Management of Venous Thromboembolism

Past, Present, and Future

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Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, represents a significant source of morbidity and mortality in the United States and worldwide. The pharmacologic management of venous thromboembolic disease has witnessed significant advances since oral anticoagulant and heparin therapies began to gain widespread use more than 50 years ago. Cumulative clinical experience gained from using these 2 classes of antithrombotic agents for the prevention and treatment of venous thromboembolism in high-risk patients pointed to a number of efficacy and safety limitations. This prompted further research and the eventual introduction, in the 1980s, of low-molecular-weight heparin(s) as a potentially superior therapeutic modality. Within the last decade the pace of development of newer classes of antithrombotic agents for venous thromboembolism prevention and treatment (as well as other indications) has accelerated. Among agents at late stages of investigation are ximelagatran (a direct thrombin inhibitor), nematode anticoagulant peptide c2 (a tissue factor VIIa inhibitor), and sodium N-[8(2-hydroxybenzoyl)amino]caprylate (SNAC)/heparin (a heparin derivative). The most recently approved agents for venous thromboembolism indications include the heparinoid, danaparoid sodium, and the newly introduced selective factor Xa inhibitor, fondaparinux.

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Venous thromboembolism (VTE) causes significant morbidity and, in the form of massive pulmonary embolism (PE), can cause sudden death. For most of the 20th century, it was clear that surgical procedures, particularly major orthopedic procedures on the lower extremity, conferred high risk for VTE. As orthopedic procedures became more complex, there was ongoing debate about how to reduce the risk of postoperative VTE. For the first 15 to 20 years after heparin became clinically available, there was considerable controversy about the need for anticoagulation in treatment of acute VTE.

Widespread use of anticoagulants for the treatment and prevention of VTE has only been ongoing for about 50 years. The timeline shown in Figure 1 begins with the seminal clinical trial testing heparin and oral anticoagulation against no anticoagulation in medical and surgical patients with acute PE. In retrospect, this small trial has obvious flaws, but the high rate of autopsy-confirmed fatal PE (25%) in the untreated patients remains persuasive.

The timeline shown is neither exhaustive nor precise, emphasizing only the major clinical trials and drug introductions that changed practice patterns. For anticoagulation in VTE, unfractionated heparin (UFH) and several oral anticoagulants were the only effective therapeutic agents available for the first 2 decades of the timeline. Low-molecular-weight heparin (LMWH) was introduced in Europe in the early 1980s but did not achieve widespread use for VTE prevention and treatment until about 10 years later. In the last decade, the pace of development has accelerated with the introduction of sev-
er nal new anticoagulants and regimens. In the vanguard of these new anticoagulants are the direct thrombin inhibitors (DTIs) and the selective indirect factor Xa inhibitor, fondaparinux. The first DTI was recombinant hirudin (lepirudin), which was introduced in the United States in 1999 for treatment of the heparin-induced thrombocytopenia thrombosis syndrome (HITTS), heparin-induced thrombocytopenia syndrome (HITS), and HITTS, heparin-induced thrombocytopenia syndrome. The evolution of UFH has seemingly culminated in fondaparinux, a unique synthetic pentasaccharide (molecular weight, 1726 d). Unlike UFH, however, fondaparinux binds to antithrombin (AT) and selectively enhances its inhibitory activity toward factor Xa without any effect on thrombin activity. Fondaparinux was approved in the United States by the Food and Drug Administration (FDA) in 2001 and in Europe in 2002 for the prevention of VTE in major hip and knee surgical procedures.

Since 1960, the clinical evaluation and validation of antithrombotic drugs has been accomplished by randomized controlled trials. More effective drugs and shorter hospitalizations with attendant cost savings have been the hallmarks of management advances. This review highlights the history of current anticoagulants and describes new antithrombotic agents, focusing primarily on those now being evaluated for use in VTE prevention and treatment.

**PE AND DEEP VENOUS THROMBOSIS**

Although questions persist about the precise relationship between deep venous thrombosis (DVT) and PE, historical studies suggest that DVT almost always precedes PE and that PE occurs in the context of a DVT, that is, in most cases, silent. The question of whether DVT always precedes PE is not inconsequential, since modern prophylactic strategies have been evaluated in terms of their efficacy in preventing venographically demonstrated DVT.

Apart from reducing long-term complications of DVT such as the postthrombotic syndrome, the ultimate goal of VTE prophylaxis is to minimize the rate of fatal PE, recognizing that even 1 such death is excessive. In contemporary major orthopedic surgery, fatal PE rates are relatively low in the absence of prophylaxis use, occurring less than once in every 100 joint replacements. Because of this relatively low frequency, the use of fatal PE as a primary outcome measure in VTE prophylaxis trials requires extremely large study populations (>10,000) to reliably determine an antithrombotic agent’s benefit in further reducing a fatal PE rate of 1% or less. Consequently, DVT, a much more common event, began to be used as a surrogate for PE in the evaluation of new drugs and regimens. For the past 15 years, the major end point used in VTE prophylaxis trials in major orthopedic surgery has been the rate of early (within 2 weeks after surgery) venographic demonstration of DVT, particularly proximal DVT, most of which is asymptomatic (Table 1).

When an agent is administered that reduces the rate of postoperative proximal DVT, the assumption is made that PE risk is also reduced.

Of course, trials that use venography give little information about the natural history of asymptomatic DVT, that is, what happens after approximately 3 months to the silent thrombus originally detected venographically within 2 weeks of surgery. Patients with a positive early venographic finding almost invariably receive anticoagulant therapy, which reduces the subsequent rate of symptomatic VTE. For information on the clinical course of asymptomatic DVT in major hip and knee surgery, we must turn to large randomized controlled trials or cohort studies with specified prophylaxis and careful follow-up (Table 2). Two points are evident from the data presented in Tables 1 and 2. First, prophylaxis with any agent reduces the incidence of VTE compared with placebo, whatever the end point used to determine efficacy. Second, it is evident that the crude incidences of venographic DVT (Table 1), subsequent clinical VTE, and fatal PE (Table 2) decline by an order of magnitude. When effective prophylaxis is used, early venographic DVT occurs in 10% to 20% of patients. Subsequent confirmed clinical VTE occurs in 1% to 2% of patients, and fatal PE occurs in 0.1% to 0.2% of patients. This relationship between the rate of asymptomatic and symptomatic events is well illustrated in a recent meta-analysis based on 6 studies of long-term prophylaxis trials in major orthopedic surgery, demonstrating a similar 50% reduction in the odds of both clinical VTE and venographically detected DVT.

**Figure 1.** Management milestones in venous thromboembolism (VTE). A timeline from approximately 1960 to the present indicates the seminal clinical trials that have influenced the use of emerging drugs for VTE prevention and treatment. HFS indicates hip fracture surgery; HITTS, heparin-induced thrombocytopenia thrombosis syndrome; LMWH, low-molecular-weight heparin; OA, oral anticoagulants; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement; and UFH, unfractionated heparin.
Some authorities have questioned the rationale for a link between asymptomatic DVT and fatal PE, while others point to evidence from a number of studies demonstrating a strong association. In one of these studies, 82% of individuals with angiographically demonstrated acute PE also had venographically demonstrated DVT. The only patients with PE who were likely to have negative venograms were those who had recently undergone childbirth or pelvic surgery. In another study, 21% of individuals with a clinical diagnosis of acute DVT also had high-probability lung scans for PE. These 2 studies also highlighted the often asymptomatic nature of VTE. Only 42% of the DVT detected by objective criteria was associated with symptoms, and there was no clinical evidence of PE in any of the patients with high-probability lung scans. The silent nature of VTE is particularly characteristic of orthopedic surgery patients, in whom most DVT and PE events are asymptomatic. Autopsy studies also support the close linkage between DVT and PE. When careful leg dissections are done in patients who died of PE, DVT or its residue is nearly always present. Most symptomatic pulmonary emboli originate from large thrombi in the deep veins of the thigh. Deep veins of the calf, upper extremity, and subclavian and jugular systems are less likely to result in clinical PE.

Table 1. Venographic DVT Rates After Hip or Knee Surgery

<table>
<thead>
<tr>
<th>Operation</th>
<th>Prophylaxis</th>
<th>No. of Trials/No. of Patients†</th>
<th>Total DVT Prevalence, % (95% CI)</th>
<th>Proximal DVT Prevalence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td>Placebo/no treatment</td>
<td>12/626</td>
<td>54.2 (50-58)</td>
<td>26.6 (23-31)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>6/473</td>
<td>40.2 (35-45)</td>
<td>11.4 (8-16)</td>
</tr>
<tr>
<td></td>
<td>Low-dose heparin</td>
<td>11/1016</td>
<td>30.1 (27-33)</td>
<td>19.3 (17-33)</td>
</tr>
<tr>
<td></td>
<td>Warfarin sodium</td>
<td>13/1828</td>
<td>22.1 (20-24)</td>
<td>5.2 (4-6)</td>
</tr>
<tr>
<td></td>
<td>LMWHs</td>
<td>30/6216</td>
<td>16.1 (15-17)</td>
<td>5.9 (5-7)</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux‡</td>
<td>1/787</td>
<td>6.0 (NR)</td>
<td>2.0 (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/908</td>
<td>4.0 (NR)</td>
<td>1.0 (NR)</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>Placebo/no treatment</td>
<td>6/199</td>
<td>64.3 (57-71)</td>
<td>15.3 (10-23)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>6/443</td>
<td>56.0 (51-61)</td>
<td>8.9 (6-12)</td>
</tr>
<tr>
<td></td>
<td>Low-dose heparin</td>
<td>2/236</td>
<td>43.2 (37-50)</td>
<td>11.4 (8-16)</td>
</tr>
<tr>
<td></td>
<td>Warfarin sodium</td>
<td>9/1294</td>
<td>46.8 (44-49)</td>
<td>10.0 (8-12)</td>
</tr>
<tr>
<td></td>
<td>LMWHs</td>
<td>13/1740</td>
<td>30.6 (29-33)</td>
<td>5.6 (4-6.5)</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux‡</td>
<td>1/361</td>
<td>12.5 (9.2-16.3)</td>
<td>2.4 (1.1-4.6)</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>Placebo/no treatment</td>
<td>9/381</td>
<td>48.0 (43-53)</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>3/171</td>
<td>34.0 (27-42)</td>
<td>§</td>
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<tr>
<td></td>
<td>Low-dose heparin</td>
<td>2/59</td>
<td>27.0 (16-40)</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td>Warfarin sodium</td>
<td>5/239</td>
<td>24.0 (19-30)</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td>LMWHs/heparinoids</td>
<td>5/437</td>
<td>27.0 (23-31)</td>
<td>§</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux‡</td>
<td>1/626</td>
<td>7.9 (5.9-10.2)</td>
<td>0.9 (0.3-2.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DVT, deep venous thrombosis; LMWHs, low-molecular-weight heparins; NR, not reported.

*Unless otherwise indicated, data presented are pooled clinical trial data from Geerts et al. Similar findings have been reported for total hip replacement surgery by Freedman et al. In the majority of studies, venography was performed early, ie, within 2 weeks after surgery.

†Patients with adequate venography.

‡Data from fondaparinux arms of phase 3 trials in hip replacement, major knee surgery, and hip fracture surgery; number of evaluable patients for primary efficacy indicated.

§Not reported for the majority of cited trials in hip fracture surgery.

Table 2. Confirmed Clinical VTE Rates After Hip or Knee Surgery: Historical (No Prophylaxis) vs Modern (With Prophylaxis) Rates

<table>
<thead>
<tr>
<th>Operation</th>
<th>VTE Prophylaxis</th>
<th>No. of Patients</th>
<th>DVT, %</th>
<th>Any PE, %</th>
<th>Fatal PE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>None†</td>
<td>2020‡</td>
<td>NR</td>
<td>11.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>None†</td>
<td>152</td>
<td>NR</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Hip fracture surgery†</td>
<td>None†</td>
<td>729</td>
<td>NR</td>
<td>11.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Modern Era Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip replacement²⁴</td>
<td>Warfarin sodium</td>
<td>1495</td>
<td>2.9</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>1516</td>
<td>2.6</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total knee replacement²⁷</td>
<td>Cohort study; heparin, warfarin, mechanical</td>
<td>24 059</td>
<td>1.4%</td>
<td>0.8</td>
<td>NR</td>
</tr>
<tr>
<td>Total knee replacement²⁸</td>
<td>Cohort study; LMWH</td>
<td>842</td>
<td>2.7%</td>
<td>NR</td>
<td>0.4</td>
</tr>
<tr>
<td>Hip fracture surgery²⁵</td>
<td>Aspirin + heparin, LMWH, ES</td>
<td>6679</td>
<td>1.0</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Placebo + heparin, LMWH, ES</td>
<td>6677</td>
<td>1.5</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep venous thrombosis; ES, elastic stockings; LMWH, low-molecular-weight heparin; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

*Data for symptomatic DVT and PE as reported in referenced trials. Symptomatic events were detected, in most cases, at 3 months’ postoperative follow-up.

†No pharmacologic prophylaxis. Mechanical prophylaxis, primarily stockings, was used to varying extent in historical trials.

‡Excluding trials in which objective criteria were used for PE detection.

§Reported as proximal DVT or PE.
Proximal DVT usually results from extension of an isolated calf DVT, 34,36 except in patients who have undergone hip surgery or trauma. 27 Venography in hip surgery patients has shown that isolated proximal thrombi can occur de novo in the femoral vein near the operative site. 11,37 In one study involving hip replacement patients, 23 of 24 femoral thrombi were venographically localized to the femoral system without deep calf vein involvement.11

The question of whether isolated calf thrombi pose a serious threat for PE continues to be debated. Most deep vein thrombi in the calf are small and some may resolve spontaneously as a result of intrinsic fibrinolysis. 34,35 In contrast, studies of hip arthroplasty patients have shown that among those discharged without prophylaxis following a false-negative venogram, 31% developed symptomatic PE within a mean of 33.5 days after surgery. 38 This finding supports the widespread conviction that thrombus progression remains a considerable source of danger to patients harboring silent distal calf thrombi at the time of discharge after orthopedic surgery. It has also given rise to the mistaken notion that ultrasound surveillance to identify and track thrombus extension into proximal veins is prudent in the absence of routine prophylaxis. Routine prophylaxis is much more cost-effective than ultrasound surveillance. 39

PE IN MAJOR ORTHOPEDIC SURGERY

Major orthopedic surgery of the hip and knee, including hip and knee replacement and hip fracture surgery, is associated with a high risk of objectively detected VTE that is not reduced to acceptably low levels even with the best prophylactic agents currently available. 22,23,40 Pooled clinical trial data indicate that, in the absence of prophylaxis, PE risk is lowest after major knee surgery; hip fracture carries the highest risk of fatal PE while hip replacement carries a PE risk that is intermediate between knee replacement and hip fracture surgery. 22 These findings are consistent with the relatively high rates of venographic proximal DVT seen with hip fracture surgery and hip replacement, in contrast to major knee surgery, in which proximal DVT is less common. These findings also support the causal relationship between proximal DVT and increased PE risk seen in these 3 surgical indications (Tables 1 and 2). The highest risk of PE occurs relatively early in these patients, with the peak incidence of both nonfatal and fatal PE occurring between the first and second weeks after hip replacement surgery 41 and 7 days after knee replacement surgery. 27

Based on the high rate of VTE and the early occurrence of PE events in patients undergoing major hip and knee surgery, 40 most, but not all, 40,42 clinicians agree that some form of VTE prophylaxis should be an integral part of the medical management of these high-risk surgical patients.

UFH FOR PE PROPHYLAXIS

For over 30 years, UFH has been tested repeatedly for its efficacy in postoperative VTE prophylaxis. The drug is usually begun perioperatively in subcutaneous doses of 5000 U 2 or 3 times daily and continued for 3 to 7 days. A meta-analysis of trials of UFH for VTE prophylaxis in general, urologic, and orthopedic surgery patients conducted up to 1988 showed a striking 64% ± 15% (SD) odds reduction in fatal PE with heparin; this study included open control trials without placebo, placebo-controlled trials, and trials in which dihydroergotamine or oral anticoagulants or aspirin were given to patients in both the heparin and “control” groups. 43 The meta-analysis included 70 randomized trials involving 16000 subjects and, therefore, approached the sample size required to detect a 50% reduction in the approximate 1% incidence of fatal PE seen in moderate-risk surgery patients who receive no VTE prophylaxis. The International Multicenter Trial, which alone included 4000 elective surgery patients, was one of the first major studies to demonstrate a clear clinical benefit of heparin prophylaxis for the prevention of fatal PE in abdominal and pelvic surgery patients. The frequency of fatal PE events in this study was 8 times higher with placebo than with heparin, as documented by autopsy. 4

For the 13 elective orthopedic surgery trials included in the meta-analysis, data based on 506 patients receiving perioperative heparin indicated generally lower nonfatal PE incidences than with placebo or other treatments. There were no fatal PE events reported with heparin prophylaxis, in contrast to a 3% to 5% incidence for the combined comparator arms. 43 Drawing conclusions about the efficacy of UFH in orthopedic surgery patients from this meta-analysis should be done with caution, however, because relatively small numbers of patients were studied.

LOW-MOLECULAR-WEIGHT HEPARIN

Large clinical trials involving LMWH began to appear around 1985. However, a decade passed before LMWH was widely used in the treatment of VTE. Most prophylaxis trials in higher-risk patients comparing UFH with LMWH or with newer antithrombotic agents have shown inferior benefit with UFH in terms of the venographic end point. 11,44,45 There have been a few exceptions, but for the most part LMWH and other newer anticoagulants have been shown to be superior to UFH in this regard. Several meta-analyses have demonstrated that LMWH offers superior benefit to UFH for VTE prevention in hip and knee surgery patients. 46-48

BLEEDING WITH UFH AND LMWH IN MAJOR ORTHOPEDIC SURGERY

Bleeding into the operative site can lead to infection and compromise the integrity of the prosthesis after total joint replacement. In the minds of most orthopedic surgeons, wound infection necessitating reoperation is the most feared complication of anticoagulant-based VTE prophylaxis after orthopedic surgery. In the last few years, concern has arisen about neuroaxial bleeding around epidural catheters when LMWH is used for VTE prophylaxis, 11 although this complication has been recognized for decades with UFH. 49
The use of LMWH for VTE prophylaxis after orthopedic surgery has actually resulted in fewer bleeding complications than is seen with UFH, but continued fear of wound bleeding has caused some orthopedists to return to warfarin sodium for VTE prophylaxis in these patients.

Prophylactic practices continue to vary by locale and individual preference. Many orthopedists combine anticoagulants with mechanical methods such as intermittent pneumatic compression or elastic stockings. Some orthopedists use warfarin but do not give a sufficient dose to achieve the therapeutic range (international normalized ratio, 2.0–3.0). This tendency is often combined with a trend to prolong the duration of prophylaxis for several weeks. Finally, some clinicians begin prophylaxis with LMWH for the inpatient phase and substitute warfarin for outpatient prophylaxis, a serial combination regimen that has never been tested in randomized controlled trials.

**TREATMENT OF VTE: THROMBUS PROGRESSION WITH UFH**

In the United States, UFH, given by intravenous infusion or large subcutaneous doses, remains the mainstay of immediate treatment of VTE. Low-molecular-weight heparin has been used increasingly during the last decade, but most patients with acute VTE still receive UFH by intravenous infusion with monitoring and dose adjustment. Meta-analyses of VTE treatment trials comparing UFH and LMWH show that LMWH therapy results in slightly less recurrent VTE, less major bleeding, and a slightly lower all-cause mortality over the ensuing 3 months. These results are analogous to outcomes in VTE prophylaxis studies in orthopedic surgery patients in that LMWH seems to perform slightly better than UFH.

The relative ineffectiveness of UFH in reducing the rate of proximal DVT following major orthopedic surgery (Table 1) suggests a limitation in the ability of UFH to prevent thrombus progression. While prophylaxis trials in orthopedic surgery provide no direct data to evaluate this putative limitation of UFH, inferences about the relative efficacy of LMWH and UFH can be drawn from treatment studies in which an objective measure of thrombus progression is available.

Serial venography or duplex ultrasound scanning for the quantitative assessment of thrombus growth reveals that 10% to 28% of patients show thrombus propagation when they receive UFH for treatment of acute DVT. Quantitative venography, using a scoring system that specifies a 30% reduction in thrombus size as an objective end point for evidence of thrombus regression, has shown a 32% incidence of improvement with UFH therapy and a 42% improvement incidence with use of the LMWH certoparin. This finding suggests that certoparin may limit thrombus growth better than UFH. A recent study comparing reduction in thrombus extension between certoparin and UFH for initial treatment of acute DVT found a significant benefit in favor of certoparin. In a study using repeated venography, the LMWH reviparin was significantly more effective than UFH in promoting thrombus regression (53% vs 40%) in patients with documented DVT. A meta-analysis of thrombus progression as an efficacy measure of UFH vs LMWH for initial therapy showed significantly less thrombus progression with LMWH, with a common odds ratio of 0.51.

These clinical studies provide direct evidence that UFH therapy does not prevent thrombus progression in a large proportion of patients with DVT. The studies also suggest an explanation for why fixed-dose UFH is suboptimal for VTE prophylaxis in high-risk surgical patients. While it remains unclear whether early thrombus progression always results in clinical DVT or PE, larger studies with careful patient follow-up strongly support this association.

**THEORETICAL BASIS FOR FAILURE OF UFH TO ARREST THROMBUS GROWTH**

Possible reasons why UFH fails to arrest thrombus growth include the failure of UFH to inhibit the activity of clot-bound thrombin and the attainment of subtherapeutic levels during heparin infusion. Both thrombin and factor Xa bind to fibrin and retain their catalytic activities on this “solid phase,” resulting in continuous local conversion of fibrinogen to fibrin and continuous local activation of prothrombin to thrombin. Direct thrombin inhibitors such as hirugen, PPACK (D-Phe-Pro-Arg-chloromethyl ketone), and hirudin effectively limit the activity of clot-bound thrombin. Unfractionated heparin is relatively ineffective against clot-bound thrombin, consistent with steric interference imposed by the larger heparin-ACT complex. Other studies have characterized the procoagulant activity of bound factor Xa and compared the relative effect of direct and indirect factor Xa inhibitors on this activity using both in vitro and animal experimental systems. Tick anticoagulant peptide and DX-9065a (direct factor Xa inhibitors) each exhibited potent inhibition of clot-associated factor Xa procoagulant activity. Fondaparinux (an indirect factor Xa inhibitor) produced equipotent inhibitory activity against clot-bound factor Xa, relative to DX-9065a, but no enhancement of AT-mediated factor Xa inhibition compared with tick anticoagulant peptide. The degree to which theoretical advantages of a direct vs an indirect mechanism of factor Xa inhibition (and its end point, the inhibition of thrombin generation) actually translate into effective thrombus prevention and/or regression will only become apparent based on clinical trial findings.

Therapy with UFH, whether given intravenously or subcutaneously, often fails to achieve an acceptable prolongation of the activated partial thromboplastin time (aPTT). Some studies indicate that early failure to achieve adequate anticoagulation results in a higher rate of VTE recurrence over the following 3 months of therapy. For example, subtherapeutic doses of heparin were found to predict the onset of VTE events, based on findings indicating a 23.3% frequency of VTE when aPTTs were not reached within 24 hours, compared with a frequency of 4% to 6% when the times...
were therapeutic or supratherapeutic. Another VTE treatment study using UFH suggested that a subtherapeutic aPTT response within the first 48 hours was not associated with an increased risk of VTE recurrence. The use of heparin nomograms has aided the management of heparin therapy by increasing the likelihood that therapeutic aPTTs will be achieved within the first 24 to 48 hours. Despite the use of treatment nomograms for UFH and increased awareness of the unpredictability of the UFH dose response, audits continue to show that approximately 25% of patients treated with UFH do not achieve adequate anticoagulation within the first 24 to 48 hours.

The difficulty and unpredictability in achieving optimum therapeutic levels stem from low bioavailability and rapid clearance of UFH. Heparin’s high degree of nonspecific binding to a variety of plasma and cellular proteins reduces its effective bioavailability to 30% to 40% when it is given subcutaneously in a low dose; such regimens include those typically recommended for prophylactic heparin use (5000 U given 2 or 3 times daily). Individual patients may have intrinsic quantitative differences in their levels of heparin-binding proteins. This leads to wide interindividual variation in antithrombotic response and, as a result, to the unpredictability of UFH therapy, which consequently necessitates frequent monitoring and dose adjustment for optimum antithrombotic efficacy.

Even when UFH is administered intravenously, its unfavorable pharmacodynamic profile means that the patient must be monitored and the dose adjusted to achieve and sustain a therapeutic effect. Compounding the effect of heparin’s limited bioavailability is its short half-life of 30 to 60 minutes. Complex dosing schemes have been developed, but they still do not achieve the desired response in a considerable number of patients.

**Figure 2.** Targeted specificity of new anticoagulants. A schematic representation of coagulation cascade components with new anticoagulants labeled to show their site of action. APC indicates activated protein C; NAPc2, nematode anticoagulant peptide c2; TF, tissue factor; and TFPI, tissue factor pathway inhibitor.

**Table 3**

<table>
<thead>
<tr>
<th>ALTERNATIVES TO UFH: BEYOND LMWH</th>
</tr>
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<tbody>
<tr>
<td>The last decade has seen the development of new anticoagulants that have the potential to replace UFH and even LMWH for a variety of different thrombotic indications, including VTE prevention and treatment. Most of these new anticoagulants specifically target individual components of the coagulation system, a theoretical advantage compared with the multitargeted mechanism of action of UFH and, albeit to a lesser extent, of LMWH as well.</td>
</tr>
</tbody>
</table>

Direct Thrombin Inhibitors

In contrast to all heparin products, which act indirectly via AT to inhibit both thrombin and factor Xa, DTIs bind to thrombin specifically and inhibit its catalytic activity without involvement of AT. Smaller DTIs theoretically offer the advantage of inhibition of both free and bound thrombin. In this way, DTIs may provide more effective inhibition of thrombus progression than agents such as UFH and LMWH that inhibit free thrombin only.

Development of DTIs began with the isolation of hirudin from the medicinal leech (*Hirudo medicinalis*). Drugs approved by the FDA now include lepirudin (a recombinant hirudin), bivalirudin (a semisynthetic DTI, formerly known as Hirulog [Biogen Inc, Cambridge, Mass]), and argatroban (GlaxoSmithKline, Research Triangle Park, NC) (a small synthetic arginine analogue that inhibits thrombin’s active site by ionic binding). All of these drugs are given intravenously and are monitored with the aPTT or activated coagulation time in the same way as UFH. Other agents in this new class of antithrombotics include desirudin (a recombinant desulfato hirudin) and the dipeptide melagatran (a reversible DTI). Small DTIs have been derivate for oral administration. Further along in development is ximelagatran, a produg given orally that is rapidly metabolized to form melagatran, its active metabolite (Table 3). Administration of ximela-
gatran twice daily appears to require no patient monitoring or dose adjustment, based on clinical trials completed to date. Excess bleeding seen with hirudin is probably attributable to its irreversible binding to thrombin. Direct thrombin inhibitors that feature more reversible binding, such as argatroban, bivalirudin, and melagatran, may be associated with less bleeding than seen with hirudin.

Among these DTIs, recombinant hirudin, 

Hirulog, 

and ximelagatran, alone or in combination with melagatran, have been evaluated in clinical trials of VTE prophylaxis in hip and knee arthroplasty. For the most part, these were open-label dose-finding studies or randomized controlled trials in which efficacy and safety were compared with UFH or LMWHs or with warfarin. These DTIs were as safe and effective as their respective comparator drug, with proximal DVT and/or PE incidences of 2% to 10% reported. Results from larger phase 3 clinical trials with the oral DTI ximelagatran also failed to show any clear superiority to warfarin in knee surgery patients or to enoxaparin in hip and knee surgery patients. These disappointing findings call into question the concept that small DTIs will inactivate clot-bound thrombin more effectively than AT-dependent drugs such as UFH and LMWH. Nevertheless, an oral drug that requires no monitoring of its anticoagulant effect is, in theory, of considerable interest.

### Direct Factor Xa Inhibitors

Unlike the heparins, the direct factor Xa inhibitors exert their anticoagulant activity by exclusive factor Xa inhibition involving an AT-independent mechanism of action. Similar to the smaller DTIs, direct factor Xa inhibitors are theoretically capable of inhibiting circulating factor Xa as well as clot-bound forms associated with the prothrombinase complex or with fibrin.

Several direct factor Xa inhibitors are under development. These include synthetic molecules such as YM-6082879 and DX-9065a, as well as the natural inhibitors antistasin and tick anticoagulant peptide, both of which have been produced by recombinant techniques.

As a class, the direct factor Xa inhibitors are not being intensively pursued in clinical studies. Most are either in preclinical development or have been withdrawn because of undesirable properties resulting from their origin as animal-sourced or recombinant materials.

### Indirect Factor Xa Inhibitors: Fondaparinux

Fondaparinux is a small synthetic pentasaccharide. Because it is produced by total chemical synthesis, it provides batch-to-batch consistency with no risk of pathogen contamination, unlike the case for heparins, which are derived from animal sources.

Fondaparinux acts as a catalyst, enhancing AT-mediated inhibitory activity against factor Xa. By selectively inactivating factor Xa, fondaparinux inhibits thrombin generation without any direct inhibitory effect on the thrombin molecule. Unlike the case with the direct factor Xa inhibitors, the antithrombotic activity of fondaparinux is absolutely dependent on AT.

Fondaparinux exhibits 100% bioavailability. It binds specifically to AT and exhibits no nonspecific binding to plasma and cellular proteins within its therapeutic range. These properties lead to a predictable dose-response effect and render the risk of heparin-induced thrombocytopenia extremely unlikely given the absence of fondaparinux binding to platelet factor 4, unlike the case for UFH.

Pharmacokinetic studies have demonstrated that fondaparinux is rapidly absorbed following subcutaneous administration, reaching its maximal plasma concentration within 1.7 hours and exhibiting a terminal half-life of approximately 17 hours. The drug’s pharmacokinetics show little interindividual variation. These properties allow for once-daily subcutaneous dosing, a rapid onset of action, and a predictable duration of effect—with no dose adjustment or dose monitoring required.

Fondaparinux, among all the new antithrombotic agents, has shown the greatest potential for prevention of venographically demon-
Nematode anticoagulant peptide c2 was first isolated from the blood-feeding canine hookworm but it is now available as a recombinant product. It combines with factors X and Xa to inhibit the TF-VIIa complex.96,97 Nematode anticoagulant peptide c2 is administered subcutaneously every 2 days and is currently being evaluated for VTE prophylaxis after elective hip replacement surgery.

While UFH and LMWHs are poorly absorbed in the gut and cannot be given orally, derivatization of UFH to sodium N-[(2-hydroxylbenzoyl)amino]caprylate (SNAC)/heparin facilitates oral administration.98 When this drug is administered, demonstrable prolongation of the aPTT occurs, although the duration of anticoagulant effect is similar to that with bolus intravenous dosing of UFH. The rapid clearance of SNAC/heparin will likely require that it be dosed frequently, especially in treatment protocols. The drug is being evaluated for VTE prophylaxis after elective hip and knee replacement. Derivatives of various LMWHs are being pursued, which may allow oral dosing of these drugs once or twice daily.

**CONCLUSIONS**

Many new anticoagulants exhibit potentially superior properties to the heparins, including improved pharmacodynamic profiles and targeted activity at single points in the coagulation cascade. Other favorable properties include total chemical synthesis, once-daily dosing without any monitoring or dose adjustment, and oral administration (Table 4). Each of the new agents offers advantages that require consideration as progress continues toward the development of better anticoagulants.

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**Table 4. Features of an Improved Anticoagulant**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Multiple indications with high benefit-risk ratios</td>
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</tr>
<tr>
<td>Infrequent dosing schedule, preferably oral administration</td>
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<tr>
<td>Rapid onset of action</td>
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<tr>
<td>Predictable pharmacodynamics/pharmacokinetics (even with mild-moderate renal/hepatic dysfunction)</td>
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</tr>
<tr>
<td>Low risk of heparin-induced thrombocytopenia, osteopenia, and other toxic effects</td>
<td></td>
</tr>
<tr>
<td>Effective antidote available</td>
<td></td>
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<tr>
<td>Cost-effective</td>
<td></td>
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</tbody>
</table>

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strated DVT associated with both major hip and knee surgery. The drug received approval by the FDA in 2001 and by European regulatory agencies in 2002 for VTE prevention in hip and knee replacement and hip fracture surgical procedures. Phase 2 trials in hip replacement surgery91 and phase 3 trials in hip replacement,17,18 hip fracture,39 and major knee surgery38 have demonstrated the superiority of fondaparinux, relative to the LMWH enoxaparin, in reducing VTE risk following major orthopedic surgery. A recent meta-analysis of these phase 3 trials indicates an overall significant 55.2% reduction in VTE risk (P < .001), in favor of fondaparinux, with no difference in clinically relevant bleeding complications at the dosing regimens used.92

Post hoc analyses have demonstrated a significant relationship between the timing of the first administration of fondaparinux after surgery and the incidence of a bleeding index of 2 or more: administration of the first dose of fondaparinux at 6 or more hours after surgery was associated with a lower incidence of a bleeding index of 2 or more compared with the administration of the first dose at less than 6 hours after surgery (1.8% vs 2.9%; P = .04). No such relationship has been found between timing and efficacy. The significant reduction in VTE risk with fondaparinux relative to enoxaparin use (the first dose administered either 12 hours before surgery or 12 to 24 hours after surgery, according to approved enoxaparin regimens) was observed whether fondaparinux was administered at less than 6 hours or 6 hours or more postoperatively.93 Related to this, earlier postoperative administration of enoxaparin (8 hours vs 12-24 hours after surgery) for VTE prevention in total knee replacement surgery has recently been reported to reduce VTE incidence more effectively than warfarin (38% vs 59%, P = .004) but at the expense of a higher rate of clinically important bleeding, including any clinically important hemorrhage (33.5% vs 23.3%; P = .04) as well as clinically important operative-site hemorrhage (7% vs 3%; P > .05).94

The superior efficacy demonstrated by fondaparinux in reducing the rate of proximal venographically detected by follow-up ultrasonography and perfusion lung scanning, were observed across the wide range of fondaparinux doses tested.95 A completed phase 3 study comparing fondaparinux with enoxaparin for the treatment of DVT and an ongoing phase 3 study of fondaparinux with UFH for the treatment of PE will provide essential information on this drug’s treatment efficacy in VTE treatment.

At present, fondaparinux, a specific factor Xa inhibitor that interferes with thrombin generation—and, thereby, feedback loops within the coagulation cascade through which thrombin activity is regulated—appears to refute the hypothesis that only agents that inhibit both circulating and clot-bound thrombin will be the most effective in preventing thrombus extension.


