Direct thrombin Inhibitors [review]
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DIRECT THROMBIN INHIBITORS (DTIS) ARE A NEW CLASS OF ANTICOAGULANTS THAT BIND DIRECTLY TO THROMBIN AND BLOCK ITS INTERACTION WITH ITS SUBSTRATES. SOME DTIS — SUCH AS RECOMBINANT HIRUDINS, BIVALIRUDIN, AND XIMELAGATRAN, EITHER ALONE OR IN COMBINATION WITH MELAGATRAN — HAVE UNDERGONE EXTENSIVE EVALUATION IN PHASE 3 TRIALS FOR THE PREVENTION AND TREATMENT OF ARTERIAL AND VENOUS THROMBOSIS. THE EVIDENCE CONCERNING THE CLINICAL APPlicABILITY OF OTHER DTIS, SUCH AS ARGATROBAN AND DABIGATRAN, IS LIMITED TO PHASE 2 STUDIES. FOUR PARENTERAL DTIS HAVE BEEN APPROVED BY THE FOOD AND DRUG ADMINISTRATION (FDA) IN NORTH AMERICA: HIRUDIN AND ARGATROBAN FOR THE TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA, BIVALIRUDIN AS AN ALTERNATIVE TO HEPARIN IN PERCUTANEOUS CORONARY INTERVENTION, AND DESIRUDIN AS PROPHYLAXIS AGAINST VENOUS THROMBOEM博LISM IN HIP REPLACEMENT. THIS REVIEW DISCUSSES FDA-APPROVED DTIS AS WELL AS THOSE UNDER EVALUATION IN PHASE 2 OR 3 CLINICAL TRIALS.

MECHANISMS OF ACTION

COAGULATION CASCADE AND GENERATION OF THROMBIN

After injury to a vessel wall, tissue factor is exposed on the surface of the damaged endothelium. The interaction of tissue factor with plasma factor VII activates the coagulation cascade, producing thrombin by stepwise activation of a series of proenzymes (Fig. 1). Thrombin is central in the clotting process: it converts soluble fibrinogen to fibrin; activates factors V, VIII, and XI, which generates more thrombin; and stimulates platelets. Furthermore, by activating factor XIII, thrombin favors the formation of cross-linked bonds among the fibrin molecules, stabilizing the clot. The coagulation cascade is regulated by natural anticoagulants, such as tissue factor pathway inhibitor, the protein C and protein S system, and antithrombin, all of which help to restrict the formation of the hemostatic plug to the site of injury.

DIFFERENCES FROM HEPARINS

Thrombin-inhibiting drugs can block the action of thrombin by binding to three domains: the active site or catalytic site and two exosites (Fig. 2). Located next to the active site, exosite 1 acts as a dock for substrates such as fibrin, thereby orienting the appropriate peptide bonds in the active site. Exosite 2 serves as the heparin-binding domain. Thrombin is inhibited indirectly by low-molecular-weight heparins, because these drugs strongly catalyze the function of antithrombin. A heparin–thrombin–antithrombin complex is formed in which heparin binds simultaneously to exosite 2 in thrombin and to antithrombin. Furthermore, heparin can act as a bridge between thrombin and fibrin by binding both to fibrin and exosite 2 (Fig. 2). Because both thrombin exosites are occupied within this fibrin–heparin–thrombin complex, the enzymatic activity of thrombin is relatively protected from inactivation by the heparin–antithrombin complex. Thus, heparins have a reduced capacity for the inhibition of fibrin-bound thrombin, which ap
pears to be detrimental, because active thrombin further triggers thrombus growth.

Since DTIs act independently of antithrombin, they can inhibit thrombin bound to fibrin or fibrin degradation products.3-5 Bivalent DTIs block thrombin at both the active site and exosite 1, whereas univalent DTIs bind only to the active site. The group of bivalent DTIs includes hirudin and bivalirudin, whereas argatroban, melagatran (and its oral precursor, ximelagatran), and dabigatran are univalent DTIs. Native hirudin and recombinant hirudins (lepirudin and desirudin) form an irreversible 1:1 stoichiometric complex with thrombin.6 In a similar way, bivalirudin, a synthetic hirudin, binds to the active site and exosite 1,7 but once bound, it is cleaved by thrombin, thereby restoring the active-site functions of thrombin.8 Therefore, in contrast to the hirudins, bivalirudin produces only a transient inhibition of thrombin.

By interacting only with the active site, univalent DTIs inactivate fibrin-bound thrombin.9,10 Argatroban and melagatran (like bivalirudin) dissociate from thrombin, leaving a small amount of free, enzymatically active thrombin available for hemostatic interactions.11,12

By reducing the thrombin-mediated activation of platelets, DTIs also have an antiplatelet effect.13,14 Since DTIs do not bind to plasma proteins, these agents should produce a more predictable response than does unfractionated heparin and should be more effective than low-molecular-weight heparins because they inhibit fibrin-bound thrombin.

Figure 1. Thrombin Generation.
The activation of coagulation proceeds through a stepwise activation of proteases that eventually results in the fibrin framework. After vascular injury, tissue-factor expression by endothelial cells is a critical step in the initial formation of fibrin, whereas the activation of factors XI, IX, and VIII is important to continue the formation of fibrin. The molecule of thrombin plays a central role within the coagulation cascade. The formation of the clot is highly regulated by natural anticoagulant mechanisms that confine the hemostatic process to the site of the injury to the vessel. Most of these natural anticoagulants are directed against the generation or action of thrombin and include antithrombin and the protein C system. Solid lines denote activation pathways, and dashed lines denote inhibitory pathways.

(This figure has been corrected from the version published on September 8, 2005.)
The routes of administration, plasma half-lives, and main sites of clearance of the various DTIs are listed in Table 1. DTIs with a predominant renal clearance such as hirudin, melagatran, and dabigatran are likely to accumulate in patients with impaired renal function. Although excessive anticoagulation with hirudin in patients with renal insufficiency can be managed with high-volume hemofiltration with hirudin-permeable hemodialysis membranes, the available data remain scarce. Studies in animals suggest that excessive plasma concentrations of melagatran can be managed by either hemodialysis or the administration of acti-

Figure 2. Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin.

In the absence of heparin, the rate of thrombin inactivation by antithrombin is relatively low, but after conformational change induced by heparin, antithrombin irreversibly binds to and inhibits the active site of thrombin. Thus, the anticoagulant activity of heparin originates from its ability to generate a ternary heparin–thrombin–antithrombin complex. The activity of DTIs is independent of the presence of antithrombin and is related to the direct interaction of these drugs with the thrombin molecule. Although bivalent DTIs simultaneously bind the exosite 1 and the active site, the univalent drugs in this class interact only with an active site of the enzyme. In the lower panel, the heparin–antithrombin complex cannot bind fibrin-bound thrombin, whereas given their mechanism of action, DTIs can bind to and inhibit the activity of not only soluble thrombin but also thrombin bound to fibrin, as is the case in a blood clot. An animated version of this figure is available with the full text of the article at www.nejm.org.
vated prothrombin complex concentrates. Since patients with severe renal impairment have been excluded from the clinical trials, the safety of DTIs that are predominantly cleared by the kidneys remains to be established. Bivalirudin is only partially excreted by the kidneys, as hepatic metabolism and proteolysis at other sites also contribute to its metabolism. However, the half-life of bivalirudin is prolonged with severe renal impairment, and dose adjustments are needed. Argatroban is predominantly cleared by hepatic metabolism and requires dose adjustments in patients with hepatic dysfunction. The use of aspirin does not appear to influence the plasma concentrations of DTIs.

**STUDIES IN ARTERIAL THROMBOSIS**

**ACUTE CORONARY SYNDROMES WITH OR WITHOUT PERCUTANEOUS CORONARY INTERVENTION**

Patients with acute coronary syndromes (acute myocardial infarction, either with or without ST-segment elevation, and unstable angina) remain at risk for recurrent myocardial ischemia, despite treatment with aspirin, clopidogrel, and heparin. The role of DTIs in the management of acute coronary syndromes was reviewed by the Direct Thrombin Inhibitor Trialists’ Collaborative Group in a meta-analysis of data on individual patients. Eleven randomized trials were pooled, providing a total of 35,970 patients who were assigned to receive either DTIs or unfractionated heparin. No difference was observed in the primary outcome of 30-day mortality between the two treatment groups, although a benefit of bivalirudin was observed for the secondary outcome of reinfarction within 96 hours. In contrast to the results of the meta-analysis, rates of serious bleeding were not lower with bivalirudin.

Some aspects regarding the role of DTIs in acute coronary syndromes require comment. In the trials reviewed in the meta-analysis and in the Hirulog and Early Reperfusion or Occlusion 2 (HERO-2) study, DTIs have been compared with unfractionated heparin. However, several analyses have suggested that low-molecular-weight heparin may be superior to unfractionated heparin in patients with
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis or Treatment</th>
<th>No. of Patients</th>
<th>DTI Regimen</th>
<th>Control Treatment</th>
<th>Major Efficacy Outcomes</th>
<th>Percentage of Patients with a Major Efficacy Outcome</th>
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<tbody>
<tr>
<td><strong>Short-term treatment of coronary artery disease</strong></td>
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<tr>
<td>Direct Thrombin Inhibitor Trialists’ Collaborative Group study</td>
<td>Acute coronary syndromes with or without percutaneous coronary intervention</td>
<td>35,970</td>
<td>Hirudin, bivalirudin, argatroban, efegatran</td>
<td>Unfractionated heparin</td>
<td>Death or myocardial infarction at 30 days</td>
<td>Combined DTIs, 7.4; unfractionated heparin, 8.2</td>
<td>Combined DTIs, 1.9; unfractionated heparin, 2.3</td>
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<td>HERO-2</td>
<td>Myocardial infarction with ST elevation</td>
<td>17,073</td>
<td>Bivalirudin at 0.25 mg/kg intravenously, followed by 0.5 mg/kg/hr for 12 hr and then 0.25 mg/kg/hr for 36 hr</td>
<td>Unfractionated heparin for 48 hr</td>
<td>Death at 30 days</td>
<td>Bivalirudin, 10.8; unfractionated heparin, 10.9</td>
<td>Bivalirudin, 0.7; unfractionated heparin, 0.5</td>
</tr>
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<td>REPLACE-2</td>
<td>Percutaneous coronary intervention</td>
<td>6,010</td>
<td>Bivalirudin at 0.75 mg/kg intravenous bolus, followed by 1.75 mg/kg/hr for duration of procedure</td>
<td>Unfractionated heparin plus GPIIb/IIIa inhibitors for 12–18 hr</td>
<td>Death, myocardial infarction, urgent repeat revascularization, or serious bleeding</td>
<td>Bivalirudin, 9.2; unfractionated heparin, 10.0</td>
<td>Bivalirudin, 2.4; unfractionated heparin, 4.1</td>
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<td><strong>Long-term treatment of coronary artery disease</strong></td>
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<td>ESTEEM</td>
<td>Myocardial infarction with or without ST elevation</td>
<td>1,883</td>
<td>Ximelagatran at 24 mg, 36 mg, 48 mg, or 60 mg twice daily for 6 mo</td>
<td>Placebo twice daily for 6 mo</td>
<td>Death from any cause, nonfatal myocardial infarction, or severe recurrent ischemia</td>
<td>Combined ximelagatran, 12.7; placebo, 16.3</td>
<td>Combined ximelagatran, 2; placebo, 1</td>
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<td><strong>Atrial fibrillation</strong></td>
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<tr>
<td>SPORTIF III</td>
<td>Nonvalvular atrial fibrillation</td>
<td>3,407</td>
<td>Ximelagatran at 36 mg twice daily for a mean of 17 mo</td>
<td>Warfarin for a mean of 17 mo</td>
<td>All strokes or systemic embolism</td>
<td>Ximelagatran, 2.3; warfarin, 3.3</td>
<td>Ximelagatran, 1.7; warfarin, 2.4</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>Nonvalvular atrial fibrillation</td>
<td>3,922</td>
<td>Ximelagatran at 36 mg twice daily for a mean of 20 mo</td>
<td>Warfarin for a mean of 20 mo</td>
<td>All strokes or systemic embolism</td>
<td>Ximelagatran, 2.6; warfarin, 1.9</td>
<td>Ximelagatran, 3.2; warfarin, 4.3</td>
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</table>

* DTI denotes direct thrombin inhibitor, HERO-2 Hirulog and Early Reperfusion or Occlusion 2, REPLACE-2 Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomyomax to Reduced Clinical Events 2, ESTEEM Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage, and SPORTIF Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.
unstable angina and myocardial infarction.\textsuperscript{29-31} Moreover, aggressive antiplatelet therapy has become the standard treatment in acute coronary syndromes, and the role of DTIs has not been established in the setting of the combined use of aspirin and clopidogrel, as well as glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors.

Therefore, hirudin is an unattractive alternative for the treatment of patients with acute coronary syndromes, given the lack of a clear efficacy benefit, the observed increase in bleeding, and the higher cost as compared with unfractionated heparin. In a similar manner, bivalirudin does not appear to be more efficacious or safer than unfractionated heparin and cannot be recommended in this setting.

\begin{center}
\textbf{PERCUTANEOUS CORONARY INTERVENTION}
\end{center}

The meta-analysis mentioned above\textsuperscript{23} suggested that the prespecified subgroup of patients undergoing percutaneous coronary intervention had no significant efficacy benefit, but the incidence of serious bleeding was less with hirudin and bivalirudin than with unfractionated heparin.

Bivalirudin was compared with heparin during coronary angioplasty for unstable or postinfarction angina. Initial results suggested that there was a benefit,\textsuperscript{32} a finding that was supported in a longer-term follow-up using an intention-to-treat analysis.\textsuperscript{33} The combined outcome of death, myocardial infarction, and revascularization at 7 and 90 days occurred less frequently with bivalirudin, mainly owing to an effect on the need for revascularization. At 90 days, serious bleeding was significantly reduced in the bivalirudin group (3.7 percent vs. 9.3 percent).\textsuperscript{33}

The meta-analysis\textsuperscript{23} pooled data from trials that were conducted before the introduction of newer therapies such as intracoronary stenting and the use of GPIIIb/IIIa inhibitors. In the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2) study, patients undergoing urgent or elective percutaneous coronary intervention were randomly assigned to receive unfractionated heparin plus GPIIb/IIIa inhibitors or to receive bivalirudin to which GPIIb/IIIa inhibitors were added only if complications occurred during the procedure.\textsuperscript{25} Aspirin was prescribed to all patients, and the use of clopidogrel was encouraged. The composite efficacy and safety outcome of death, myocardial infarction, urgent repeat revascularization, and serious bleeding was not significantly different between the two groups. However, the use of bivalirudin was associated with a lower rate of serious bleeding. GPIIb/IIIa inhibitors were used in only 7.2 percent of the bivalirudin recipients, which may have contributed to the lower costs associated with this approach.\textsuperscript{34} The composite outcome remained not significantly different at six months\textsuperscript{35} and was not affected by concomitant clopidogrel treatment.\textsuperscript{36} A subanalysis of this trial confirmed the similar efficacy and the lower incidence of bleeding for bivalirudin, regardless of renal function.\textsuperscript{37}

In summary, bivalirudin appears to be safer than heparin in patients undergoing percutaneous coronary intervention, provided that GPIIIb/IIIa inhibitors are administered if complications occur during the procedure.

\begin{center}
\textbf{LONG-TERM TREATMENT OF ACUTE CORONARY SYNDROMES}
\end{center}

In patients with acute coronary syndromes, long-term treatment with aspirin leads to a reduction in the relative risk of recurrent ischemic events of approximately 23 percent.\textsuperscript{21,22} The addition of vitamin K antagonists further reduces cardiovascular complications, but at the expense of more bleeding.\textsuperscript{21,22} Long-term treatment with low-molecular-weight heparin does not offer an additional benefit over aspirin alone.\textsuperscript{21,22,38} The role of DTIs for long-term secondary prophylaxis in patients also receiving aspirin was investigated in the Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM) trial.\textsuperscript{26} Ximelagatran in four oral doses was compared with placebo in patients with myocardial infarction. Ximelagatran significantly reduced the incidence of the combined outcome of all-cause mortality, nonfatal myocardial infarction, and severe recurrent ischemia during the six-month treatment period as compared with placebo, without a dose–response effect. The use of ximelagatran was not associated with a rate of serious bleeding higher than that of aspirin alone, but the total risk of bleeding was higher and dose-related. Elevation of alanine aminotransferase of more than three times the upper limit of normal occurred in 11 percent of the patients treated with ximelagatran and in 2 percent of those receiving placebo.

In summary, the investigation of the role of ximelagatran in the long-term treatment of acute coronary syndromes is limited to one phase 2 trial that was promising with respect to efficacy but identified possible hepatic toxicity as an important concern.
Thus, at present, ximelagatran should not be considered for long-term treatment after acute coronary syndromes.

**ATRIAL FIBRILLATION**
The most serious clinical complication of atrial fibrillation is ischemic stroke. Although aspirin is the treatment of choice for low-risk patients, vitamin K antagonists are preferred for high-risk patients since there is a 36 percent reduction in the relative risk of stroke as compared with aspirin. Ximelagatran was compared with dose-adjusted warfarin for the prevention of all strokes and systemic embolism in patients with nonvalvular atrial fibrillation and at least one additional risk factor in the trials called Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation III (SPORTIF III) and SPORTIF V. These two studies had an identical design, except that the SPORTIF III trial was open-label, whereas the SPORTIF V trial was double-blinded. Ximelagatran was observed to be as effective as warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. Furthermore, ximelagatran conferred a significantly lower risk of serious bleeding in the pooled analysis. Ximelagatran was associated with a significant increase in the proportion of patients with alanine aminotransferase levels at least three times the upper limit of normal as compared with warfarin (6.1 percent vs. 0.8 percent).

On the basis of the SPORTIF trials, ximelagatran might be a convenient alternative for vitamin K antagonists in patients who have atrial fibrillation plus at least one additional risk factor. However, the safety of this management strategy remains to be determined.

**OTHER INDICATIONS**
Recently, data have become available from phase 2 studies on the efficacy and safety of argatroban in acute stroke and bivalirudin in coronary artery bypass surgery. However, these studies included small numbers of patients and will not be discussed further.

**PREVENTION OF VENOUS THROMBOEMBOLISM**

Despite prophyaxis, the rate of symptomatic venous thromboembolism in patients undergoing serious orthopedic surgery remains as high as 1.5 to 10 percent in the three months following surgery. De-
sirudin, melagatran, and ximelagatran have been studied in phase 3 trials in patients undergoing hip or knee surgery (Table 3). Recently, a pilot study investigated the role of the combination of melagatran and ximelagatran in elective abdominal surgery.

**XIMELAGATRAN**
Oral ximelagatran has been investigated either alone or in combination with subcutaneous melagatran for the prevention of venous thromboembolism after orthopedic surgery. In a double-blind, randomized trial among patients undergoing total hip replacement, the efficacy and safety of initiating oral ximelagatran after surgery, as compared with enoxaparin, were evaluated. The rates of both overall venous thromboembolism and proximal deep venous thrombosis (with or without pulmonary embolism) were significantly higher in patients receiving ximelagatran than they were among those treated with enoxaparin; the incidence of episodes of serious bleeding was similar.

Warfarin (with the use of a target international normalized ratio of 2.5) has been the control treatment in two phase 3 trials among patients undergoing total knee replacement. Both treatments were started postoperatively. In the first study, the incidence of overall venous thromboembolism and proximal deep venous thrombosis (with or without symptomatic pulmonary embolism) was not significantly lower in patients receiving ximelagatran than in the warfarin group; the incidence of serious bleeding was similar in the two groups. In the second trial, two doses of ximelagatran were compared with warfarin in order to demonstrate superiority of the higher ximelagatran dose. A dose of 36 mg of ximelagatran reduced the rate of overall deep venous thrombosis as compared with both 24 mg of ximelagatran and warfarin. Serious bleeding occurred with a similar frequency in all groups. Elevations of alanine aminotransferase that were more than three times the upper limit of normal were observed less frequently with both doses of ximelagatran than with warfarin at the end of treatment, though the levels had normalized in the warfarin group four to six weeks later, whereas persistent increases in levels of alanine aminotransferase were observed in some patients in the ximelagatran groups (0.6 percent and 0.1 percent in the high- and low-dose groups, respectively).

**MELAGATRAN—XIMELAGATRAN**
The efficacy of the use of subcutaneous melagatran followed by oral ximelagatran was tested in two...
Table 3. Clinical Studies Comparing Direct Thrombin Inhibitors with Control Therapy for Prophylaxis and Treatment of Venous Thromboembolism.

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<tr>
<th>Study</th>
<th>Diagnosis or Treatment</th>
<th>No. of Patients</th>
<th>DTI Regimen</th>
<th>Control Treatment</th>
<th>Primary Efficacy Outcomes</th>
<th>Results for Efficacy Outcomes (percentage)</th>
<th>Serious Bleeding (percentage)</th>
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<td>Postoperative initiation of prophylaxis</td>
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<tr>
<td>Colwell et al.43</td>
<td>Total hip replacement</td>
<td>1838</td>
<td>Ximelagatran at 24 mg twice daily for 7–12 days</td>
<td>Enoxaparin for 7–12 days</td>
<td>Proximal deep venous thrombosis with or without pulmonary embolism</td>
<td>Ximelagatran, 3.6; enoxaparin, 1.2</td>
<td>Ximelagatran, 0.8; enoxaparin, 0.9</td>
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<tr>
<td>Francis et al.44</td>
<td>Total knee replacement</td>
<td>680</td>
<td>Ximelagatran at 24 mg twice daily for 7–12 days</td>
<td>Warfarin for 7–12 days</td>
<td>Overall venous thromboembolism</td>
<td>Ximelagatran, 19.2; warfarin, 23.7</td>
<td>Ximelagatran, 1.7; warfarin, 0.9</td>
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<tr>
<td>EXULT A45*</td>
<td>Total knee replacement</td>
<td>1851</td>
<td>Ximelagatran at 36 mg and 24 mg twice daily for 7–12 days</td>
<td>Warfarin for 7–12 days</td>
<td>Overall venous thromboembolism or death</td>
<td>Ximelagatran (36 mg), 20.3; ximelagatran (24 mg), 24.9; warfarin, 27.6</td>
<td>Ximelagatran (36 mg), 0.8; ximelagatran (24 mg), 0.8; warfarin, 0.7</td>
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<td>METHRO III46</td>
<td>Total hip replacement or total knee replacement</td>
<td>2788</td>
<td>Melagatran subcutaneously at 3 mg, followed by ximelagatran at 24 mg twice daily for 8–11 days</td>
<td>Enoxaparin for 8–11 days</td>
<td>Total venous thromboembolism†</td>
<td>Melagatran–ximelagatran, 31.0; enoxaparin, 27.3</td>
<td>Melagatran–ximelagatran, 1.4; enoxaparin, 1.7</td>
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<td>BISTRO II47</td>
<td>Total hip replacement or total knee replacement</td>
<td>1973</td>
<td>Dabigatran at 50 mg, 150 mg, or 225 mg twice daily or 300 mg once daily for 6–10 days</td>
<td>Enoxaparin for 6–10 days</td>
<td>Overall venous thromboembolism</td>
<td>Dabigatran (50 mg), 28.5; dabigatran (150 mg), 17.4; dabigatran (225 mg), 13.1; dabigatran (300 mg), 16.6; enoxaparin, 24.0</td>
<td>Dabigatran (50 mg), 0.3; dabigatran (150 mg), 4.1; dabigatran (225 mg), 3.8; dabigatran (300 mg), 4.7; enoxaparin, 2.0</td>
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<td>PREoperative initiation of prophylaxis</td>
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<td>EXPRESS48</td>
<td>Total hip replacement or total knee replacement</td>
<td>2835</td>
<td>Melagatran subcutaneously at 2 mg/hr before surgery and 3 mg/hr after surgery, followed by ximelagatran at 24 mg twice daily for 8–11 days</td>
<td>Enoxaparin for 8–11 days</td>
<td>Serious venous thromboembolism mg‡</td>
<td>Melagatran–ximelagatran, 2.3; enoxaparin, 6.3</td>
<td>Melagatran–ximelagatran, 3.3; enoxaparin, 1.2</td>
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<tr>
<td>Eriksson et al.49</td>
<td>Total hip replacement</td>
<td>2079</td>
<td>Desirudin at 15 mg subcutaneously twice daily for 8–12 days</td>
<td>Enoxaparin for 8–12 days</td>
<td>Overall deep venous thrombosis</td>
<td>Desirudin, 18.4; enoxaparin, 25.5</td>
<td>Desirudin, 19.9; enoxaparin, 2.0</td>
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<td>Eriksson et al.50</td>
<td>Total hip replacement</td>
<td>445</td>
<td>Desirudin at 15 mg subcutaneously twice daily for 8–11 days</td>
<td>Unfractionated heparin for 8–11 days</td>
<td>Overall deep venous thrombosis</td>
<td>Desirudin, 7; unfractionated heparin, 23</td>
<td>No cases of serious bleeding</td>
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<td>Initial treatment</td>
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<td>THRIVE51</td>
<td>Acute deep venous thrombosis</td>
<td>2489</td>
<td>Ximelagatran at 36 mg twice daily for 6 mo</td>
<td>Enoxaparin–warfarin</td>
<td>Total recurrent venous thromboembolism</td>
<td>Ximelagatran, 2.1; enoxaparin–warfarin, 2.0</td>
<td>Ximelagatran, 1.3; enoxaparin–warfarin, 2.2</td>
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<td>THRIVE III52</td>
<td>Venous thromboembolism</td>
<td>1233</td>
<td>Ximelagatran at 24 mg twice daily for 18 mo</td>
<td>Placebo for 18 mo</td>
<td>Recurrent venous thromboembolism</td>
<td>Ximelagatran, 2.8; placebo, 12.6</td>
<td>Ximelagatran, 1.1; placebo, 1.3</td>
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</table>

* DTI denotes direct thrombin inhibitor, EXULT A Exanta (Ximelagatran) Used to Lessen Thrombosis A, METHRO III Melagatran for Thrombin Inhibition in Orthopedic Surgery III, BISTRO II Boehringer Ingelheim Study in Thrombosis II, EXPRESS Expanded Prophylaxis Evaluation Surgery Study, and THRIVE Thrombin Inhibitor in Venous Thromboembolism. †Total venous thromboembolism includes deep venous thrombosis, fatal or nonfatal pulmonary embolism, and unexplained death. ‡Serious venous thromboembolism includes proximal deep venous thrombosis, symptomatic pulmonary embolism, and death in which pulmonary embolism cannot be ruled out.
phase 3 trials among patients undergoing total hip or total knee replacement.46,48 In the Melagatran for Thrombin Inhibition in Orthopedic Surgery III (METHRO III) study, postoperative initiation of melagatran followed by ximelagatran was compared with preoperative initiation of enoxaparin.46 Both groups in the study were associated with similar rates of venous thromboembolism and of serious bleeding. In the Expanded Prophylaxis Evaluation Surgery Study (EXPRESS), the administration of melagatran before surgery followed by ximelagatran was compared with preoperative administration of enoxaparin.46 The rates of venous thromboembolism were significantly lower with the melagatran–ximelagatran regimen, but both serious and minor bleeding were observed more frequently.

**Desirudin**

Two phase 3 trials have evaluated preoperative administration of desirudin among patients undergoing hip replacement.49,50 In one study, desirudin was compared with preoperative administration of enoxaparin.49 The incidence of overall and proximal deep venous thrombosis was lower in patients treated with desirudin, with a similar risk of serious bleeding in the two groups. In the other study, preoperative administration of desirudin was compared with preoperative administration of unfractionated heparin.50 Desirudin reduced the incidence of overall and proximal deep venous thrombosis. Serious bleeding episodes were similar in the two groups.

**Dabigatran**

The Boehringer Ingelheim Study in Thrombosis II (BISTRO II) trial, a phase 2 study, compared oral dabigatran with enoxaparin in the prevention of venous thromboembolism after orthopedic surgery.47 Dabigatran was started 1 to 4 hours after surgery, whereas enoxaparin was initiated 12 hours before surgery. The highest doses of dabigatran were associated with a significantly lower incidence of venous thromboembolism than was enoxaparin. However, the risk of serious bleeding with dabigatran increased in a dose-dependent manner.

**Perioperative Timing**

The timing for the initiation of thromboprophylaxis relative to surgery might be more important with the administration of DTIs than with low-molecular-weight heparin, although, to our knowledge, a direct comparison has not been performed.42 The administration of ximelagatran alone or combined with subcutaneous melagatran postoperatively appears to be less effective than low-molecular-weight heparin but more effective than warfarin, with similar bleeding risks. In the administration of preoperative prophylaxis, both desirudin and the combination of melagatran and ximelagatran were observed to be more effective than either unfractionated or low-molecular-weight heparin.48-50 However, the reduction in thromboembolic events with either ximelagatran or melagatran was offset by more bleeding episodes.

Current data, taken together, suggest no important advantages to using most DTIs as compared with the routine use of low-molecular-weight heparin for prophylaxis of venous thromboembolism. The one exception appears to be desirudin, which can be recommended for prophylaxis among patients undergoing hip replacement.

**Treatment of Established Venous Thromboembolism**

**Initial Treatment**

Phase 2 studies with recombinant hirudin and melagatran have consistently suggested a similar efficacy and safety of DTIs as compared with standard treatment with low-molecular-weight heparin plus vitamin K antagonists for the initial treatment of venous thromboembolism.54,55 In the phase 3 Thrombin Inhibitor in Venous Thromboembolism (THRIVE) study, patients with deep venous thrombosis were randomly assigned to receive either six months of oral ximelagatran or initial treatment with subcutaneous enoxaparin combined with warfarin.51 Ximelagatran was as effective as the combination therapy, and rates of bleeding complications were similar. However, alanine aminotransferase levels increased to more than three times the upper limit of normal in 9.6 percent of the patients receiving ximelagatran and in 2.0 percent of those treated with the combination of enoxaparin and warfarin. Thus, oral ximelagatran was as effective for the treatment of venous thromboembolism without the need for monitoring, but there was concern about safety, given increases in hepatic enzymes.

**Long-term Secondary Prophylaxis**

After six months of treatment with vitamin K antagonists, patients with venous thromboembolism have a 5 to 7 percent risk of recurrence in the first year after discontinuation.56 Therefore, long-term
DRUG THERAPY

Heparin-induced thrombocytopenia is an adverse drug reaction mediated by the immune system, with clinical manifestations initiated by antibodies directed against platelet factor 4, which becomes an antigenic target when bound to heparin. This antibody–platelet factor 4–heparin complex is able to activate platelets and may cause venous and arterial thrombosis. Although the immediate discontinuation of heparin is mandatory in this condition, the strategy is insufficient, given the high cumulative risk of thrombosis during 30-day administration of the drug — up to 53 percent without antithrombotic treatment. Thus, for patients with suspected or confirmed heparin-induced thrombocytopenia, the use of alternative anticoagulants is recommended. The use of DTIs for this condition is theoretically supported by the intense thrombin activity observed in these patients.

Two DTIs, lepirudin and argatroban, are approved in the United States for heparin-induced thrombocytopenia. The data about the efficacy and safety of lepirudin and argatroban come from prospective cohort studies that used historical controls. In patients with proven heparin-induced thrombocytopenia who were treated with lepirudin, a thrombotic event occurred in approximately 4 percent of patients, as compared with 15 percent in historical controls, but the administration of lepirudin was associated with a higher rate of serious bleeding (14 percent vs. 8 percent). Similar results were reported for patients with heparin-induced thrombocytopenia with thromboembolic complications. In two series of patients with a clinical diagnosis of heparin-induced thrombocytopenia and thrombosis who were treated with argatroban, the rates of new thrombotic episodes were 13 and 19 percent, as compared with approximately 35 percent in historical controls, with bleeding rates of 6 and 11 percent.

Antithirudin antibodies develop in 40 to 74 percent of patients receiving lepirudin after four days or more of treatment. Of note, fatal anaphylaxis has been described with lepirudin, particularly in patients who are treated again within three months of a previous exposure to this agent. In contrast, argatroban does not appear to be immunogenic. Thus, lepirudin and argatroban appear to be effective in patients with heparin-induced thrombocytopenia, but drawbacks are an enhanced risk of bleeding and immunogenicity of lepirudin.

HEPARIN-INDUCED THROMBOCYTOPENIA

DIRECT THROMBIN INHIBITORS AND LIVER FUNCTION

No available data report about hepatic dysfunction with the use of recombinant hirudins, bivalirudin, or argatroban. The pharmacokinetic and pharmacodynamic properties of ximelagatran and melagatran do not appear to be influenced in the presence of mild-to-moderate impairment of liver function, and short-term exposure to ximelagatran (about 12 days) does not appear to increase the risk of hepatotoxicity. However, data on longer-term use of ximelagatran and melagatran indicate that alanine aminotransferase levels can become elevated after one to six months in 6 to 10 percent of patients. Although increases that have been reported so far are usually asymptomatic and reversible, even if the medication is continued, the few cases of fatal hepatotoxicity observed with prolonged administration of ximelagatran have led the FDA to deny approval of ximelagatran in the United States, and only short-term use of ximelagatran has been approved in Europe. The mechanisms of these liver-enzyme abnormalities are still unknown.

MONITORING ACTIVITY

The best method to monitor therapy with DTIs has not been clearly established. The usefulness of the activated partial-thromboplastin time seems limited by its poor linearity and reproducibility, especially when heparin or a vitamin K antagonist is coadministered. The ecarin clotting time better reflects the actual plasma concentration of DTIs, but this test is not widely available.
Recombinant hirudins and argatroban can be monitored with the use of the activated partial-thromboplastin time and bivalirudin with the activated clotting time. In patients with heparin-induced immune thrombocytopenia, antihirudin antibodies form complexes with lepirudin that may reduce the renal clearance of the drug. This phenomenon often results in a need to reduce and monitor the dose to maintain the lepirudin anticoagulant effect within the therapeutic range, especially in patients with impaired renal function.

Since there is no antidote for rapidly reversing the effect of DTIs, monitoring these drugs is important for patients who have a high risk of bleeding. However, given the short half-life of most DTIs, the major anticoagulant effects of DTIs should have disappeared by 12 to 24 hours after the last dose. Preliminary data suggest that recombinant factor VIIa has a limited capacity to reverse the anticoagulant effects of melagatran.

**CONCLUSIONS**

Despite many well-performed clinical trials, there are few clinical indications for DTIs. For acute coronary syndromes, none of the DTIs have consistently shown superior efficacy combined with a similar safety in comparison with the present standard treatment with heparin and antiplatelet agents. For patients with unstable angina who are undergoing a percutaneous coronary intervention, bivalirudin may be superior to heparin plus GPIIb/IIIa inhibitors administered in case of intraprocedural complications. No DTIs have been convincingly demonstrated to be efficacious and safe for long-term treatment after acute coronary syndromes. In contrast, the efficacy data of ximelagatran in atrial fibrillation are promising, but concern with regard to hepatic toxicity with long-term use must be resolved. When thromboprophylaxis is initiated after serious orthopedic surgery, ximelagatran-containing regimens are less effective than is treatment with low-molecular-weight heparin, but such regimens are superior to warfarin therapy and have a similar safety profile. Preoperative initiation of desirudin is an alternative to the standard approach, but preoperative initiation of melagatran plus ximelagatran increases the risk of bleeding.

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**REFERENCES**


20. Fager C, Cullberg M, Eriksson-Lepkowska M, Frison L, Eriksson UG. Pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct
thrombin inhibitor ximelagatran, are not influ-
enced by acetylsalicylic acid. Eur J Clin Phar-
cm 2003;59:283-9.
21. Harrington RA, Becker RC, Ezekowitz M,
et al. Antithrombotic therapy for coro-
nary artery disease: the Seventh ACCP Con-
ference on Antithrombotic and Thrombo-
ytic Therapy. Chest 2004;126:Suppl 3:
513S-548S.
22. Menon V, Harrington RA, Hochman JS,
et al. Thrombolysis and adjunctive therapy in
acute myocardial infarction: the Seventh
ACCP Conference on Antithrombotic and
Thrombolytic Therapy. Chest 2004;126:
Suppl 3:549S-578S.
23. The Direct Thrombin Inhibitor Trials’
Collaborative Group. Direct thrombin in-
hibitors in acute coronary syndromes:
principal results of a meta-analysis based on
individual patients’ data. Lancet 2002;359:
294-302.
24. White H, Hiruglo and Early Reperfusion
or Occlusion (HERO)-2 Trial Investigators.
Thrombin-specific anticoagulation with bi-
valirudin versus heparin in patients receiv-
ing fibrinolytic therapy for acute myocardial
infarction: the HERO-2 randomized trial.
25. Lincoff AM, Bittl JA, Harrington RA,
et al. Bivalirudin and provisional glycopro-
in IIb/IIIa blockade compared with heparin
and planned glycoprotein IIb/IIIa blockade
during percutaneous coronary intervention:
REPLACE-2 randomized trial. JAMA 2003;
289:853-63. [Erratum, JAMA 2003;289:
1638.]
26. Wallentin L, Wilcox KG, Weaver WD,
et al. Oral ximelagatran for secondary prophyl-
axis after myocardial infarction: the ESTEEM
randomised controlled trial. Lancet
27. Olsson SB. Stroke prevention with the
oral direct thrombin inhibitor ximelagatran
compared with warfarin in patients with
non-valvular atrial fibrillation (SPORTIF
III): randomised controlled trial. Lancet
28. Albers GW, Diener HC, Frison L,
et al. Ximelagatran vs warfarin for stroke pre-
vention in patients with nonvalvular atrial fibril-
lation: a randomized trial. JAMA 2005;293:
690-8.
29. Antman EM, Cohen M, Radley D,
et al. Assessment of the treatment effect of enox-
aparin for unstable angina/non-Q-wave my-
cardial infarction: TIMI 11B-ESSENCE
meta-analysis. Circulation 1999;100:1602-
8.
30. The Assessment of the Safety and Efficacy
of a New Thrombolytic Regimen (ASSENT-3)
Investigators. Efficacy and safety of tenecteplase in combination with
oxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in
acute myocardial infarction. Lancet 2001;
31. Petersen JL, Mahaffey KW, Hassellblad V,
et al. Efficacy and bleeding complications
among patients randomized to enoxaparin
or unfractionated heparin for antithrombin
therapy in non-ST-segment elevation acute
myocardial syndromes: a systematic overview.
JAMA 2004;292:89-96.
32. Bittl JA, Strong J, Brinker JA, et al. Treat-
ment with bivalirudin (Hiruglo) as com-
pared with heparin during coronary angiop-
Iasty for unstable or postinfarction angina.
33. Bittl JA, Chatman BR, Feit F, Kimball W,
Topol EJ. Bivalirudin versus heparin during
coronary angioplasty for unstable or postin-
farction angina: final report reanalysis of the
Bivalirudin Angioplasty Study. Am Heart J
Economic evaluation of bivalirudin with
provisional glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein
IIb/IIIa inhibition for percutaneous coro-
nary intervention: results from the
REPLACE-2 trial. J Am Coll Cardiol 2004;
44:1792-800.
35. Lincoff AM, Kleiman NS, Kereiakes DJ,
et al. Long-term efficacy of bivalirudin and
provisional glycoprotein IIb/IIIa blockade vs
heparin and planned glycoprotein IIb/IIIa
blockade during percutaneous coronary re-
vascularization: REPLACE-2 randomized
of clopidogrel pretreatment effect on the
relative efficacy of bivalirudin with provi-
sional glycoprotein IIb/IIIa blockade com-
pared to heparin with routine glycoprotein
IIb/IIIa blockade: a REPLACE-2 substudy.
Bivalirudin versus heparin and glycoprotein
IIb/IIIa inhibition among patients with renal
impairment undergoing percutaneous coro-
nary intervention (a subanalysis of the
REPLACE-2 trial). Am J Cardiol 2005;
95:581-5.
38. Eikelboom JW, Anand SS, Malmberg K,
Weitz JJ, Ginsberg JS, Yusuf S. Unfractionat-
ed heparin and low-molecular-weight hepa-
in in acute coronary syndrome without ST
elevation: a meta-analysis. Lancet 2000;
356:600.]
39. Singer DE, Albers GW, Dalen JE, Go AS,
Halperin JL, Manning WJ. Antithrombotic
therapy in atrial fibrillation: the Seventh
ACCP Conference on Antithrombotic and
Thrombolytic Therapy. Chest 2004;126:
Suppl 3:3429S-456S.
40. LaMonte MP, Nash ML, Wang DZ, et al.
Argatroban anticoagulation in patients with
acute ischemic stroke (ARGIS-1): a random-
ized, placebo-controlled safety study. Stroke
2004;35:1677-82.
41. Merry AF, Raudkivi PJ, Middleton NG,
et al. Bivalirudin versus heparin and prota-
mine in off-pump coronary artery bypass
42. Geerts WH, Pineo GF, Heit JA, et al. Pre-
vention of venous thromboembolism: the
Seventh ACCP Conference on Antithrom-
bolic and Thrombolytic Therapy. Chest
2004;126:Suppl 3:3385-400S.
43. Colwell CW Jr, Berkowitz SD, Davidson
BL, et al. Comparison of ximelagatran, an
oral direct thrombin inhibitor, with enox-
aparin for the prevention of venous throm-
boembolism following total hip replace-
ment: a randomized, double-blind study.
44. Francis CW, Davidson BL, Berkowitz
SD, et al. Ximelagatran versus warfarin for
the prevention of venous thromboembolism
after total knee arthroplasty: a randomized,
137:648-55.
45. Francis CW, Berkowitz SD, Comp PC,
et al. Comparison of ximelagatran with war-
farin for the prevention of venous thrombo-
embolism after total knee replacement. N
Direct thrombin inhibitor melagatran fol-
lowed by oral ximelagatran in comparison
with enoxaparin for prevention of venous
thromboembolism after total hip or knee re-
placement. Thromb Haemost 2003;90:288-
96.
47. Eriksson BI, Dahl OE, Buller HR, et al.
A new oral direct thrombin inhibitor albig-
agatran etexilate, compared with enoxaparin
for prevention of thromboembolic events
following total hip or knee replacement: the
BISTRO II randomized trial. J Thromb
The direct thrombin inhibitor melagatran
compared with enoxaparin for the prevent-
ion of venous thromboembolism after total hip
or knee replacement: the EXPRESS study.
49. Eriksson BI, Wille-Jorgensen P, Kaleb
P, et al. A comparison of recombinant hiru-
drin with a low-molecular-weight heparin to
prevent thromboembolic complications af-
1997;337:1329-35.
Prevention of thromboembolism with use of
recombinant hirudin: results of a double-
blind, multicenter trial comparing the effi-
cacy of desirudin (Revasc) with that of unfrac-
tionated heparin in patients having a total hip
79:326-33.
51. Fiesinger J-N, Huisman MV, Davidson
BL, et al. Ximelagatran vs low-molecular-
weight heparin and warfarin for the treat-
ment of deep vein thrombosis: a random-
52. Schulman S, Wadhander K, Lundstrom
T, Clason SB, Eriksson H. Secondary pre-
vention of venous thromboembolism with the
oral direct thrombin inhibitor ximelaga-
53. Bergqvist D, Solhaug J-H, Holmdal L,
et al. Pharmacokinetics, preliminary effica-

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cy and safety of subcutaneous melagatran and oral ximelagatran: a multicenter study of thromboprophylaxis in elective abdomi-
54. Schiele F, Lindgaard F, Eriksson H, et al. Subcutaneous recombinant hirudin (HBW 023) versus intravenous sodium hep-
55. Eriksson H, Eriksson UG, Frison L, et al. Pharmacokinetics and pharmacodynamic-
56. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic dis-
58. Kasparian MT, Berkemans RJ, Mor-
rrien-Salomon WM, et al. Monitoring anti-
coagulant therapy by activated partial thromboplastin time: hirudin assessment: an evaluation of native blood and plasma as-
59. Callas DD, Hoppensteadt D, Iqbal O, Fa-
reed J. Ecarin clotting time (ECT) is a reliable method for the monitoring of hirudins, ar-
60. Callas DD, Fareed J. Comparative anti-
coagulant effects of various thrombin inhibi-
61. Wardlaw N, Breidin RK, Esslinger H-U. Ecarin clotting time is more suitable to moni-
tor PEG-hirudin treatment compared to aPTT, TT, ACT, or a-lla-activity. Ann Hema-
62. Warkentin TE, Greinacher A, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopo-
CORRECTION

Direct Thrombin Inhibitors

Direct Thrombin Inhibitors. On page 1029, in Figure 1, the arrow pointing from activated protein C and protein S to factors IXa and VIIIa should have been dashed (indicating an inhibitory pathway), rather than solid (indicating an activation pathway). Also, a dashed-line arrow should have been pointing from activated protein C and protein S to factors Xa and Va, rather than the reverse, as printed. These corrections to the figure appear with the full text of the article at www.nejm.org.