



Thrombophilia and New Anticoagulant Drugs

Jeffrey I. Weitz, Saskia Middeldorp, William Geerts, and John A. Heit

Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, is the result of an imbalance among procoagulant, anticoagulant and profibrinolytic processes. This imbalance reflects a complex interplay between genetic and environmental or acquired risk factors. Genetic thrombophilic defects influence the risk of a first episode of thrombosis. How these defects influence the risk of recurrence in patients whose first episode of venous thromboembolism was unprovoked is less certain. Thus, when anticoagulants are stopped, patients with unprovoked venous thromboembolism have a risk of recurrence of at least 7% to 10% per year, even in the absence of an underlying thrombophilic defect. Consequently, there is a trend toward longer durations of anticoagulation therapy for these patients, which is problematic given the limitation of existing anticoagulants. This chapter provides an overview of the thrombophilic defects and how they influence the risk of venous thromboembolism. The chapter also details advances in anticoagulant therapy, focusing on new inhibitors of factor Xa and thrombin.

I. THROMBOPHILIC DEFECTS

*Saskia Middeldorp, MD**

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are manifestations of a single disease, venous thromboembolism (VTE). The pathogenesis of VTE is multifactorial, often involving acquired or environmental risk factors, as well as a genetic predisposition. Patients whose VTE occurs in conjunction with a self-limited risk factor, such as surgery, have a low risk of recurrence when anticoagulant treatment is stopped. In contrast, approximately one-third of those with unprovoked VTE will suffer a recurrence over the subsequent decade once anticoagulant therapy is stopped. Given this high risk of recurrent VTE, some experts recommend long-term anticoagulant therapy after a first episode of

In Section I, Dr. Saskia Middeldorp describes the various thrombophilic defects and reviews their relative importance in the pathogenesis of a first episode of venous thromboembolism. She then discusses the influence of these defects on the risk of recurrent thrombotic events in patients with unprovoked venous thromboembolism and in those whose thrombosis occurred in association with a known risk factor, such as surgery.

In Section II, Dr. William Geerts reviews the pharmacology of new parenteral and oral factor Xa inhibitors and describes the results of the Phase II and III clinical trials with these agents. He then provides perspective on the potential advantages and drawbacks of these drugs for the prevention and treatment of venous thromboembolism.

In Section III, Dr. John Heit focuses on direct thrombin inhibitors. He discusses their mechanism of action and compares and contrasts their pharmacological profiles prior to describing the results of Phase II and III clinical trials. Dr. Heit then provides perspective on the potential advantages and limitations of these drugs relative to existing anticoagulants.

unprovoked VTE. This approach is suboptimal because the risk of major bleeding with coumarin derivatives is 2% per year. Consequently, there is a need for patient-specific markers that predict the risk of recurrent VTE so that those at highest risk can be targeted for long-term anticoagulation therapy.

At least 50% of patients presenting with unprovoked VTE have an underlying thrombophilic defect. The prevalence of common thrombophilic defects, such as the factor V Leiden and the prothrombin G20210A mutation, varies according to ethnicity. Thus, in Caucasians, these mutations are found in 2%–7% and 1%–3% of the population, respectively. In contrast, both mu-

* Academic Medical Center, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands

tations are rare in Asians and Africans. In this paper, the impact of the various inherited and acquired thrombophilic defects on the risk of VTE is reviewed and the potential importance of other factors is discussed.

Thrombophilia and the Risk for VTE

Inherited abnormalities associated with an increased risk of VTE include deficiencies of antithrombin, protein C, and protein S, activated protein C resistance (which is usually caused by the factor V Leiden mutation), and the prothrombin G20210A mutation. Hyperhomocysteinemia and elevated levels of various clotting factors (including factors VIII, IX and XI) also have been associated with an increased risk of VTE. Although hyperhomocysteinemia and elevated levels of factor VIII often occur in families, most studies show no direct association between VTE and mutations known to cause hyperhomocysteinemia or polymorphisms in the factor VIII gene. Acquired thrombophilic disorders include antiphospholipid antibodies, a heterogeneous group of antibodies that can be detected as a lupus anticoagulant and/or anticardiolipin antibodies.

The relative risk of a first episode of VTE in individuals with these various thrombophilic defects ranges from 2 to 11 (**Table 1**). These figures were derived from family- and population-based cohort or case-control studies. Individuals homozygous for thrombophilic defects, such as the prothrombin G20210A or factor V Leiden mutation, are at higher risk for VTE than het-

erozygotes. Likewise, patients with combined thrombophilic disorders have a higher risk of VTE than those with a single defect.

The increase in risk with these thrombophilic defects must be considered on the background of the baseline risk of VTE, which is about 2–3 per 1000 per year in Western societies and increases with age.¹ Prospective studies in thrombophilic families have shown that the risk for a first episode of VTE in relatives with antithrombin deficiency is approximately 4.0% per year, and for those with protein C or protein S deficiency is about 1.5% per year.² This risk is higher than the 0.6% annual incidence found in carriers of the factor V Leiden mutation.³

Thrombophilia and the Risk of Recurrent VTE

Although thrombophilic defects are a well-established risk factor for a first episode of VTE, their influence on the risk of recurrent VTE is less certain. In a recent analysis, pooled odds ratios were calculated from prospective studies using the Mantel-Haenszel method (**Table 2**).⁴ Since this review, additional data have become available from two large cohorts of patients with a first episode of objectively documented VTE, one from the United Kingdom⁵ and one from Italy⁶ (references from original studies reviewed in this section are listed in **Table 2**). It should be noted that comparison of recurrence risks across various studies may not be completely valid, given for instance differences between

Table 1. Estimated relative risks for a first episode of venous thromboembolism (VTE) in individuals with a thrombophilic defect as compared to individuals without a defect; derived from family and population-based case-control studies.

Thrombophilic Defect	Estimated Relative Risk	References
Antithrombin deficiency	8–10	Martinelli I. <i>Blood</i> 1998;92:2353-2358. Simioni P. <i>Thromb Haemost.</i> 1999;81:198-202.
Protein C deficiency	7–10	Martinelli I. <i>Blood</i> 1998;92:2353-2358. Simioni P. <i>Thromb Haemost.</i> 1999;81:198-202.
Protein S deficiency	8–10	Martinelli I. <i>Blood</i> 1998;92:2353-2358. Simioni P. <i>Thromb Haemost.</i> 1999;81:198-202.
Factor V Leiden/APC resistance	3–7	Middeldorp S. <i>Ann Int Med.</i> 1998;128:15-20. Koster T. <i>Lancet.</i> 1993;342:1503-1506.
Prothrombin 20210A mutation	3	Poort SR. <i>Blood.</i> 1996;88:3698-3703.
Elevated factor VIII:c (dose-dependent)	2–11	Koster T. <i>Lancet.</i> 1995;345:152-155. Kraaijenhagen RA. <i>Thromb Haemost.</i> 2000;83:5-9.
Elevated factor IX:c	2–3	van Hylckama Vlieg A. <i>Blood.</i> 2000;95:3678-3682.
Elevated factor XI:c (> 90th percentile)	2	Meijers JCM. <i>N Eng J Med.</i> 2000;342:696-701.
Mild hyperhomocysteinemia (fasting or post-methionine loading)	2.5–2.6	den Heijer M. <i>Thromb Haemost.</i> 1998;80:874-877.
Anticardiolipin antibodies		Wahl DG. <i>Lupus.</i> 1998;7:15-22
all	1.6	
high titers only	3.2	
Lupus anticoagulant	11	Wahl DG. <i>Lupus.</i> 1998;7:15-22.

Table 2. References to studies used to describe the risks of recurrent venous thromboembolism (VTE) in individuals with a thrombophilic defect as compared to individuals with a first episode of VTE without a thrombophilic defect.

Thrombophilic Defect	Estimated Relative Risk	References
Antithrombin, protein C, or protein S deficiency	2.5	De Stefano V. <i>Thromb Haemost.</i> 1994;72:352-358. Van den Belt AG. <i>Arch Int Med.</i> 1997;157:2227-2232. Margaglione M. <i>Thromb Haemost.</i> 1999;82:1583-1587.
Factor V Leiden mutation	1.4*	Lindmarker P. <i>Thromb Haemost.</i> 1999;81:684-689. Simioni P. <i>N Eng J Med.</i> 1997;336:399-403. Ridker PM. <i>Circulation</i> 1995;92:2800-2802. Eichinger S. <i>Arch Intern Med</i> 2002;162:2357-2360. Rintelen C. <i>Thromb Haemost.</i> 1996;75:229-232. Baglin T. <i>Lancet</i> 2003;362:523-526. Palareti G. <i>Circulation</i> 2003;108:313-318.
Prothrombin 20210A mutation	1.4*	Lindmarker P. <i>Thromb Haemost.</i> 1999;81:684-689. Baglin T. <i>Lancet</i> 2003;362:523-526. Eichinger S. <i>Thromb Haemost.</i> 1999;81:14-17. De Stefano V. <i>Br J Haematol.</i> 2001;113:630-635. Miles JS. <i>J Am Coll Cardiol.</i> 2001;37:215-218.
Elevated levels of factor VIII:c	6–11	Kraaijenhagen RA. <i>Thromb Haemost.</i> 2000;83:5-9. Kyrle PA. <i>N Eng J Med.</i> 2000;343:457-462. Legnani C. <i>Br J Haematol.</i> 2004;124:504-510.
Mild hyperhomocysteinemia	2.6–3.1	Den Heijer M. <i>Lancet.</i> 1995;345:882-885. Eichinger S. <i>Thromb Haemost.</i> 1998;80:566-569.
Antiphospholipid antibodies	2–9	Prandoni P. <i>Thromb Haemost.</i> 1996;75:859. Rance A. <i>Thromb Haemost.</i> 1997;77:221-222. Schulman S. <i>Am J Med.</i> 1998;104:332-338.

* pooled using the using the Mantel-Haenszel method

study populations. Furthermore, direct comparisons of the risks for recurrent VTE between various thrombophilic defects are not available and the differences between relative risks for individual thrombophilic defects should thus be interpreted with caution.

Analysis of a prospectively followed cohort of 599 Italian patients showed that the hazard ratio for recurrent VTE in patients with thrombophilia was 1.78 (95% confidence interval [CI], 1.04–3.66).⁶ Of 130 identified patients with thrombophilia, 24 had either a deficiency of antithrombin, protein C, or protein S, were homozygous for the factor V Leiden, or had combinations of various hereditary thrombophilic defects.

Three retrospective studies have assessed the risk of recurrent VTE in patients with deficiencies of antithrombin, protein C or protein S. The estimated relative risk for recurrent VTE in patients with these disorders is 2.5. In a cohort of 570 patients from Cambridge that was prospectively followed for 2 years after cessation of anticoagulation after a first episode of objectively documented VTE, thrombophilia screening was performed in over 75%.⁵ Two of 8 identified patients with antithrombin deficiency, 1 of 5 with protein C deficiency, an individual who also was heterozygous for the factor V Leiden mutation, and 3 (including 1 who also was heterozygous for the factor V Leiden mutation) of 27 with low levels of protein S suffered re-

current VTE during follow-up. Compared with those without thrombophilic defects, the hazard ratios for patients with deficiencies of antithrombin, protein C and protein S were 2.59 (95% CI, 0.8–8.8), 1.84 (95% CI, 0.3–10.8), and 1.00 (95% CI, 0.3–3.0), respectively.

In several prospective studies, carriers of the factor V Leiden mutation have been followed for 1–6 years after a first episode of VTE. Most of these studies demonstrated that heterozygosity for the factor V Leiden mutation is a weak risk factor for recurrent VTE. The calculated pooled odds ratio using data from all of the prospective studies is 1.4 (95% CI, 1.1–1.8) (**Table 2**).

Four studies examined the risk of recurrent VTE in heterozygotes for the prothrombin G20210A mutation. When the results were pooled, the odds ratio for recurrence was 1.4 (95% CI, 0.9–2.0), a value that did not reach statistical significance. In contrast, patients with elevated levels of factor VIII have a 6- to 11-fold higher risk of recurrent VTE, and the risk is 3-fold higher in those with hyperhomocysteinemia.^{7,8} Patients who are homozygous for the factor V Leiden or prothrombin G20210A mutation and those with combined thrombophilic defects have a much higher risk. Likewise, those with antiphospholipid antibodies or the lupus anticoagulant have a 2- to 9-fold higher risk of recurrent VTE.

In conclusion, the risk of recurrence after a first

episode of VTE is slightly increased in patients with the factor V Leiden or the prothrombin gene mutation, moderately increased in those with mild hyperhomocysteinemia, and highest in those with factor VIII levels persistently above the 90th percentile, the lupus anticoagulant, or antiphospholipid antibodies.

Other Predictors for Recurrent VTE

Current investigations are focusing on patient characteristics that predict an increased risk of recurrence. In addition to a history of idiopathic VTE, other features that may be of prognostic value include residual thrombosis on compression ultrasound and persistently elevated levels of D-dimer.

Idiopathic VTE

At least half of the patients with VTE have no identifiable risk factors. Cohort studies and data from randomized controlled trials have shown that patients with idiopathic VTE and those with an ongoing risk factor, such as cancer, have a higher risk of recurrence than those whose VTE occurred in association with a transient risk factor. For example, surgery-related VTE confers a lower risk with an odds ratio (OR) of 0.3–0.5 for recurrent VTE.⁹

Residual DVT

There is mounting evidence that residual thrombosis on compression ultrasound may be a risk factor for recurrent DVT. Residual thrombosis may impair venous outflow, thereby enhancing stasis and promoting recurrence. This cannot be the sole mechanism responsible for recurrent VTE, however, because at least half of the recurrences occur in the contralateral leg or manifest as PE. Instead, it is more likely that residual thrombosis reflects a generalized hypercoagulable state.

Prospective studies have shown that approximately 60% of patients with symptomatic DVT have normal compression ultrasound findings after 1 year of follow-up.^{10,11} In a cohort study of 179 patients with a history of symptomatic DVT, the likelihood for recurrence in the same venous segment or at a different site was more than 5-fold higher in patients whose compression ultrasound failed to normalize at 3 and 6 months.¹⁰ For patients without cancer, the OR for recurrent DVT in the absence of ultrasound normalization at 3 and 6 months was 11.6 (95% CI, 1.5–91.8) and 11.3 (95% CI, 2.4–3.6), respectively. Another prospective study, which followed 313 patients for 6 years after an initial episode of DVT, defined residual thrombosis as a non-compressible venous segment of at least 3 mm on a single test or at least 2 mm on 2 consecutive tests.¹¹ The normalization rate after 3 years was 73.8%;

this rate did not differ significantly between patients with or without thrombophilic defects, or between patients with idiopathic or secondary DVT. The hazard ratio for recurrent VTE was 2.9 (95% CI, 1.6–5.2) in patients with residual thrombosis, and one-third of the patients had their second DVT in the contralateral leg or suffered a PE. Management studies are needed to determine whether residual thrombosis on ultrasound can be used to identify patients who require longer-term anticoagulation.

Elevated D-dimer levels

In a cohort of 599 patients, elevated D-dimer levels were found in 37% one month after stopping anticoagulant therapy; patients whose first episode of VTE was unprovoked had a cumulative probability of recurrence of 18% 2 years after stopping anticoagulant therapy. In contrast, the risk of recurrence was 7% in those with normal D-dimer levels; hazard ratio 2.43, (95% CI, 1.18–4.61).⁶ This difference was even more striking in patients with thrombophilia and persisted after adjustment for potential confounders (relative risk 5.9, 95% CI, 1.5–23.7). A similar study in a cohort of patients from Austria revealed a similar result, and the authors demonstrated a dose-dependent relationship between D-dimer levels measured 3 weeks after cessation of anticoagulation and the risk of recurrence.¹² In a post-hoc analysis that divided D-dimer levels into quartiles, the cumulative probability of recurrence after cessation of oral anticoagulant therapy was approximately 12% at 2 years in those whose D-dimer levels were in the highest quartile compared with 3.7% in those with D-dimer levels in the lowest quartile. Ongoing studies are investigating whether elevated D-dimer levels can be used to identify patients who benefit from extended anticoagulation therapy.

Other Clinical Manifestations of Thrombophilia

Inherited thrombophilic defects do not appear to be important risk factors for arterial thrombosis.^{13,14} Obstetric complications, particularly recurrent spontaneous abortions or intra-uterine fetal death, may be a key feature of the antiphospholipid antibody syndrome. For women with any of the inherited thrombophilic defects, the risk of pregnancy loss, intrauterine growth retardation, severe pre-eclampsia and the HELLP syndrome is increased about 2-fold.^{15,16} A plausible mechanism is microvascular thrombosis in the placental vessels with subsequent placental insufficiency.

Implications for Clinical Practice

Routine screening of patients with VTE for an underlying thrombophilic defect cannot be justified on the

basis of major therapeutic consequences. However, a nihilistic approach is unwise. Even a modest increase in the risk of recurrent VTE may be clinically important given the high probability of recurrence in patients with a first episode of idiopathic VTE. If the cumulative risk increases from 30% to 42% over a time span of 8 years (baseline risk multiplied by 1.4, as is probably the case for the factor V Leiden and the prothrombin gene mutation), 12% of recurrences would be prevented if patients with these defects were treated for a longer period than the currently recommended 6–12 months. This issue has been formally addressed in decision analyses, but these can be criticized for their dependence on the accuracy of baseline risk estimates.^{17,18} It is possible that residual thrombosis on ultrasound and/or elevated D-dimer levels after cessation of anticoagulant therapy may be important predictors of recurrent VTE. Ongoing management studies will address these possibilities. In addition, the bleeding risk and patients' preference also need to be taken into account when making decisions about the duration of anticoagulant therapy. With the prospect for new oral anticoagulants in the near future, long-term anticoagulation may be simplified and the bleeding risk may be lower.

A specific subcategory of patients may benefit from thrombophilia screening. Women with a history of VTE who wish to become pregnant or are pregnant may receive different treatment if they are found to have a thrombophilic defect. In a prospective study of 125 women with a history of VTE in whom anticoagulant prophylaxis was withheld during pregnancy, the risk of antenatal recurrence was 0.0% (95% CI, 0.0–8.0%) in patients with a history of secondary VTE and no thrombophilic defects, 7.7% (95% CI, 0.01–25.1%) in those with a history of idiopathic VTE, and 13% (95% CI, 1.7–40.5%) and 20% (95% CI, 2.5–55.6%) in women with a thrombophilic defect and a history of

either secondary or idiopathic VTE, respectively.¹⁹

At this time, there are no data supporting the use of aspirin and/or low-molecular-weight heparin to improve pregnancy outcome in women with thrombophilia and a history of adverse obstetrical outcomes. Until such data are available, these treatments should not be applied.^{20,21}

II. FACTOR Xa INHIBITORS

*William Geerts, MD**

The serine protease, factor Xa (FXa), is an attractive target for anticoagulants because of its pivotal “upstream” location in the coagulation cascade. FXa is situated at the start of the common pathway, where the intrinsic and extrinsic pathways converge, and at the primary site of amplification of the cascade. FXa is the rate-limiting component in the generation of thrombin. As a result, inhibition of one molecule of FXa prevents approximately 138 molecules of thrombin from being generated. Finally, the only function of FXa is to promote coagulation, without any of the other functions that are possessed by thrombin.^{1,2} For these reasons, the past decade has seen a virtual explosion of research into inhibitors of FXa as potential new antithrombotic agents.²⁻⁵

Classification of FXa Inhibitors

The action of *indirect FXa inhibitors* is mediated through their binding to and activation of antithrombin which then inhibits free FXa. *Direct FXa inhibitors* act by binding to and inhibiting FXa without the need for antithrombin. **Table 3** lists the FXa inhibitors that have undergone the most extensive clinical evaluation to date.

Indirect FXa Inhibitors

Fondaparinux and idraparinux are synthetic analogs of the antithrombin-binding pentasaccharide sequence found in heparin and low molecular weight heparin (LMWH). These analogues are chemically modified to increase their affinity for antithrombin compared with heparin or LMWH. The chain length of these molecules is too short to bridge antithrombin to thrombin, a requirement for catalysis of inhibition of thrombin by antithrombin. Therefore, pentasaccharide-activated antithrombin is a specific inhibitor of FXa only. The properties of the indirect FXa inhibitors are very different from those of LMWH (**Table 4**).

Table 3. Specific factor Xa (FXa) inhibitors.*

Indirect (Antithrombin-Dependent) FXa Inhibitors

fondaparinux (Arixtra®) [GlaxoSmithKline] - parenteral
 idraparinux [Sanofi-Synthelabo] - parenteral

Direct (Antithrombin-Independent) FXa Inhibitors

BAY 59-7939 [Bayer] – oral
 DPC-423 [Bristol-Myers Squibb] – oral
 DX-9065a [Daiichi] – parenteral/oral
 LY517717 [Lilly] – oral
 Razaxaban (DPC906) [Bristol-Myers Squibb] – oral

* Partial list of factor Xa inhibitors available or in development

* Sunnybrook and Women's College Health Sciences Centre, 2075 Bayview Ave., Room D674, Toronto ONT M4N 3M5, Canada

Table 4. Properties of low-molecular-weight heparin (LMWH), fondaparinux and idraparinux.

Property	LMWH	Fondaparinux	Idraparinux
Source	Porcine mucosal heparin	Chemical synthesis	Chemical synthesis
Molecular weight (daltons)	Mean 5000	1728	1727
SC bioavailability	~ 90%	100%	100%
Target(s)	Multiple: FXa > FIIa > FIXa, FXIa, FXIIa	FXa only	FXa only
Binding to proteins other than target	Yes	No	No
Anti-Xa:anti-IIa	2–5:1	Anti-Xa only	Anti-Xa only
TFPI release from endothelium	Yes	No	No
Clearance	Renal primarily	Renal	Renal
Half life (SC route)	3–4 hrs	17–21 hrs	80–130 hours
Effects of protamine	Partial neutralization	No effect	No effect
Potential for HIT	Low	Very low	Very low

Abbreviations: FXa, factor Xa; FIIa, factor IIa; FIXa, factor IXa; FXIa, factor XIa; FXIIa, factor XIIa; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; HIT, heparin-induced thrombocytopenia

Fondaparinux (Arixtra®)

Fondaparinux is a chemically modified (hypersulfated) pentasaccharide that binds avidly to antithrombin. This interaction induces a conformational change in antithrombin that increases its activity to selectively neutralize FXa (about 300-fold), thereby reducing thrombin generation.^{6,7} Once fondaparinux has activated antithrombin and the activated antithrombin binds to FXa, fondaparinux is released and is then available to bind to other antithrombin molecules in succession.⁸ Fondaparinux has almost 100% bioavailability after subcutaneous injection, has rapid onset of action, does not bind to other plasma proteins, platelets, or endothelium, and is eliminated unchanged by the kidneys. The high affinity of fondaparinux for antithrombin results in a long half-life (approximately 18 hours), which enables once-daily dosing. Even at therapeutic doses, fondaparinux has minimal or no effect on the activated partial thromboplastin time (aPTT), international normalized ratio (INR), or bleeding time.

Some of the potential advantages of fondaparinux over LMWH include its synthetic derivation, uniform composition, longer half-life, and absence of binding to plasma proteins (other than antithrombin). Fondaparinux does not bind to platelet factor-4 (PF4) or platelets and is, therefore, likely to be a safe and effective anticoagulant in patients with heparin-induced thrombocytopenia (HIT).⁹⁻¹² Neither fondaparinux nor LMWH requires laboratory monitoring, while both agents are administered subcutaneously and both accumulate in the presence of renal insufficiency. The use of fondaparinux is contraindicated in patients with a creatinine clearance less than 30 mL/min and the drug should be used with caution in patients with moderate renal

impairment (creatinine clearance 30–50 mL/min). Bleeding rates with fondaparinux were slightly increased in some prophylaxis trials, perhaps related to earlier initiation of dosing than LMWH comparators. Although approximately 1/3 of the patients in the four large orthopedic prophylaxis trials underwent neuraxial anesthesia and then received postoperative fondaparinux without a single epidural hematoma, the safety of fondaparinux in the setting of indwelling epidural catheters for postoperative analgesia has not been established. The anticoagulant and bleeding effects of fondaparinux are not reversed by protamine. However, high doses of recombinant FVIIa may be effective in this situation.¹³

An extensive research program has evaluated fondaparinux as thromboprophylaxis in hospitalized patients, as therapy for VTE, and as an antithrombotic agent in cardiac disease.

Thromboprophylaxis after orthopedic surgery: More than 7,000 patients undergoing elective hip or knee arthroplasty or hip fracture surgery were randomized in four large trials to receive 2.5 mg of fondaparinux or enoxaparin (EPHESUS, PENTATHLON 2000, PENTAMAKS, PENTHIFRA). Fondaparinux, started an average of 6 hours after the end of surgery, was significantly more efficacious than enoxaparin commenced 12–24 hours postoperatively.¹⁴ Major bleeding (but not bleeding that was life-threatening or that required re-operation) was slightly more common in the patients who received fondaparinux. The difference in bleeding was seen only in the patients who started fondaparinux less than 6 hours after surgery; when fondaparinux was started 6 hours or more after surgery, bleeding was comparable to that seen with

enoxaparin.¹⁵ Therefore, the first dose of fondaparinux should be given at least 6 hours postoperatively. A recently completed trial (FLEXTRA) has compared the initiation of fondaparinux either 6 hours after hip and knee arthroplasty or the following morning. Results are pending.

Extended thromboprophylaxis after hip fracture: The PENTHIFRA-Plus trial randomized 656 hip fracture surgery patients to 1 week or 1 month of fondaparinux 2.5 mg daily.¹⁶ Extended prophylaxis dramatically reduced the rates of both venographic DVT at 1 month (from 35% to 1%) and symptomatic VTE (from 3% to 0.3%). Although major bleeding was increased with extended prophylaxis (from 0.6% to 2.4%), clinically important bleeding was not increased.

Thromboprophylaxis after general surgery: The PEGASUS Trial compared prophylaxis with dalteparin 5000 U once daily (started preoperatively) to fondaparinux 2.5 mg once daily (started postoperatively) in almost 3000 high-risk patients undergoing abdominal surgery.¹⁷ The two interventions had comparable efficacy and safety, except in the subgroup of patients with cancer, in which fondaparinux was more efficacious. APOLLO is an ongoing trial that is evaluating the addition of fondaparinux to sequential compression devices in general surgery patients.

Thromboprophylaxis in medical patients: The ARTEMIS Trial recently demonstrated that fondaparinux 2.5 mg SC significantly reduced the rate of asymptomatic DVT compared to placebo in 849 elderly medical patients, without causing major bleeding.¹⁸ The secondary outcome, symptomatic VTE, was seen in 1.2% of placebo patients and in none of those who received fondaparinux ($P = 0.03$).

Acute treatment of DVT and PE: Among patients who presented with acute VTE, the MATISSE-DVT and MATISSE-PE trials have shown that fondaparinux once daily was as at least as efficacious and safe as usual therapy with intravenous heparin or LMWH.^{19,20} In these studies, the fondaparinux dose was 7.5 mg for patients 50–100 kg, 5 mg for those less than 50 kg, and 10 mg for those heavier than 100 kg.

Anticoagulation in acute coronary syndrome: Fondaparinux appears to be at least as effective as IV heparin in acute myocardial infarction (PENTALYSE) or as LMWH in unstable angina (PENTUA).^{21,22} Further Phase III studies are ongoing, including the Michelangelo OASIS-5 and OASIS-6 mega-trials in acute coronary syndrome and myocardial infarction, respectively.

Percutaneous coronary intervention: The ASPIRE Pilot Study has compared intravenous fondaparinux with heparin in patients undergoing urgent or elective per-

cutaneous coronary interventions with concomitant aspirin plus clopidogrel.

The extensive research program with fondaparinux demonstrates that it is a highly efficacious antithrombotic agent for prevention and treatment of both venous and arterial thromboembolic disorders. Fondaparinux is currently approved as thromboprophylaxis following hip and knee arthroplasty and hip fracture surgery, and as initial treatment for VTE. To date, fondaparinux has been studied in highly selected patients at relatively low bleeding risk. In these patients, bleeding was uncommon, although the risk appears to be increased by renal dysfunction (creatinine clearance < 30 mL/min), weight < 50 kg and initiation within 6 hours of a surgical procedure.¹⁵ More data on the effectiveness and safety of fondaparinux in a more diverse spectrum of patients are necessary.²³

Idraparinix

Idraparinix is a chemically modified analog of fondaparinux that binds to antithrombin with such high affinity that the half-life of the drug approximates the half-life of antithrombin (80–130 hours).⁶ This allows once-weekly subcutaneous dosing. The Phase II PERSIST study compared four doses of idraparinix, given once a week, to warfarin in the treatment of acute DVT.²⁴ The lowest idraparinix dose, 2.5 mg, was as effective as higher doses and was associated with the least bleeding. Idraparinix is now being studied in large Phase III studies of VTE treatment (the Van Gogh DVT and PE trials), as well as in the long-term prevention of stroke among patients with atrial fibrillation (AMADEUS). Idraparinix may be useful in patients for whom therapeutic anticoagulation with vitamin K antagonists is problematic. However, the long half-life and lack of an antidote may be of concern especially if bleeding occurs or if a patient requires an invasive procedure. At least in healthy volunteers, the anticoagulant effect of idraparinix is reversed by recombinant FVIIa.²⁵

Direct FXa Inhibitors

A number of synthetic direct FXa inhibitors are undergoing clinical evaluation. These agents inhibit both free FXa and FXa bound to activated platelets that are trapped within a thrombus as part of the prothrombinase complex. This property may confer a therapeutic advantage to the direct FXa inhibitors compared with heparin, LMWH, and the indirect FXa inhibitors. These drugs appear to inhibit thrombus formation while allowing sufficient thrombin to be generated to activate platelets (and therefore to maintain the ability to form a hemostatic plug). As a result, these agents may also have a lower bleeding potential than conventional anti-

coagulants and direct thrombin inhibitors.²⁶

Intravenous administration of the direct FXa inhibitor, DX-9065a, is being assessed in patients with acute coronary syndrome and those undergoing percutaneous coronary interventions, while the oral preparation of this anticoagulant is being evaluated after major knee surgery.²⁷

Razaxaban (DPC906) is an oral direct FXa inhibitor that has recently been tested in a Phase II trial of thromboprophylaxis following knee arthroplasty.²⁸

Another oral FXa inhibitor, LY517717, is undergoing Phase II evaluation as thromboprophylaxis following elective hip and knee arthroplasty.

BAY 59-7939 is also an oral FXa inhibitor that is currently being assessed in Phase II trials of the treatment of acute DVT (ODIXa-DVT) and prevention of DVT after knee arthroplasty.

Monitoring of Anticoagulant Activity of FXa Inhibitors

Because of their predictable pharmacokinetics, monitoring of the various FXa inhibitors appears to be unnecessary for most patients. Furthermore, the assay techniques and target ranges for the anti-Xa activity of these agents have not been rigorously standardized. In fact, there is very little information relating anti-Xa levels to clinical outcomes (thrombosis prevention or bleeding) for any anticoagulant. If laboratory monitoring of fondaparinux is performed, the anti-Xa assay must be calibrated with fondaparinux.²⁹

Conclusions and Future Directions

The development and evaluation of FXa inhibitors may identify new parenteral and oral antithrombotic agents that demonstrate improvements in effectiveness, safety, convenience and cost-effectiveness compared with current anticoagulants. It is not yet clear whether fondaparinux has a clinically important advantage over LMWH, although it may be safer from the perspective of HIT risk. As a once-weekly injection, idraparinix may be more convenient than LMWH in treatment and prophylaxis, and it may replace oral vitamin K antagonists in selected patients. The parenteral direct FXa inhibitors may compete with bivalirudin in coronary interventions. Finally, the oral direct FXa inhibitors might be used in situations where oral vitamin K antagonists are currently used. They will also need to be compared to oral direct thrombin inhibitors. The ultimate role of each of these new agents requires further clinical trials.

III. DIRECT THROMBIN INHIBITORS

*John A. Heit, MD**

Thrombin is a trypsin-like serine protease. Among its many biologic roles, alpha-thrombin functions as a procoagulant by hydrolyzing (“activating”) its substrates, including factor (F) I (fibrinogen), FV, FVIII, FXI, FXIII, and the platelet protease activated receptors (PAR), PAR-1 and PAR-4. Thrombin’s exquisite substrate specificity derives from surface binding sites (e.g., exosite 1) that are specific for its substrates.

Glycosaminoglycans, such as unfractionated heparin and low-molecular-weight heparin, indirectly inhibit thrombin by catalyzing the serine protease inhibitor, antithrombin, which covalently binds to the active site of thrombin. In contrast, direct thrombin inhibitors (DTIs) inhibit thrombin by *directly* binding to exosite 1 and/or the active site of thrombin. DTIs have potential advantages over heparin. Unlike heparin, they produce a predictable anticoagulant response because they exhibit minimal binding to plasma protein. DTIs also do not bind platelet factor 4 and, thus, do not crossreact with autoantibodies that cause heparin-induced thrombocytopenia (HIT). DTIs inhibit fibrin-bound thrombin as well as fluid-phase thrombin. DTIs do not act through inhibition of vitamin K. Thus, DTIs do not suffer the same problems with food interactions as do oral vitamin K inhibitors (e.g., warfarin), and the potential for drug-drug interactions appears to be low. Finally, the therapeutic window of some DTIs (e.g., melagatran/ximelagatran) is sufficiently broad that routine laboratory monitoring and dose adjustment is unnecessary.

DTIs also have potential disadvantages. Currently, there is no antidote for rapid reversal of their anticoagulant effect. In animal models, activated prothrombin complex concentrates (e.g., Feiba[®], Autoplex[®]) appear to be effective in reducing the bleeding time and blood loss associated with high plasma DTI concentrations, as does activated factor VII (FVIIa, Novoseven[®]). In addition, available DTIs exhibit substantive differences in their pharmacology that may translate into important differences in efficacy, safety and convenience, and they are considerably more expensive than heparin or warfarin.

* Mayo Clinic, 200 First Street, SW, Rochester MN 55905

Funded, in part, by grants from the National Institutes of Health (HL66216), the Centers for Disease Control and Prevention (TS306), U.S. Public Health Service; and by Mayo Foundation.

This section contrasts the pharmacology of recombinant hirudin (desirudin, lepirudin), bivalirudin (hirulog), argatroban, melagatran/ximelagatran, and dabigatran/BIBR-1048 (**Table 5**), and the results of clinical trials testing these DTIs as prophylaxis against and therapy for venous and arterial thrombosis.

Pharmacology of Direct Thrombin Inhibitors

Recombinant hirudin

Originally isolated from the medicinal leech, hirudin is a 65-amino-acid polypeptide that binds thrombin at both the active site and exosite 1. Hirudin forms a 1:1 stoichiometric complex with thrombin of such high affinity that thrombin inhibition is essentially irreversible. Recombinant hirudins (e.g., desirudin, lepirudin) have a leucine for isoleucine substitution at the N-terminal end of the molecule. Desirudin differs from lepirudin by having a valine-1, valine-2 substitution for the wild-type leucine-1, threonine-2. Both desirudin and lepirudin lack a sulfate group on tyrosine-63. Lepirudin (Refludan[®]) is approved in the US for anticoagulation in patients with HIT and associated thrombosis (HITT).

Hirudin must be administered parenterally. The plasma half-life ($t_{1/2}$) ranges from 1 hour when administered intravenously to 2 hours when administered subcutaneously, and the drug is eliminated via the kidneys. Hirudin has a narrow therapeutic window. Consequently, the anticoagulant effect must be monitored and the dose adjusted to maintain the activated partial thromboplastin time (aPTT) within a therapeutic range (aPTT ratio of 1.5–2.0 4 hours after initiation or a dose change). The correlation between plasma hirudin levels and the aPTT is not linear. Consequently, at higher hirudin doses, monitoring with the ecarin clotting time (ECT) is preferable. Dose adjustment is required for patients with

impaired renal function. Rarely, patients treated with hirudin may develop non-neutralizing anti-hirudin antibodies that prolong the hirudin anticoagulant effect because of delayed hirudin-antibody complex clearance.

Bivalirudin

Bivalirudin (hirulog), a synthetic 20-amino-acid polypeptide hirudin analog, consists of an NH₂-terminal D-Phe-Pro-Arg-Pro domain that interacts with the thrombin active site, a linker region of 4 glycine residues, and a dodecapeptide analog of the hirudin carboxy-terminus that binds exosite 1 on thrombin. Once bound, thrombin cleaves the Pro-Arg bond within the NH₂-terminus of bivalirudin. Thus, unlike hirudin, bivalirudin is a reversible inhibitor. Bivalirudin is currently marketed in the US as an alternative to heparin in patients undergoing percutaneous coronary interventions (PCI). Bivalirudin also must be administered parenterally and has a plasma half-life of 25 minutes after intravenous injection. Elimination is via degradation by endogenous peptidases. Bivalirudin typically is administered as a weight-adjusted (1 mg/kg) bolus dose given immediately prior to PCI, followed by a 4-hour infusion (0.2 mg/kg/h). The anticoagulant effect is monitored using the activated clotting time (ACT), and additional bolus dosing is given if the ACT is less than 350 seconds. Compared with hirudin, bivalirudin appears to cause less bleeding, possibly due to the reversible thrombin inhibition and shorter plasma half-life.

Argatroban

Argatroban, a synthetic L-arginine derivative, is a competitive direct thrombin inhibitor. Argatroban is currently marketed in the US for prophylaxis or therapy of patients with HIT and for anticoagulation in HIT patients undergoing PCI. Argatroban is administered

Table 5. Pharmacology of direct thrombin inhibitors (DTI).

DTI	Valence	M_r (Da) [†]	K_i (mol/L) [‡]	$t_{1/2}$ [§]	Excretion
Lepirudin (Refludan [®])	Bivalent: active site and exosite 1	698	0.2×10^{-12}	60–80 mins (IV)	renal
Desirudin (Revasc [®])				120 mins (SC)	
Bivalirudin (Hirulog [®] , Angiomax [®])		218	2.3×10^{-9}	25 mins	non renal, non hepatic
Argatroban (Novastan [®])	Univalent: active site, noncovalent	527	3.9×10^{-8}	45 mins	biliary secretion
Melagatran		430	0.2×10^{-8}	2–3 hrs	renal
Ximelagatran (Exanta [®])		474	37×10^{-8}	3–5 hrs	
Dabigatran/BIBR-1048		–	4.5×10^{-8}	12 hrs	–

[†] Molecular weight (daltons)

[‡] Inhibition constant.

[§] Plasma half-life

intravenously and has a plasma half-life of 45 minutes. The anticoagulant activity of argatroban is monitored using the aPTT and the dose is adjusted to achieve an aPTT ratio of 1.5–3.0. Argatroban is metabolized in the liver and must be used with caution among patients with hepatic dysfunction; it is the drug of choice for patients with severe renal impairment. Argatroban prolongs the INR more than other DTIs, a feature that can complicate overlap therapy with vitamin K antagonists.

Melagatran/ximelagatran

Melagatran is a dipeptide mimetic of the region of fibrinopeptide A that interacts with thrombin's active site. Melagatran has poor oral bioavailability and must be given subcutaneously. Ximelagatran, an uncharged, lipophilic prodrug, exhibits 20% bioavailability after oral administration. Once absorbed, ximelagatran is rapidly transformed to melagatran, which has a half-life of about 4–5 hours. About 80% of melagatran is excreted via the kidneys.

Ximelagatran produces a predictable anticoagulant response, and no food or drug interactions have been documented. Consequently, routine anticoagulation monitoring is unnecessary. About 6% of patients treated with ximelagatran develop an increase in alanine aminotransferase (ALT) that is usually asymptomatic, unaccompanied by a concomitant increase in bilirubin, and reversible whether or not ximelagatran is continued.

Dabigatran etexilate

Dabigatran etexilate is an oral prodrug that is converted to dabigatran, a potent benzamidine-based thrombin inhibitor. The plasma half-life of dabigatran is 14–17 hours, and elimination is primarily via renal excretion. Dabigatran is currently undergoing Phase III evaluation for thromboprophylaxis after total knee replacement surgery (TKR) and Phase II evaluation for treatment of VTE and for stroke prevention in atrial fibrillation.

Clinical Trials

VTE prophylaxis (primary prevention)

Desirudin, bivalirudin, melagatran/ximelagatran, and ximelagatran alone have been evaluated as VTE prophylaxis after elective total hip replacement (THR) or TKR. All studies used symptomatic VTE and DVT detected by routine venography as the endpoint. In addition, recombinant hirudin, bivalirudin, melagatran, ximelagatran, and LMWH were administered as fixed doses without laboratory monitoring. In a Phase III trial, 1587 THR patients were randomized to desirudin or enoxaparin sodium (40 mg SC QD).¹ The overall VTE

and proximal DVT rates after surgery were significantly lower with desirudin than with enoxaparin. There was no significant difference in bleeding between the two groups. Bivalirudin was evaluated in a small Phase II trial involving 177 patients undergoing THR or TKR.² The highest bivalirudin dose regimen tested (1.0 mg/kg SC Q 8 hours) was associated with a 17% overall (2% proximal) postoperative DVT rate. Bleeding rates were low with all doses tested.

Ximelagatran

Ximelagatran has been compared with either LMWH or warfarin prophylaxis in a series of trials (**Table 6**). In an initial Phase II study, 600 TKR patients were randomly assigned to ximelagatran in blinded twice-daily doses of 8, 12, 18, or 24 mg, or open-label enoxaparin (30 mg SC twice daily).³ Treatments were started 12–24 hours after surgery and continued for 6–12 days. The postoperative rates of overall VTE and proximal DVT or pulmonary embolism (PE) with ximelagatran 24 mg and enoxaparin did not differ significantly. In a subsequent Phase III trial, 1838 patients undergoing elective THR were randomly assigned to prophylaxis with oral ximelagatran (24 mg BID) or enoxaparin (30 mg SC BID) started the morning after surgery.⁴ Both the overall VTE and proximal DVT or PE rates were higher with ximelagatran. Rates of major bleeding were low.

Two clinical trials compared ximelagatran with adjusted-dose warfarin (**Table 6**). In a Phase III trial, 680 patients undergoing TKR were randomly assigned to ximelagatran (24 mg BID, started on the morning after surgery) or warfarin (INR 2.5, range 1.8–3.0, started on the evening after surgery).⁵ Overall VTE and proximal DVT rates were not significantly different between the ximelagatran and warfarin groups (19.2% vs 25.7%, respectively, $P = 0.07$, and 3.3% vs 5.0%, respectively, $P > 0.2$). Rates of major and minor bleeding were low and not significantly different. In the second trial (EXULT phase 1), 2301 patients undergoing TKR were randomly assigned to ximelagatran (24 mg or 36 mg BID, started the morning after surgery) or warfarin (target INR 2.5; range 1.8–3.0; started the evening of surgery).⁶ The rates of overall VTE and death were significantly lower in the ximelagatran 36 mg group than in the warfarin group ($P = 0.003$). Rates for proximal DVT and major and minor bleeding were not significantly different. Based on these data, the second phase of the EXULT trial randomized an additional 2300 patients to ximelagatran (36 mg BID) or warfarin. The results are not yet available.

Three large studies compared the combination of melagatran and ximelagatran with LMWH as prophylaxis

Table 6. Ximelagatran versus low-molecular-weight heparin (LMWH) or warfarin in the prevention of venous thromboembolism (VTE).

Surgery	Variable	Ximelagatran BID				LMWH or Warfarin
TKR ³ (N = 600)	Dose	8 mg	12 mg	18 mg	24 mg	Enoxaparin 30 mg BID
	Overall VTE	27.0%	19.8%	28.7%	15.8%	22.7%
	Proximal DVT	6.6%	2.0%	5.8%	3.2%	3.1%
	Major Bleeding	0	0	2.4%	0	0.8%
TKR ⁴ (N = 1838)	Dose	24 mg				Enoxaparin 30 mg BID
	Overall VTE	7.9%				4.6%
	Proximal DVT	3.6%				1.2%
	Major Bleeding	0.8%				0.9%
TKR ⁵ (N = 680)	Dose	24 mg				Warfarin INR 2.5, range 1.8–3.0
	Overall VTE	19.2%				25.7%
	Proximal DVT	3.3%				5.2%
	Major Bleeding	1.7%				0.9%
TKR ⁶ EXULT (N = 2301)	Dose	24 mg		36 mg		Warfarin INR 2.5, range 1.8–3.0
	Overall VTE	24.9%		20.3%		27.6%
	Proximal DVT	2.5%		2.7%		4.1%
	Major Bleeding	4.8%		5.3%		4.5%

Abbreviations: TKR, total knee replacement

laxis for THR or TKR patients. In a Phase II study (METHRO II), 1900 patients were randomly assigned to one of four melagatran/ximelagatran doses (1.0/8 mg, 1.5/12 mg, 2.25/18 mg, or 3.0/24 mg) (Table 7).⁷ The first melagatran dose was injected subcutaneously immediately *before* surgery but after administration of neuraxial (spinal or epidural) anesthesia. A second melagatran injection was given 7–11 hours after surgery, followed by twice daily injections until oral ximelagatran could be started (usually 1–3 days after surgery). A highly significant dose-dependent decrease

in VTE (both overall and proximal DVT) was seen with increasing doses of melagatran/ximelagatran.

In a subsequent Phase III study (METHRO III), 2788 patients undergoing elective THR or TKR were randomized to melagatran/ximelagatran or enoxaparin.⁸ Melagatran (3 mg SC) was given 4–12 hours *after* surgery followed by oral ximelagatran (24 mg BID). Enoxaparin (40 mg SC) was started on the evening before surgery and continued daily thereafter. The overall VTE rate was lower with enoxaparin (absolute difference 3.7% [$P = 0.053$] in favor of enoxaparin). This

Table 7. Melagatran/ximelagatran versus low molecular weight heparin (LWMH) in the prevention of venous thromboembolism (VTE).

Surgery	Variable	Melagatran SC/Ximelagatran PO BID				LMWH
THR or TKR ⁷ (N = 1900) MEHTRO II	Dose	Melagatran/Ximelagatran 1 mg/8 mg 1.5 mg/12 mg 2.25 mg/18 mg 3 mg/24 mg				Dalteparin 5000 IU QD
	Overall VTE	37.8	24.1	23.7	15.1	28.2%
	Proximal DVT	8.5	6.2	3.3	2.1	5.5
	Major bleeding	0.8	1.2	3.5	5.5	2.3
THR or TKR ⁸ (N = 2788) METHRO III	Dose	3 mg Melagatran/Ximelagatran 24 mg				Enoxaparin 40 mg QD
	Overall VTE	31.0%				27.3%
	Proximal DVT	5.7%				6.2%
	Major bleeding	1.4%				1.7%
THR or TKR ⁹ (N = 2764) EXPRESS	Dose	2/3 mg Melagatran/Ximelagatran 24 mg				Enoxaparin 40 mg QD
	Overall VTE	20.3%				26.7%
	Proximal DVT	2.3%				6.3%
	Major bleeding	3.3%				1.2%

Abbreviations: THR, total hip replacement; TKR, total knee replacement

difference was entirely accounted for by an increased rate of calf vein thrombosis in the melagatran/ximelagatran group. The major VTE rates of proximal DVT or PE did not differ significantly (melagatran/ximelagatran, 5.7%, vs enoxaparin, 6.2%), nor did severe bleeding, transfusion requirements, or blood loss.

In a final Phase III study (EXPRESS), 2764 patients undergoing THR or TKR were randomly assigned to melagatran started *before* surgery and postoperative oral ximelagatran, or enoxaparin in the same dose schedule as the METHRO III study.⁹ Melagatran (2 mg SC) was given immediately before surgery and again (3 mg SC) on the evening of surgery, followed by oral ximelagatran (24 mg BID). The overall VTE and proximal DVT rates were significantly lower in the melagatran/ximelagatran group than in the enoxaparin group. While bleeding events (3.3% and 1.2%) and transfusion rates (66.8% and 61.7%) were more common in the melagatran/ximelagatran group, there were no significant differences between the two groups in fatal bleeding, critical organ bleeding, or bleeding requiring reoperation.

In summary, postoperative ximelagatran (36 mg BID) is at least as effective as warfarin for thromboprophylaxis after TKR. Because routine lab monitoring is unnecessary, ximelagatran may be particularly useful for extended out-of-hospital prophylaxis in high-risk orthopedic patients. The combination of subcutaneous melagatran started prior to surgery followed by oral ximelagatran postoperatively is more effective than enoxaparin for thromboprophylaxis after THR or TKR, but may cause more bleeding.

Acute Venous Thromboembolism Therapy (Secondary Prevention)

Only one study has tested recombinant hirudin as treatment for acute VTE. In a Phase II trial, 155 DVT patients were randomly allocated to one of three subcutaneous hirudin doses (0.75, 1.25, or 2.0 mg/kg SC BID) or to adjusted-dose intravenous unfractionated heparin.¹⁰ All patients received baseline and post-treatment venograms and ventilation/perfusion lung scans. After 5 days of treatment, the rates of DVT progression or regression, new ventilation/perfusion mismatches, and adverse events did not differ between the four groups.

A series of clinical trials tested ximelagatran as treatment for acute VTE. Similar to the prophylaxis trials, ximelagatran was administered as a fixed oral dose and without laboratory monitoring or dose adjustment. In the THRIVE treatment trial, 2489 patients with acute DVT (~35% with associated PE) were randomly assigned to either ximelagatran 36 mg BID or enoxaparin 1 mg/kg SC BID (5–20 days) followed by warfarin

(INR 2.0–3.0).¹¹ After 6 months of therapy, the cumulative incidence of recurrent VTE was 2.0% in the enoxaparin/warfarin group and 2.1% in the ximelagatran group. Major bleeding and all-cause mortality were 2.2% and 3.4%, respectively, in the enoxaparin/warfarin group, and 1.3% and 2.3% in the ximelagatran group. The incidence of increased ALT (> 3-fold above the upper normal limit) was 2% in the enoxaparin/warfarin group and 9.6% in the ximelagatran group. In the THRIVE III trial, 1233 VTE patients who had completed 6 months of conventional anticoagulation therapy were randomized to ximelagatran (24 mg BID) or placebo for an additional 18 months.¹² Among the 612 patients receiving ximelagatran, 12 developed recurrent VTE. In contrast, 71 of the 611 patients receiving placebo developed recurrent VTE (hazard ratio 0.16; 95% CI: 0.09–0.30; $P < 0.001$). All-cause mortality, and major and minor bleeding rates did not differ significantly between the two groups. Again, patients given ximelagatran were more likely to develop increased serum ALT than those randomized to placebo (6.4% and 1.2%, respectively).

In summary, oral ximelagatran is as effective as conventional anticoagulation with LMWH followed by warfarin for initial treatment of patients with VTE. Rates of major bleeding are similar with ximelagatran and conventional therapy.

Acute Coronary Syndromes

Recombinant hirudin is as effective as unfractionated heparin for adjunctive therapy among patients with unstable angina or acute myocardial infarction (MI) undergoing thrombolysis.¹³ However, because of its narrow therapeutic window and high bleeding risk, hirudin has not replaced heparin for this indication.

In the Phase II ESTEEM trial, 1883 patients with documented ST-elevation or non-ST-elevation MI within the past 14 days were randomized to ximelagatran (24, 36, 38 or 60 mg BID) or placebo for 6 months as secondary prevention.¹⁴ All patients received aspirin (160 mg daily) and optimal medical management, including statins and ACE inhibitors. All four ximelagatran doses significantly reduced the frequency of the primary endpoint, a composite of all-cause mortality, MI and severe recurrent ischemia, by about 4% compared with placebo. There was no evidence of a dose-response. When placebo was compared with the four combined ximelagatran dose groups, ximelagatran produced a statistically significant 24% reduction in the composite endpoint from 16.3% to 12.7% (hazard ratio 0.76; 95% CI of 0.59–0.98; $P = 0.036$). Major bleeding and mortality rates were low and similar between the groups. However, minor bleeding occurred in 13% and 22% of those

given placebo and ximelagatran, respectively. Based on this information, a Phase III trial using the 24 mg twice-daily dose of ximelagatran is under consideration.

Percutaneous Coronary Intervention

Bivalirudin is approved as an alternative to heparin in patients undergoing PCI¹³; recent meta-analyses suggest that bivalirudin is more effective than heparin for this indication.¹⁵ Compared with unfractionated heparin, bivalirudin also appears to cause less bleeding and to reduce the need for adjunctive treatment with glycoprotein (GP) IIb/IIIa antagonists in patients undergoing coronary stenting.¹⁶ The incidence of death, MI, or repeat revascularization by 6 months, and death by 1 year, also were no different among PCI patients receiving bivalirudin and provisional GPIIb/IIIa blockade versus unfractionated heparin and planned GPIIb/IIIa blockade.¹⁷

Stroke Prevention in Atrial Fibrillation

Two Phase III trials evaluated ximelagatran as stroke prevention among patients with non-valvular atrial fibrillation and at least one additional stroke risk factor. The SPORTIF III trial (N = 3410) was an open-label study conducted in Europe, whereas the SPORTIF V trial (N = 3922) was a double-blind study done in North America. Both trials randomized patients to either warfarin (INR 2.0–3.0) or ximelagatran 36 mg BID. In the SPORTIF III trial, the stroke or systemic arterial embolism rates were 2.3% and 1.6% per year for warfarin and ximelagatran, respectively ($P = 0.10$), over 4941 person-years of treatment.¹⁸ While rates for disabling or fatal stroke, mortality, and major bleeding were similar, combined major and minor bleeding rates were significantly lower in the ximelagatran group (25.8% vs. 29.8% per year). In the SPORTIF V trial, the stroke or systemic arterial embolism rates were 1.6% and 1.2% for ximelagatran and warfarin, respectively ($P = 0.13$). Rates of major bleeding were 2.4% and 3.1% in those given ximelagatran and warfarin, respectively ($P = 0.16$), whereas total bleeding (major and minor bleeding) were 37% and 47%, respectively ($P < 0.001$).

When the results of SPORTIF III and SPORTIF V are combined, ximelagatran was associated with a .03% absolute risk reduction in the rate of stroke and systemic embolism relative to warfarin ($P = 0.94$) and a 0.6% reduction in the rate of major hemorrhage ($P = 0.05$). Using the composite outcome of stroke, systemic embolism, major hemorrhage and death, ximelagatran produced a relative risk reduction of 16%, reducing the rate from 6.2% to 5.2% ($P = 0.038$). In summary, ximelagatran is at least as effective as warfarin in preventing stroke and systemic embolic events without an increased risk of major bleeding.

REFERENCE

I. Thrombophilic Defects

1. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med.* 1992;232:155-160.
2. Sanson BJ, Simioni P, Prins MH, on behalf of the TACT-study group. The incidence of venous thromboembolism in asymptomatic carriers of a marker of thrombophilia. *Blood.* 1999;94:3702-3706.
3. Middeldorp S, Meinardi JR, Koopman MMW, et al. A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. *Ann Intern Med.* 2001;135:322-327.
4. Vink R, Kraaijenhagen RA, Levi M, Buller HR. Individualised duration of oral anticoagulant therapy for deep vein thrombosis based on a decision model. *J Thromb Haemost.* 2003;1:2523-2530.
5. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet.* 2003;362:523-526.
6. Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation.* 2003;108:313-318.
7. Eichinger S, Stumpflen A, Hirschl M, et al. Hyperhomocysteinemia is a risk factor of recurrent venous thromboembolism. *Thromb Haemost.* 1998;80:566-569.
8. den Heijer M, Blom HJ, Gerrits WB, et al. Is hyperhomocysteinemia a risk factor for recurrent venous thrombosis? *Lancet.* 1995;345:882-885.
9. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med.* 2000;160:769-774.
10. Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. *Haematologica.* 2002;87:515-522.
11. Prandoni P, Lensing AW, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med.* 2002;137:955-960.
12. Eichinger S, Minar E, Bialonczyk C, et al. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA.* 2003;290:1071-1074.
13. Boekholdt SM, Bijsterveld NR, Moons AH, Levi M, Buller HR, Peters RJ. Genetic variation in coagulation and fibrinolytic proteins and their relation with acute myocardial infarction: a systematic review. *Circulation.* 2001;104:3063-3068.
14. Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group. No evidence of association between prothrombotic gene polymorphisms and the development of acute myocardial infarction at a young age. *Circulation.* 2003;107:1117-1122.
15. Morrison ER, Miedzybrodzka ZH, Campbell DM, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. *Thromb Haemost.* 2002;87:779-785.
16. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders

- and fetal loss: a meta-analysis. *Lancet*. 2003;361:901-908.
17. Sarasin FP, Bounameaux H. Decision analysis model of prolonged oral anticoagulant treatment in factor V Leiden carriers with first episode of deep vein thrombosis. *Br Med J*. 1998;316:95-99.
 18. Marchetti M, Pistorio A, Barosi G. Extended anticoagulation for prevention of recurrent venous thromboembolism in carriers of factor V Leiden: cost-effectiveness analysis. *Thromb Haemost*. 2000;84:752-757.
 19. Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med*. 2000;343:1439-1444.
 20. DiNisio M, Peters LW, Middeldorp S. Anticoagulants for the treatment of recurrent pregnancy loss in women without antiphospholipid syndrome (Protocol for a Cochrane Review). *The Cochrane Library*. 2004.
 21. Middeldorp S. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications - No. *J Thromb Haemost*. 2003;1:2073-2074.

II. Factor Xa Inhibitors

1. Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. *Arterioscler Thromb Vasc Biol*. 2003;23:17-25.
2. Samama MM, Gerotziapas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb Res*. 2003;109:1-11.
3. Keam SJ, Goa KL. Fondaparinux sodium. *Drugs*. 2002;62:1673-1685.
4. Hoppensteadt D, Walenga JM, Fareed J, Bick RL. Heparin, low-molecular-weight heparins, and heparin pentasaccharide: basic and clinical differentiation. *Hematol Oncol Clin N Am*. 2003;17:313-341.
5. Weitz JI, Hirsh J, Samama MM. New anticoagulant drugs: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl):265S-286S.
6. Herbert JM, Hérault JP, Bernat A, et al. Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting synthetic pentasaccharide. *Blood*. 1998;91:4197-4205.
7. Petitou M, Duchaussoy P, Herbert JM, et al. The synthetic pentasaccharide fondaparinux: first in the class of antithrombotic agents that selectively inhibit coagulation factor Xa. *Semin Thromb Hemost*. 2002;28:393-402.
8. Bauer KA. New pentasaccharides for prophylaxis of deep vein thrombosis: pharmacology. *Chest*. 2003;124:364S-370S.
9. Amiral J, Lormeau JC, Marfaing-Koka A, et al. Absence of cross-reactivity of SR90107A/ORG31540 pentasaccharide with antibodies to heparin-PF4 complexes developed in heparin-induced thrombocytopenia. *Blood Coag Fibrinolysis*. 1997;8:114-117.
10. Kuo KHM, Kovacs MJ. Successful treatment of heparin induced thrombocytopenia (HIT) with fondaparinux [abstract]. *Blood*. 2003;102:319a.
11. Savi P, Chong B, Greinacher A, et al. Effect of fondaparinux on platelet activation in the presence of heparin-dependent anti-platelet antibodies. A blinded comparative multicenter study with unfractionated heparin [abstract]. *Blood*. 2003;102:319a.
12. Warkentin TE, Cook RJ, Marder VJ, Kelton JG. Comparison of heparin-induced thrombocytopenia antibody (HIT-Ab) generation and in vitro cross-reactivity after elective hip or knee replacement surgery in patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin [abstract]. *Blood*. 2003;102:164a.
13. Lisman T, Bijsterveld NR, Adelmeijer J, et al. Recombinant factor VIIa reverses the *in vitro* and *ex vivo* anticoagulant and profibrinolytic effects of fondaparinux. *J Thromb Haemost*. 2003;1:2368-2373.
14. Turpie AGG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162:1833-1840.
15. Turpie A, Bauer K, Eriksson B, Lassen M. Efficacy and safety of fondaparinux in major orthopedic surgery according to the timing of its first administration. *Thromb Haemost*. 2003;90:364-366.
16. Eriksson BI, Lassen MR, for the PENTasaccharide in Hip-FRActure Surgery Plus (PENTHIFRA-Plus) Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2003;163:1337-1342.
17. Agnelli G, Bergqvist D, Cohen A, et al. A randomized double-blind study to compare the efficacy and safety of postoperative fondaparinux (Arixtra®) and preoperative dalteparin in the prevention of venous thromboembolism after high-risk abdominal surgery: The PEGASUS Study [abstract]. *Blood*. 2003;102:15a.
18. Cohen AT, Davidson BL, Gallus AS, et al. Fondaparinux for the prevention of VTE in acutely ill medical patients [abstract]. *Blood*. 2003;102:15a.
19. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695-1702.
20. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140:867-873.
21. Coussement PK, Bassand JP, Convens C, et al. A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The PENTALYSE study. *Eur Heart J*. 2001;22:1716-1724.
22. Simoons M, Lobo PI. The PENTUA Study: double-blind ranging study of fondaparinux (pentasaccharide) in unstable angina. *Circulation*. 2001;104:1b-4b.
23. Lowe GDO, Sandercock PAG. Prevention of venous thromboembolism after major orthopaedic surgery: is fondaparinux an advance? *Lancet*. 2003;362:504-505.
24. The PERSIST Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis: a phase II evaluation. *J Thromb Haemost*. 2004;2:47-53.
25. Bijsterveld NR, Vink R, Benien E, et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol*. 2004;124:653-658.
26. Ieko M, Tarumi T, Takeda M, et al. Synthetic selective inhibitors of coagulation factor Xa strongly inhibit thrombin generation without affecting initial thrombin forming time necessary for platelet activation in hemostasis. *J Thromb Haemostas*. 2004;2:612-618.
27. Alexander JH, Dyke CK, Yang H, et al. Initial experience with factor-Xa inhibition in percutaneous coronary intervention: the XaNADU-PCI Pilot. *J Thromb Haemostas*. 2004;2:234-241.
28. Lassen MR, Davidson BL, Gallus A, et al. A phase II randomized, double-blind, five-arm, parallel-group, dose-response study of a new oral directly-acting factor Xa inhibitor, razaxaban, for the prevention of deep vein thrombosis in knee replacement surgery [abstract]. *Blood*. 2003;102:15a.
29. Paolucci F, Frasa H, Van Aarle F, et al. Two sensitive and rapid

chromogenic assays of fondaparinux sodium (Arixtra) in human plasma and other biological matrices. *Clin Lab*. 2003;49:451-460.

III. Direct Thrombin Inhibitors

1. Eriksson BI, Wille-Jørgensen P, Kälebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med*. 1997;337:1329-1335.
2. Ginsberg JS, Nurmohamed MT, Gent M, et al. Use of Hirulog in the prevention of venous thrombosis after major hip or knee surgery. *Circulation*. 1994;90:2385-2389.
3. Heit JA, Colwell CW Jr, Francis CW, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. *Arch Intern Med*. 2001;161:2215-2221.
4. Colwell CW, Berkowitz SD, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. *J Thromb Haemost*. 2003;1(10):2119-2130.
5. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized double-blind trial. *Ann Intern Med*. 2002;137:648-655.
6. Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran and warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med*. 2003;349:1703-1712.
7. Eriksson BI, Bergqvist D, Kälebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet*. 2002;360(9344):1441-1447.
8. Eriksson BI, Agnelli GA, Cohen AT, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. The METHRO III Study. *Thromb Haemost*. 2003;89:288-296.
9. Eriksson BI, Agnelli GA, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. *J Thromb Haemost*. 2003;1:2490-6.
10. Schiele F, Lindgaerde F, Eriksson H, et al. Subcutaneous recombinant hirudin (HBW 023) versus intravenous sodium heparin in treatment of established acute deep vein thrombosis of the legs: a multicentre prospective dose-ranging randomized trial. *Thromb Haemost*. 1997;77:834-838.
11. Huisman MV, on behalf of the THRIVE II & V investigators. Efficacy and safety of the oral direct thrombin inhibitor ximelagatran compared with current standard therapy for acute symptomatic deep vein thrombosis, with or without pulmonary embolism: a randomized, double-blind, multinational study [abstract]. *J Thromb Haemost* 2003, supplement 1, #OC003.
12. Schulman S, Wählander K, Lundström, Billing Clason S, Eriksson H, for the Thrive III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349:1713-1721.
13. Bates SM, Weitz JI. Emerging anticoagulant drugs. *Arterioscler Thromb Vasc Biol*. 2003;23:1491-1500.
14. Wallentin L, Wilcox RG, Weaver WD, et al; ESTEEM Investigators. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. *Lancet*. 2003;362(9386):789-797.
15. The Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patient's data. *Lancet*. 2002;359:294-302.
16. Lincoff MA, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIa/IIIa blockade during percutaneous coronary intervention. REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
17. Lincoff MA, 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 revascularization. REPLACE-2 randomized trial. *JAMA* 2004;292:696-703.
18. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet*. 2003;362:1691-1698.