrombin therapy in patients with ST-segment elevation MI treated with accelerated tPA demonstrated trends toward greater 90-minute normal coronary blood flow in the infarct-related artery and lower reocclusion rates in patients who received enoxaparin compared with those who were treated with standard unfractionated heparin.

The Enoxaparin and TNK-tPA With or Without GP-IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation MI (ENTIRE)–TIMI 23 trial will help tie together advances in antiplatelet, antithrombin, and thrombolytic therapy, and will compare treatment with tenecteplase (TNK-tPA) and unfractionated heparin or enoxaparin with therapy with tenecteplase (TNK-tPA) plus abciximab and unfractionated heparin or enoxaparin.

RECOMMENDATIONS

Clinical studies now provide a wealth of information to guide treatment in patients with acute coronary syndromes. Planned and ongoing studies should help serve to further refine and define these recommendations.

Non–ST-Segment Acute Coronary Syndromes

All patients who present with unstable angina or non–ST-segment MI (non–Q-wave MI) should be treated with aspirin. Although there is scant clinical data, it seems reasonable to treat those with true aspirin allergies with clopidogrel or ticlopidine. Patients who present with ST-segment depression, transient ST-segment elevation, ischemic T-wave inversion, and/or positive cardiac enzymes and without contraindications should be strongly considered for additional antiplatelet therapy with a GPIIb-IIIa inhibitor.

All patients without bleeding contraindications should be treated with antithrombin therapy. Should those patients treated with unfractionated heparin, a weight-adjusted dosing regimen should be used, with an initial 80-U/kg bolus followed by an initial maintenance infusion dose of 18 U/kg, subsequently adjusted to maintain the aPTT at 1.5 to 2.5 times control. The direct thrombin inhibitor hirudin (possibly at a dose of a 0.4-mg/kg bolus then an initial infusion dose of 0.15 mg/kg per hour, subsequently adjusted to an aPTT level at 1.5-2.5 times control) can be considered instead of intravenous unfractionated heparin. Higher-risk patients (those with ischemic ECG abnormalities or positive CPK-MB or troponin levels) should be treated preferentially with enoxaparin (Lovenox). It may be reasonable to treat all patients with non–ST-elevation acute coronary syndrome preferentially with such an LMWH, given other advantages including patient comfort, ease of administration, and the fact that aPTT levels do not need to be monitored.

Thrombolytic therapy in patients with non–ST-segment elevation acute coronary syndromes is of no benefit (and indeed may be harmful) and should not be used.

ST-Segment Elevation MI

All patients with ST-segment elevation MI (as well as those with bundle-branch block obscuring ST-segment evaluation) should be treated with aspirin. No clinical data exist as to whether thienopyridines should be administered to those with true aspirin allergies, although this seems to be a reasonable approach.

In current practice, patients with ST-segment elevation and treated with tPA as well as reteplase (r-PA) (and tenecteplase [TNK-tPA] when approved) are treated with unfractionated heparin also; studies of tenecteplase (TNK-tPA) have also used intravenous heparin therapy. The recommended dose of heparin sodium in patients treated with tPA has recently revised to a gentler dosing regimen of an initial bolus dose of 60 U/kg (up to a maximum dose of 4000 U) at the initiation of tPA infusion and an initial maintenance infusion of approximately 12 U/kg per hour (maximum, 1000 U/h), subsequently adjusted to a target aPTT of 1.5 to 2.0 times control (50-70 seconds). It seems reasonable to extrapolate this recommendation to patients treated with reteplase (r-PA) or tenecteplase (TNK-tPA). The routine use of heparin in patients treated with streptokinase is not recommended (although the use of heparin may be appropriate in such patients for other indications). No data recommend the direct thrombin inhibitor hirudin compared with unfractionated heparin in patients treated with thrombolytic therapy; results of the HERO-2 study may help to determine whether there is an adjunctive role for bivalirudin (Hirulog) in patients treated with streptokinase. Low-molecular-weight heparin therapy in patients treated with thrombolytic agents appears promising, but further study is necessary before its use in this setting can be recommended.

Although preliminary studies combining GPIIb-IIIa inhibitors with half-dose thrombolytic therapy are encouraging, such therapy cannot at present be recommended outside the setting of clinical trials, pending the results of planned and ongoing studies evaluating this combination therapy.

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