Most acute coronary syndromes are caused by intracoronary thrombus superimposed on disrupted atherosclerotic plaque. Platelets adhere to subendothelial proteins exposed at sites of plaque disruption where they become activated, release vasoactive and procoagulant substances, and aggregate.1 Tissue factor in the lipid-rich core of the plaque initiates coagulation, which leads to thrombin generation. A potent platelet agonist, thrombin recruits additional platelets to the site of vascular injury. Thrombin also converts fibrinogen to fibrin, which serves to stabilize platelet-rich thrombi formed at sites of plaque disruption. Depending on the extent and duration of coronary artery obstruction, clinical manifestations range from unstable angina to acute myocardial infarction.1

Aspirin and heparin, the cornerstones of therapy for acute coronary syndromes, reduce the risk of myocardial infarction and death.2,3 Despite the widespread use of these treatments, however, patients with unstable angina or acute myocardial infarction remain at risk for recurrent ischemic events, suggesting that intracoronary thrombus formation is incompletely attenuated by aspirin and heparin. High concentrations of thrombin are generated by tissue factor exposed at sites of arterial injury.4 When bound to fibrin,5,6 fibrin degradation products,7 or subendothelial matrix,8 thrombin is resistant to inactivation by the heparin/antithrombin complex. Bound thrombin, which remains enzymatically active, triggers thrombosis growth by activating factors V, VIII, and XI,9 thereby amplifying thrombin generation. Bound thrombin also activates platelets,10 at least in part, via thromboxane A2-independent pathways that are not blocked by aspirin.

Because thrombin plays a central role in arterial thrombogenesis, the goal of most treatment regimens is to block thrombin generation or inhibit its activity. Direct thrombin inhibitors were developed to overcome the inability of the heparin/antithrombin complex to inactivate bound thrombin. In contrast to heparin and low-molecular-weight heparin, which catalyze the inactivation of thrombin by antithrombin,11,12 direct thrombin inhibitors bind to the enzyme and block its interaction with its substrates. This paper will outline the mechanisms responsible for protection of fibrin-bound thrombin from inhibition by the heparin/antithrombin complex, describe the potential advantages of direct thrombin inhibitors over heparin and low-molecular-weight heparin, review the clinical data with hirudin, bivalirudin (formerly known as Hirulog), and argatroban, and outline the opportunities and challenges for direct thrombin inhibitors in the face of new anticoagulant drugs currently under development.

Mechanisms of Protection of Fibrin-Bound Thrombin From Inactivation by the Heparin/Antithrombin Complex

Three distinct domains can be identified on thrombin.13 In addition to its active site, thrombin possesses 2 exosites, or positively charged domains located at opposite poles of the enzyme (Figure 1A). Thrombin uses exosite 1 to dock on its substrates, thereby orienting the appropriate peptide bonds into its active site cleft. Exosite 2 serves as the heparin-binding domain. To catalyze the inactivation of thrombin by antithrombin, heparin bridges the enzyme and the inhibitor by simultaneously binding to antithrombin and exosite 2 on thrombin. A unique pentasaccharide sequence found on one third of the chains of commercial heparin mediates its high affinity interaction with antithrombin.11

Thrombin binds to fibrin via exosite 1.14,15 By simultaneously binding to exosite 2 on thrombin and to fibrin, heparin bridges more thrombin to fibrin (Figure 2). Formation of this ternary heparin/thrombin/fibrin complex heightens the apparent affinity of the thrombin/fibrin interaction. When both thrombin exosites are ligated within this ternary complex, the enzyme is relatively protected from inactivation by the heparin/antithrombin complex.15 This protection reflects, at least in part, the inaccessibility of exosite 2 on thrombin within the ternary complex to antithrombin-bound heparin (Figure 1B). Thus, because exosite 2 is occupied by the heparin chain that tethers thrombin to fibrin, antithrombin-bound heparin is unable to connect the inhibitor to the enzyme. In contrast to the heparin/antithrombin complex, direct thrombin inhibitors can inactivate fibrin-bound thrombin (Figure 1C).

Direct Thrombin Inhibitors

Hirudin, bivalirudin, and argatroban are the 3 parenteral direct thrombin inhibitors currently approved by the US Food and Drug Administration. Hirudin and argatroban are li-

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Native and recombinant hirudins bind to thrombin with high affinity, forming an essentially irreversible 1:1 stoichiometric complex with thrombin. Although desulfatohirudins bind thrombin with 10-fold lower affinity than hirudin, they remain potent inhibitors of thrombin.

The terminal half-life of desulfatohirudins in healthy volunteers is 60 minutes. Desulfatohirudins are cleared via the kidneys and accumulate in patients with renal insufficiency. Because no specific antidote is available to reverse their anticoagulant effect, desulfatohirudins should not be used in patients with impaired renal function.

**Bivalirudin**

A 20 amino acid polypeptide,\(^{18}\) bivalirudin is a synthetic version of hirudin (Table 1). Its amino-terminal D-Phe-Pro-Arg-Pro domain, which interacts with the active site of thrombin, is linked via 4 Gly residues to a dodecapeptide analogue of the carboxy-terminal of hirudin. Like hirudin, bivalirudin forms a 1:1 stoichiometric complex with thrombin. Once bound, however, the Arg-Pro bond at the amino-terminal of bivalirudin is cleaved by thrombin, thereby restoring active site functions of the enzyme.\(^{19}\)

Bivalirudin has a half-life of 25 minutes.\(^{20}\) In contrast to hirudin, renal excretion is not the major route of bivalirudin clearance.\(^{21}\) Instead, it is likely that bivalirudin is degraded by endogenous peptidases. Consequently, bivalirudin may be safer than hirudin in patients with renal impairment.

**Argatroban**

A synthetic small molecule, argatroban acts as a competitive inhibitor of thrombin. An arginine derivative, argatroban is an Arg-Pro-Arg-Pro-Arg-Pro analogue of the carboxy-terminal of hirudin. Because recombinant hirudins lack this sulfate group, they are known as desulfatohirudins or desirudins.\(^{17}\)

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**TABLE 1. Comparison of the Properties of Hirudin, Bivalirudin, and Argatroban**

<table>
<thead>
<tr>
<th>Property</th>
<th>Hirudin</th>
<th>Bivalirudin</th>
<th>Argatroban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass</td>
<td>7000</td>
<td>1980</td>
<td>527</td>
</tr>
<tr>
<td>Site(s) of interaction with thrombin</td>
<td>Active site and exosite 1</td>
<td>Active site and exosite 1</td>
<td>Active site</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatic metabolism</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Plasma half-life, min</td>
<td>60</td>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>
interacts only with the active site of thrombin. Argatroban is metabolized in the liver, a process that generates at least 3 active intermediates. The half-life of argatroban is 45 minutes, but the half-life is prolonged in patients with hepatic dysfunction.

Other active site-directed inhibitors of thrombin that have been evaluated in patients with acute coronary syndromes include efegatran and inogatran.

### Potential Advantages of Direct Thrombin Inhibitors Over Heparin

Direct thrombin inhibitors have potential advantages over heparin (Table 2). Because heparin binds to plasma proteins, some of which are acute phase reactants and others of which are released from platelets or endothelial cells activated by products of clotting, the anticoagulant response to heparin varies among patients. Careful laboratory monitoring is therefore necessary to ensure that a therapeutic anticoagulant effect is obtained. In contrast, direct thrombin inhibitors produce a more predictable anticoagulant response because they do not bind to plasma proteins.

Platelet factor 4, a cationic protein released from activated platelets, binds heparin with high affinity. Consequently, platelet factor 4 released in the vicinity of platelet-rich thrombi can locally abrogate heparin activity. In contrast, platelet factor 4 does not affect direct thrombin inhibitors.

Thrombin bound to fibrin or fibrin degradation products is resistant to inhibition by the heparin/antithrombin complex, but is susceptible to inactivation by direct thrombin inhibitors. Because the active site of thrombin is not involved in the interaction of the enzyme with fibrin, it remains accessible to active site-directed thrombin inhibitors, even when thrombin is bound to fibrin. Consequently, these agents inactivate fibrin-bound thrombin without displacing the enzyme from fibrin. In contrast, bivalent thrombin inhibitors, such as Hirudin and Bivalirudin, displace bound thrombin during the inhibition reaction by competing with fibrin for access to exosite 1 on thrombin (Figure 1C).

Lower molecular-weight direct thrombin inhibitors, such as Bivalirudin and Argatroban, are better able to inhibit thrombin bound to fibrin clots than Hirudin. This ability likely reflects size-restricted diffusion of Hirudin into intact thrombi because once thrombi are solubilized, Hirudin and smaller inhibitors have equivalent activity against bound thrombin.

The potential advantages of direct thrombin inhibitors over heparin prompted comparisons of these agents for treatment of acute coronary syndromes. This review will primarily focus on Phase III trials with Hirudin and Bivalirudin. To provide perspective, Phase II trial results with Argatroban and other active site-directed thrombin inhibitors also will be briefly discussed.

### Clinical Trials

#### Hirudin

**Unstable Angina**

The largest phase II study to compare hirudin with heparin, the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-1 pilot trial, randomized 909 with unstable angina or non–ST-elevation myocardial infarction to a 72-hour infusion of hirudin, in either low or medium dose, or to heparin. Doses of hirudin and heparin were adjusted to maintain the activated partial thromboplastin time (APTT) between 60 and 100 sec. Compared with heparin, hirudin produced a promising reduction in the primary outcome, a composite of cardiovascular death, myocardial infarction, or refractory angina at 7 days (OR 0.57, 95% CI: 0.32 to 1.02) and a significant reduction in the secondary outcome, a composite of death, myocardial infarction, or refractory or severe angina requiring revascularization at 7 days (OR 0.49, 95% CI: 0.27 to 0.86). Major bleeding occurred in about 1% of patients in both treatment groups and was not significantly higher in those given hirudin (OR 0.86, 95% CI: 0.23 to 3.19). Minor bleeding, however, was more frequent in patients given medium or low dose hirudin than in those treated with heparin (21.3%, 16.2%, and 10.5%, respectively), differences that were statistically significant (P = 0.033 and 0.001, respectively).

The results of the OASIS-1 trial prompted OASIS-2, a phase III trial that randomized 10,141 patients with unstable angina or non–ST-elevation myocardial infarction to a 72-hour infusion of either medium-dose hirudin (Table 3) or heparin. During treatment, hirudin produced a significant reduction in the composite endpoint of death or myocardial infarction compared with heparin (2.0% and 2.6%, respectively; OR 0.76, 95% CI: 0.59 to 0.99). Although the primary outcomes, a composite of death or myocardial infarction at 7 days (3.6% and 4.2%, respectively; OR 0.84, 95% CI: 0.69 to 1.02) and 35 days (6.8% and 7.7%, respectively; OR 0.87, 95% CI: 0.75 to 1.01) were not significantly different.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bolus, mg/kg</th>
<th>Infusion, mg/kg per h</th>
</tr>
</thead>
<tbody>
<tr>
<td>OASIS-1</td>
<td>0.2</td>
<td>0.10</td>
</tr>
<tr>
<td>OASIS-2</td>
<td>0.4</td>
<td>0.15</td>
</tr>
<tr>
<td>HIT-III</td>
<td>0.4</td>
<td>0.15</td>
</tr>
<tr>
<td>TIMI-9A</td>
<td>0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>GUSTO-2A</td>
<td>0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>TIMI-9B</td>
<td>0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>GUSTO-2B</td>
<td>0.1</td>
<td>0.10</td>
</tr>
</tbody>
</table>

---

**TABLE 2. Potential Advantages of Direct Thrombin Inhibitors Over Heparin**

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No binding to plasma proteins</td>
<td>Predictable anticoagulant response</td>
</tr>
<tr>
<td>Not neutralized by platelet factor 4</td>
<td>Maintained anticoagulant activity in the vicinity of platelet-rich thrombi</td>
</tr>
<tr>
<td>Inhibition of fibrin-bound thrombin as well as fluid-phase thrombin</td>
<td>Greater attenuation of thrombus growth</td>
</tr>
</tbody>
</table>

---

**TABLE 3. Comparison of Hirudin Doses Used in Clinical Trials Evaluating its Utility in Acute Coronary Syndromes**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bolus, mg/kg</th>
<th>Infusion, mg/kg per h</th>
</tr>
</thead>
<tbody>
<tr>
<td>OASIS-1</td>
<td>0.2</td>
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</tr>
<tr>
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<td>0.6</td>
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</tr>
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<td>TIMI-9B</td>
<td>0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>GUSTO-2B</td>
<td>0.1</td>
<td>0.10</td>
</tr>
</tbody>
</table>
between the two groups, the absolute risk reduction in death or myocardial infarction produced by hirudin during the 72-hour treatment period was maintained at 7 and 35 days. Major bleeding occurred more frequently with hirudin than with heparin (1.2% and 0.7%, respectively; OR 1.73, 95% CI: 1.13 to 2.63), but rates of life-threatening bleeding were similar (0.4% in both groups).

When the results of the OASIS-1 and OASIS-2 trials are combined, hirudin shows a significant reduction in the composite outcome of death or myocardial infarction at 35 days compared with heparin (6.7% and 7.7%, respectively; OR 0.86, 95% CI: 0.74 to 0.99). Thus, the early treatment benefits of hirudin observed in both trials were maintained at least for 1 month.

**Adjunct to Thrombolytic Therapy**

Hirudin was compared with heparin as adjuncts to thrombolytic therapy in 3 trials. The Thrombolysis in Myocardial Infarction (TIMI)-9A and Hirudin for Improvement of Thrombolysis (HIT)-III trials only enrolled patients with acute myocardial infarction, whereas the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-2A trial also included patients with unstable angina and those with myocardial infarction who were ineligible for thrombolytic therapy. The doses of hirudin given in the TIMI-9A and GUSTO-2A studies, which are illustrated in Table 3, were higher than that used in the OASIS-2 trial. In contrast, the HIT-III trial used a hirudin regimen identical to that used in the OASIS-2 study.

All 3 initial phase III trials were stopped prematurely because of unacceptably high rates of major hemorrhage. Although the rate of major bleeding was higher with hirudin than with heparin in the TIMI-9A trial and there was a trend for more intracranial bleeding with hirudin in the TIMI-9A and HIT-III trials, the rates of major bleeding with heparin also were higher in the GUSTO-2A and TIMI-9A trials than that observed in the GUSTO-1 study. Consequently, the TIMI-9B and GUSTO-2B trials were restarted with doses of hirudin lower than that used in the OASIS-2 trial (Table 3), and the hirudin dose was adjusted to achieve a target APTT of 55 to 85 sec in the TIMI-9B and 60 to 85 sec in GUSTO-2B trials. The dose of heparin also was reduced to more closely match that used in the TIMI-9B trials. With lower doses of anticoagulants, both trials completed their planned enrollment.

In GUSTO-2B, hirudin produced a modest reduction in the primary outcome, a composite of death or myocardial infarction at 30 days, compared with heparin (OR 0.89; 95% CI: 0.79 to 1.00). During the initial 24 hours of treatment, hirudin produced a significant reduction in death or myocardial infarction compared with heparin (1.3% and 2.1%, respectively; OR 0.61, 95% CI: 0.46 to 0.81). Retrospective subgroup analysis suggested that when used as adjuncts to streptokinase, hirudin produced a 39% greater reduction in death or myocardial infarction at 30 days than did heparin (9.1% and 14.9%, respectively; OR 0.57, 95% CI: 0.38 to 0.87). In contrast, hirudin was not superior to heparin in patients given tissue-type plasminogen activator (t-PA).

Hirudin was no better than heparin in the TIMI-9B trial. Thus, the primary outcome, a composite of death, myocardial infarction, cardiac failure, or cardiogenic shock at 30 days, was similar in the hirudin and heparin groups (OR 1.09, 95% CI: 0.88 to 1.36), as was the composite of death or myocardial infarction at 30 days (OR 1.02, 95% CI: 0.80 to 1.31). There was a trend for a reduction in non-fatal myocardial infarction with hirudin during hospitalization (OR 0.65, 95% CI: 0.42 to 1.01) and at 30 days (OR 0.81, 95% CI: 0.56 to 1.18). Rates of major bleeding and intracranial hemorrhage were similar with hirudin and heparin in both the TIMI-9B and GUSTO-2B trials.

Taken together, the TIMI-9B and GUSTO-2B trials suggest that hirudin is at least as effective as heparin when used as an adjunct to thrombolytic therapy. When the results of these trials are pooled with those of the OASIS-1 and OASIS-2 study, hirudin produces a 10% reduction in the risk of death or myocardial infarction at 30 to 35 days compared with heparin. However, the lack of a clear benefit of hirudin over heparin at 30 days in the GUSTO-2B and TIMI-9B trials limits the strength of this conclusion in patients with acute myocardial infarction.

There are several potential explanations for the disappointing results of the GUSTO-2B and TIMI-9B trials. One possibility is that the hirudin dose was too low. Support for this concept comes from the results of the OASIS-1 and OASIS-2 trials. When used at a slightly higher dose, hirudin was more effective than heparin. Based on the results of the HIT-III trial, it is unlikely that this medium-dose hirudin regimen would be safe in conjunction with thrombolytic agents.

Another potential explanation for the disappointing results of the GUSTO-2B and TIMI-9B trials relates to the timing of initiation of anticoagulant therapy. In these trials, hirudin or heparin therapy was initiated 30 to 40 minutes after starting thrombolytic therapy. Because more thrombin is exposed during the thrombolytic process, concomitant anticoagulant therapy may be necessary for optimal efficacy.

Finally, the duration of anticoagulant therapy also may be important. There is biochemical evidence that activation of coagulation persists for at least 6 months after onset of acute coronary syndromes, suggesting that the disrupted plaque is slow to heal. Although short-term treatment with heparin or hirudin suppresses coagulation, rebound activation occurs once therapy is stopped. This phenomenon likely reflects the inability of direct thrombin inhibitors to block thrombin generation, which can trigger ongoing clotting once the thrombin inhibitor is cleared. These observations suggest that long-term anticoagulant treatment may be better than short-term therapy.

**Hirudin for Coronary Angioplasty**

Hirudin was compared with heparin for prevention of restenosis after percutaneous coronary angioplasty in the Hirudin in a European restenosis prevention trial, versus heparin treatment in PTCA patients (HELVEtica) study.

A total of 1141 patients scheduled for coronary angioplasty were randomized to either hirudin given as a bolus plus infusion for 24 hours, followed by subcutaneous hirudin or
placebo for an additional 72 hours, or to heparin given as a bolus plus infusion for 24 hours, followed by subcutaneous placebo injections for 72 hours. An additional bolus of placebo (in the hirudin group) or heparin (in those randomized to heparin) could be given if the procedure lasted longer than 1 hour, but no subsequent dose adjustments were allowed. The primary outcome was event-free survival at 30 weeks, defined as absence of death, myocardial infarction, coronary artery bypass grafting, or bailout angioplasty with or without coronary stenting at the previous angioplasty site.

At 7 months, event-free survival was similar in those given heparin, intravenous hirudin, or intravenous hirudin followed by subcutaneous hirudin (67.3%, 63.5%, and 68.0%, respectively). Likewise, on repeat angiography at 6 months, there was no significant difference in mean luminal diameter of the dilated vessel among the 3 groups. Compared with heparin, however, hirudin produced a significant reduction in death or myocardial infarction in the primary composite outcome at 96 hours (OR 0.61, 95% CI: 0.41 to 0.90) that was preserved at 30 days. The time-to-event curves converged thereafter, possibly reflecting the development of restenosis in both groups. No excess bleeding was seen with hirudin.

It is not surprising that hirudin failed to prevent restenosis because none of the antithrombotic agents tested to-date has influenced this process. The observation that hirudin was superior to heparin at 96 hours, and that this benefit was maintained at 30 days, is consistent with the results of other studies. In the OASIS-2 trial, 117 patients randomized to hirudin or heparin for unstable angina underwent percutaneous coronary intervention. At 35 days, hirudin produced a significant reduction in death or myocardial infarction compared with heparin (6.4% and 22.9%, respectively; OR 0.25, 95% CI: 0.07 to 0.86). Likewise, in the GUSTO-2B trial, 1404 patients received hirudin or heparin during percutaneous coronary interventions and for 72 hours thereafter. The risk of death or myocardial infarction was lower in the hirudin group than in those given heparin (2.1% and 3.8%, respectively; P = 0.05). Thus, hirudin produces a greater reduction in death or myocardial infarction than heparin in patients undergoing coronary angioplasty, suggesting that potent antithrombotic drugs are needed to prevent thrombosis after mechanical injury to the coronary artery.

**Bivalirudin**

**Bivalirudin for Coronary Angioplasty**

Bivalirudin was compared with heparin in 4,098 patients undergoing coronary angioplasty for unstable or postinfarction angina. Bivalirudin did not reduce the primary endpoint, a composite of in-hospital death, myocardial infarction, abrupt vessel closure, or clinical deterioration of cardiac origin necessitating coronary intervention (OR 0.9, 95% CI: 0.8 to 1.1). Major bleeding, however, was significantly less frequent in patients randomized to bivalirudin than in those given heparin (3.8% and 9.8%, respectively; P < 0.001). In a prospectively stratified subgroup of 704 patients with postinfarction angina, the primary endpoint occurred in significantly fewer patients receiving bivalirudin (OR 0.6, 95% CI: 0.40 to 0.90, P = 0.004). Bleeding rates in this group were significantly lower with bivalirudin than with heparin (3.0% and 11.1%, respectively, P < 0.001).

Despite these promising results, development of bivalirudin was temporarily halted. This decision was based on lack of clear evidence of superior efficacy in lower-risk patients. Although bivalirudin was safer than heparin, the initial process used to manufacture bivalirudin was complex, resulting in an expensive product. Consequently, there was an impression that the high cost of bivalirudin would limit its use in all but the highest risk patients.

A number of factors have changed the outlook for bivalirudin. By streamlining the manufacturing process, the cost of bivalirudin has now been reduced. Moreover, the decision to stop the development of bivalirudin was based on analysis of an incomplete data set because the original publication lacked information on some patients and follow-up was limited. A recent reanalysis of the results of the angioplasty trial suggests that bivalirudin is not only of benefit in the high-risk population, but also is superior to heparin in those at lower risk. Using the same closed database as the initial study, this reanalysis includes results on the entire intention-to-treat cohort of 4312 patients, as was specified in the initial protocol. In addition, it provides complete follow-up information and a more contemporary definition of myocardial infarction. When this additional information is included, bivalirudin significantly reduced the combined endpoint of death, myocardial infarction, or repeat revascularization in the entire cohort at 7 days (OR 0.78, 95% CI: 0.62 to 0.99, P = 0.04) and at 90 days (OR 0.82, 95% CI: 0.70 to 0.96, P = 0.01). Although the absolute risk reduction with bivalirudin at 180 days was similar to that at 7 days, the difference was no longer significant (OR 0.9, 95% CI: 0.78 to 1.04, P = 0.15). Major bleeding events were significantly less frequent with bivalirudin than with heparin (3.5% and 9.3%, respectively; P < 0.001).

Like hirudin, bivalirudin appears to be more effective than heparin in patients undergoing coronary angioplasty. However, bivalirudin produces a 50% reduction in major bleeding compared with heparin. Some investigators have suggested that the dose of heparin used in the bivalirudin angioplasty trial was excessive, resulting in a higher than usual rate of bleeding in the control arm. Heparin was given as a 175 U/kg bolus followed by an infusion of 15 U · kg⁻¹ · h⁻¹ so as to achieve an activated clotting time (ACT) over 350 sec. An additional 60 U/kg heparin bolus was administered if the ACT was below this target. With this heparin regimen, the median ACT was 383 sec and the interquartile range was 332 to 450 sec. This result is close to ideal anticoagulation because a recent pooled analysis of data from 6 contemporary randomized trials indicates that an ACT of 350 to 375 sec with heparin produces the lowest rate of ischemic events at 7 days in coronary angioplasty patients not receiving glycoprotein (GP) IIb/IIIa antagonists. Moreover, the rates of major bleeding are not significantly greater in patients with a higher ACT than in those with a lower ACT.

**Argatroban and Other Active Site-directed Thrombin Inhibitors**

None of the active site-directed thrombin inhibitors has yet to undergo Phase III testing. In Phase II evaluation, argatroban...
has been compared with heparin as an adjunct to t-PA in patients with acute myocardial infarction, whereas efegatran and inogatran have been compared with heparin in patients with unstable angina, and efegatran has been compared with heparin as an adjunct to thrombolytic therapy. In contrast to the promising Phase II results with hirudin or bivalirudin, none of the active site-directed thrombin inhibitors tested to-date appears to be superior to heparin. Further trials are needed to determine whether this reflects inappropriate dosing or an intrinsic problem with this type of inhibitor.

Conclusions and Future Directions
Based on randomized trials, hirudin appears to be superior to heparin in patients with unstable angina, and both hirudin and bivalirudin are at least as effective as heparin in patients undergoing coronary angioplasty. Despite these data, however, the role of hirudin in acute coronary syndromes has yet to be established. In patients with unstable angina, hirudin and GPIIb/IIIa antagonists produce similar reductions in the risk of recurrent ischemia. The major concerns about the use of hirudin in acute coronary syndromes relate to its safety and cost. Although safety is an issue, the relative increase in bleeding with hirudin compared with heparin is similar to that produced by addition of a GPIIb/IIIa antagonist to heparin. Furthermore, it is possible that the safety of hirudin could be improved by monitoring its anticoagulant effect and adjusting the dose accordingly. Cost of goods also is an issue with hirudin. Because it is considerably more expensive than heparin, hirudin would need to be reserved for high-risk patients.

Despite its promise, further development of hirudin is unlikely. The disappointing experience with hirudin highlights the need for adequately powered phase II trials when selecting appropriate doses for phase III evaluation. Currently, bivalirudin is the only direct thrombin inhibitor with an established indication in acute coronary syndromes. Bivalirudin is safer and more effective than heparin in patients undergoing coronary angioplasty for post-infarction angina, and is used as an adjunct to thrombolytic therapy. In contrast, the active site-directed thrombin inhibitors, such as GPIIb/IIIa antagonists, may also be advantageous in lower-risk individuals. Consequently, bivalirudin may provide a safer platform on which to add other antithrombotic agents, such as GPIIb/IIIa antagonists. Alternatively, by better inhibiting thrombin-mediated platelet aggregation, bivalirudin may obviate the need for additional therapy. These concepts are currently under investigation in patients undergoing coronary artery stenting.

In patients with a history of heparin-induced thrombocytopenia, direct thrombin inhibitors can be used for antiocoagulation during percutaneous coronary interventions. Bivalirudin is the only agent licensed for this indication, although the others have been used. Bivalirudin is given as an intravenous bolus followed by a 4-hour infusion, and its short half-life facilitates early sheath removal. When used for treatment of patients with established heparin-induced thrombocytopenia and thrombosis, direct thrombin inhibitors are given by continuous intravenous infusion until the platelet count rises, at which time warfarin therapy can be initiated.

Although a meta-analysis suggests that bivalirudin is safer than heparin for all clinical indications in which the 2 agents were compared, recent data from the Hirulog Early Reperfusion Occlusion (HERO)-2 trial indicate that bivalirudin produces more bleeding than heparin when used in conjunction with streptokinase. Post hoc analysis suggests that the excess bleeding can be explained by the fact that bivalirudin produced a higher APTT than heparin. These data indicate that, like hirudin, bivalirudin needs careful monitoring when used as an adjunct to thrombolytic therapy. In contrast, unmonitored enoxaparin appears to be better than heparin as an adjunct to coronary thrombolyis with tenectaplaste. Consequently, low-molecular-weight heparin may be a more useful and less costly adjunct to plasminogen activators than direct thrombin inhibitors.

The advantages of hirudin and bivalirudin over heparin have prompted development of orally bioavailable direct thrombin inhibitors. The drug in most advanced development is ximelagatran, a prodrug form of melagatran that targets the active site of thrombin. Although a meta-analysis suggests that bivalirudin is safer than heparin for all clinical indications in which the 2 agents were compared, recent data from the Hirulog Early Reperfusion Occlusion (HERO)-2 trial indicate that bivalirudin produces more bleeding than heparin when used in conjunction with streptokinase. Post hoc analysis suggests that the excess bleeding can be explained by the fact that bivalirudin produced a higher APTT than heparin. These data indicate that, like hirudin, bivalirudin needs careful monitoring when used as an adjunct to thrombolytic therapy. In contrast, unmonitored enoxaparin appears to be better than heparin as an adjunct to coronary thrombolyis with tenectaplaste. Consequently, low-molecular-weight heparin may be a more useful and less costly adjunct to plasminogen activators than direct thrombin inhibitors.

The advantages of hirudin and bivalirudin over heparin have prompted development of orally bioavailable direct thrombin inhibitors. The drug in most advanced development is ximelagatran, a prodrug form of melagatran that targets the active site of thrombin. With predictable pharmacokinetics and no food or drug interactions, ximelagatran may not require laboratory monitoring, thereby rendering it more convenient than warfarin. Based on promising Phase II data, a phase III trial comparing ximelagatran with warfarin in patients with atrial fibrillation has been initiated. To explore the possibility that long-term anticoagulant therapy may be of benefit in patients with unstable angina, a phase II trial comparing ximelagatran with placebo is underway.

Recent attention has focused on blocking coagulation above the level of thrombin. Indirect and direct inhibitors of factor Xa are under investigation (Figure 3). Synthetic pen-
tasaccharide, an analogue of the pentasaccharide sequence of heparin that mediates its interaction with antithrombin, catalyzes the inhibition of factor Xa by antithrombin. Phase III clinical trials indicate that synthetic pentasaccharide is superior to low-molecular-weight heparin for thromboprophylaxis after major orthopedic surgery when given once-daily subcutaneously. A phase II trial comparing pentasaccharide with low–molecular-weight heparin for unstable angina is underway.

DX9065a is a direct factor Xa inhibitor that blocks the active site of the enzyme. Given intravenously, DX9065a is undergoing phase III evaluation in patients with coronary artery disease. Several orally bioavailable agents that target the active site of factor Xa will soon be entering phase II evaluation.

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References


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