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REVIEW ARTICLE

DRUG THERAPY

Direct Thrombin Inhibitors

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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 thromboembolism 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.[1] 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.[2-4] Thus, heparins have a reduced capacity for the inhibition of fibrin-bound thrombin, which ap-

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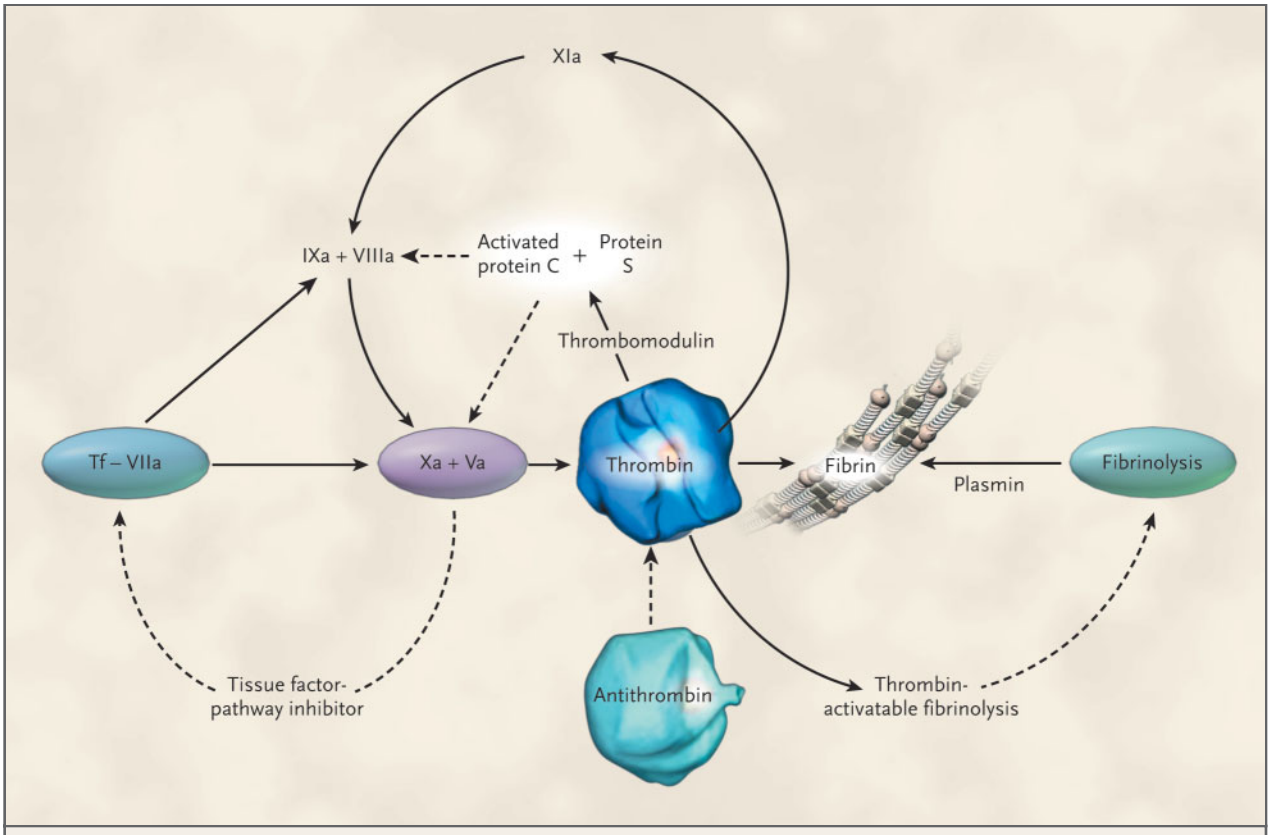

Figure 1. Thrombin Generation.

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.)

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.

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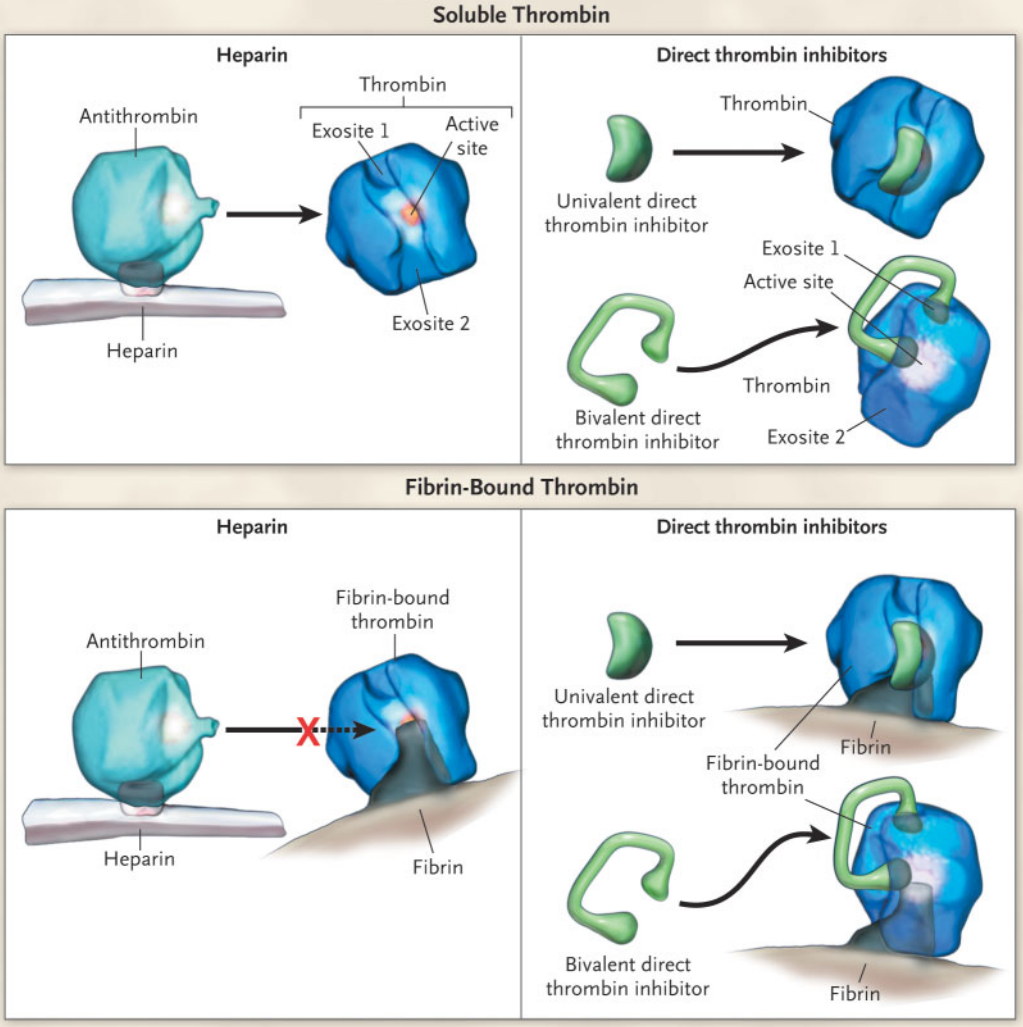

Figure 2. Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin.

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.

PHARMACOKINETICS AND PHARMACODYNAMICS

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.[12,15] Although excessive anticoagulation with hirudin in patients with renal insufficiency can be managed with high-volume hemofiltration with hirudin-permeable hemodialysis membranes,[15] 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-

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Table 1. Main Properties and Pharmacokinetic Characteristics of Direct Thrombin Inhibitors.

Characteristic	Recombinant Hirudins*	Bivalirudin (Hirulog)	Argatroban (Novastan)	Ximelagatran and Melagatran (Exanta)	Dabigatran
Route of administration	Intravenous, subcutaneous	Intravenous	Intravenous	Intravenous, subcutaneous (melagatran), oral (ximelagatran)	Oral
Plasma half-life	Intravenous, 60 min; subcutaneous, 120 min	25 min	45 min	Intravenous and subcutaneous, 2–3 hr; oral, 3–5 hr	12 hr
Main site of clearance	Kidney	Kidney, liver, other sites	Liver	Kidney	Kidney

* Recombinant hirudins include lepirudin (Refludan) and desirudin (Iprivask).

vated prothrombin complex concentrates.[12] 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.[16] However, the half-life of bivalirudin is prolonged with severe renal impairment, and dose adjustments are needed.[17]

Argatroban is predominantly cleared by hepatic metabolism and requires dose adjustments in patients with hepatic dysfunction.[18] The use of aspirin does not appear to influence the plasma concentrations of DTIs.[19,20]

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.[21,22] 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.[23] Eleven randomized trials were pooled, providing a total of 35,970 patients who were assigned to receive either DTIs or unfractionated heparin from 24 hours up to 7 days and then were followed for at least 30 days. As compared with heparin, DTIs reduced the incidence of the composite outcome of death and myocardial infarction both at the end of treatment and at 30 days (Table 2). The difference in risk appeared to be due mainly to a significant reduction in myocardial infarction, without a significant effect on death. The analysis by agent revealed that benefits were similar for hirudin and bivalirudin, whereas a nonsignificant, small increase in the risk of death or myocardial infarction was observed with univalent DTIs. Serious bleeding occurred less frequently among patients receiving DTIs than among those receiving heparin, but there was substantial heterogeneity for this outcome. Serious bleeding occurred more frequently with hirudin than with heparin but less often with bivalirudin and univalent inhibitors. The data on univalent DTIs should be interpreted with caution owing to the rather small number of events and the fact that these results are derived from dose-finding studies, with all dosage groups combined.

In 2001, the data from another randomized clinical trial in acute coronary syndromes became available.[24] In this study, patients with myocardial infarction characterized by ST-segment elevation were randomly assigned to receive either bivalirudin or unfractionated heparin combined with streptokinase.[24] 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[23] and in the Hirulog and Early Reperfusion or Occlusion 2 (HERO-2) study,[24] 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

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Table 2. Clinical Studies Comparing Direct Thrombin Inhibitors with Control Therapy in Patients with Coronary Syndromes (with or without Percutaneous Coronary Intervention) or Atrial Fibrillation.*

Study	Diagnosis or Treatment	No. of Patients	DTI Regimen	Control Treatment	Major Efficacy Outcomes	Percentage of Patients with a Major Efficacy Outcome	Serious Bleeding (percentage)
Short-term treatment of coronary artery disease							
Direct Thrombin Inhibitor Trialists' Collaborative Group[23] study	Acute coronary syndromes with or without percutaneous coronary intervention	35,970	Hirudin, bivalirudin, argatroban, efegatran	Unfractionated heparin	Death or myocardial infarction at 30 days	Combined DTIs, 7.4; unfractionated heparin, 8.2	Combined DTIs, 1.9; unfractionated heparin, 2.3
HERO-2[24]	Myocardial infarction with ST elevation	17,073	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	Unfractionated heparin for 48 hr	Death at 30 days	Bivalirudin, 10.8; unfractionated heparin, 10.9	Bivalirudin, 0.7; unfractionated heparin, 0.5
REPLACE-2[25]	Percutaneous coronary intervention	6,010	Bivalirudin at 0.75 mg/kg intravenous bolus, followed by 1.75 mg/kg/hr for duration of procedure	Unfractionated heparin plus GPIIb/IIIa inhibitors for 12–18 hr	Death, myocardial infarction, urgent repeat revascularization, or serious bleeding	Bivalirudin, 9.2; unfractionated heparin, 10.0	Bivalirudin, 2.4; unfractionated heparin, 4.1
Long-term treatment of coronary artery disease							
ESTEEM[26]	Myocardial infarction with or without ST elevation	1,883	Ximelagatran at 24 mg, 36 mg, 48 mg, or 60 mg twice daily for 6 mo	Placebo twice daily for 6 mo	Death from any cause, nonfatal myocardial infarction, or severe recurrent ischemia	Combined ximelagatran, 12.7; placebo, 16.3	Combined ximelagatran, 2; placebo, 1
Atrial fibrillation							
SPORTIF III[27]	Nonvalvular atrial fibrillation	3,407	Ximelagatran at 36 mg twice daily for a mean of 17 mo	Warfarin for a mean of 17 mo	All strokes or systemic embolism	Ximelagatran, 2.3; warfarin, 3.3	Ximelagatran, 1.7; warfarin, 2.4
SPORTIF V[28]	Nonvalvular atrial fibrillation	3,922	Ximelagatran at 36 mg twice daily for a mean of 20 mo	Warfarin for a mean of 20 mo	All strokes or systemic embolism	Ximelagatran, 2.6; warfarin, 1.9	Ximelagatran, 3.2; warfarin, 4.3

* DTI denotes direct thrombin inhibitor, HERO-2 Hirulog and Early Reperfusion or Occlusion 2, REPLACE-2 Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax 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.

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unstable angina and myocardial infarction.[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.

PERCUTANEOUS CORONARY INTERVENTION

The meta-analysis mentioned above[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,[32] a finding that was supported in a longer-term follow-up using an intention-to-treat analysis.[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).[33]

The meta-analysis[23] pooled data from trials that were conducted before the introduction of newer therapies such as intracoronary stenting and the use of GPIIb/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.[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.[34] The composite outcome remained not significantly different at six months[35] and was not affected by concomitant clopidogrel treatment.[36] A subanalysis of this trial confirmed the similar efficacy and the lower incidence of bleeding for bivalirudin, regardless of renal function.[37]

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

LONG-TERM TREATMENT OF ACUTE CORONARY SYNDROMES

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.[21,22] The addition of vitamin K antagonists further reduces cardiovascular complications, but at the expense of more bleeding.[21,22] Long-term treatment with low-molecular-weight heparin does not offer an additional benefit over aspirin alone.[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.[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.

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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.[39] 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.[39]

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.[27,28] 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[40] and bivalirudin in coronary artery bypass surgery.[41] However, these studies included small numbers of patients and will not be discussed further.

PREVENTION OF VENOUS THROMBOEMBOLISM

Despite prophylaxis, 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.[42] Desirudin, 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.[53]

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.[43] 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.[44,45] 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; the incidence of serious bleeding was similar in the two groups.[44] In the second trial, two doses of ximelagatran were compared with warfarin in order to demonstrate superiority of the higher ximelagatran dose.[45] 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

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Table 3. Clinical Studies Comparing Direct Thrombin Inhibitors with Control Therapy for Prophylaxis and Treatment of Venous Thromboembolism.

Study	Diagnosis or Treatment	No. of Patients	DTI Regimen	Control Treatment	Primary Efficacy Outcomes	Results for Efficacy Outcomes (percentage)	Serious Bleeding (percentage)
Postoperative initiation of prophylaxis							
Colwell et al.[43]	Total hip replacement	1838	Ximelagatran at 24 mg twice daily for 7–12 days	Enoxaparin for 7–12 days	Proximal deep venous thrombosis with or without pulmonary embolism	Ximelagatran, 3.6; enoxaparin, 1.2	Ximelagatran, 0.8; enoxaparin, 0.9
Francis et al.[44]	Total knee replacement	680	Ximelagatran at 24 mg twice daily for 7–12 days	Warfarin for 7–12 days	Overall venous thromboembolism	Ximelagatran, 19.2; warfarin, 25.7	Ximelagatran, 1.7; warfarin, 0.9
EXULT A[45]*	Total knee replacement	1851	Ximelagatran at 36 mg and 24 mg twice daily for 7–12 days	Warfarin for 7–12 days	Overall venous thromboembolism or death	Ximelagatran (36 mg), 20.3; ximelagatran (24 mg), 24.9; warfarin, 27.6	Ximelagatran (36 mg), 0.8; ximelagatran (24 mg), 0.8; warfarin, 0.7
METHRO III[46]	Total hip replacement or total knee replacement	2788	Melagatran subcutaneously at 3 mg, followed by ximelagatran at 24 mg twice daily for 8–11 days	Enoxaparin for 8–11 days	Total venous thromboembolism†	Melagatran–ximelagatran, 31.0; enoxaparin, 27.3	Melagatran–ximelagatran, 1.4; enoxaparin, 1.7
BISTRO II[47]	Total hip replacement or total knee replacement	1973	Dabigatran at 50 mg, 150 mg, or 225 mg twice daily or 300 mg once daily for 6–10 days	Enoxaparin for 6–10 days	Overall venous thromboembolism	Dabigatran (50 mg), 28.5; dabigatran (150 mg), 17.4; dabigatran (225 mg), 13.1; dabigatran (300 mg), 16.6; enoxaparin, 24.0	Dabigatran (50 mg), 0.3; dabigatran (150 mg), 4.1; dabigatran (225 mg), 3.8; dabigatran (300 mg), 4.7; enoxaparin, 2.0
Preoperative initiation of prophylaxis							
EXPRESS[48]	Total hip replacement or total knee replacement	2835	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	Enoxaparin for 8–11 days	Serious venous thromboembolism‡	Melagatran–ximelagatran, 2.3; enoxaparin, 6.3	Melagatran–ximelagatran, 3.3; enoxaparin, 1.2
Eriksson et al.[49]	Total hip replacement	2079	Desirudin at 15 mg subcutaneously twice daily for 8–12 days	Enoxaparin for 8–12 days	Overall deep venous thrombosis	Desirudin, 18.4; enoxaparin, 25.5	Desirudin, 1.9; enoxaparin, 2.0
Eriksson et al.[50]	Total hip replacement	445	Desirudin at 15 mg subcutaneously twice daily for 8–11 days	Unfractionated heparin for 8–11 days	Overall deep venous thrombosis	Desirudin, 7; unfractionated heparin, 23	No cases of serious bleeding
Initial treatment							
THRIVE[51]	Acute deep venous thrombosis	2489	Ximelagatran at 36 mg twice daily for 6 mo	Enoxaparin–warfarin	Total recurrent venous thromboembolism	Ximelagatran, 2.1; enoxaparin–warfarin, 2.0	Ximelagatran, 1.3; enoxaparin–warfarin, 2.2
Long-term secondary prophylaxis							
THRIVE III[52]	Venous thromboembolism	1233	Ximelagatran at 24 mg twice daily for 18 mo	Placebo for 18 mo	Recurrent venous thromboembolism	Ximelagatran, 2.8; placebo, 12.6	Ximelagatran, 1.1; placebo, 1.3

* 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.

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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.[48] 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

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treatment has been recommended for patients at high risk for recurrence. Extended prophylaxis with ximelagatran was compared with placebo for 18 months in patients with thromboembolism who had been treated with vitamin K antagonists for at least 6 months.[52] Ximelagatran significantly reduced the rate of recurrent venous thromboembolism without a significant increase in the incidence of either serious or minor bleeding. However, ximelagatran was associated with a significantly increased rate of elevated alanine aminotransferase levels (6.4 percent vs. 1.2 percent). Thus, there is concern about hepatic toxicity with long-term use of ximelagatran.

HEPARIN-INDUCED THROMBOCYTOPENIA

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.[57] Thus, for patients with suspected or confirmed heparin-induced thrombocytopenia, the use of alternative anticoagulants is recommended.[57] The use of DTIs for this condition is theoretically supported by the intense thrombin activity observed in these patients.[57-59]

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.[59-61] 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).[59] Similar results were reported for patients with heparin-induced thrombocytopenia with thromboembolic complications.[62] 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.[60,61]

Antihirudin antibodies develop in 40 to 74 percent of patients receiving lepirudin after four days or more of treatment.[59,63,64] 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.[65] In contrast, argatroban does not appear to be immunogenic.[66] 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.

REMAINING ISSUES

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,[67] and short-term exposure to ximelagatran (about 12 days) does not appear to increase the risk of hepatotoxicity.[68] 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,[69] and only short-term use of ximelagatran has been approved in Europe.[70] 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.[71-76] 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.[71-73,77-79] The ecarin clotting time better reflects the actual plasma concentration of DTIs, but this test is not widely available.[74-77,80-82]

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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.[63] 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.[57]

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.[83]

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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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.

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