Anticoagulants are widely used by cardiologists. Unfractionated heparin (UFH) and coumarins were discovered more than 60 years ago, and for more than 40 years, they have been the sole anticoagulant drugs available to clinicians.1,2 Now, in 2007, several new anticoagulants have been introduced, and many more are under clinical development. Will these new anticoagulants replace the established drugs, and if so, how will these new anticoagulants fit into the therapeutic armamentarium of the practicing cardiologist?

Both UFH and coumarins were in clinical use long before their mechanism of action was completely understood. Both were also discovered by chance: UFH from extracts of dog liver and coumarins from extracts of vegetable matter (spoiled sweet clover). Low-molecular-weight heparin (LMWH) was also discovered by chance in the late 1970s and early 1980s and was in clinical use for at least a decade before its mechanistic advantages over UFH were identified.3 In the quest for new anticoagulants, scientists often turned to extracting natural anticoagulants from hemophagic animals and insects and from snake venoms.4 Defibrinating enzymes, factor Xa inhibitors, and thrombin inhibitors were isolated, purified, and in some cases synthesized by recombinant techniques. Of these anticoagulants, recombinant hirudin (from leeches) and recombinant NAPC2 (from hookworm) have been tested clinically. A few new anticoagulants (thrombomodulin, activated protein C) are synthesized by recombinant techniques, but with advances in structure-based design, most new anticoagulants are small molecules designed specifically to block the activity of coagulation enzymes either by fitting into their catalytic pockets, like a key into a lock, or by interacting with and activating anticoagulant proteins such as antithrombin (AT; eg, fondaparinux). On the basis of these technological advances, it is now possible to modulate the coagulation process at almost every step.

The first wave of new anticoagulants was not orally active, thereby limiting their value for long-term treatment. These new parenteral anticoagulants (LMWH, bivalirudin, and fondaparinux) are effective and, because of their advantages over UFH, have replaced or are likely to replace UFH for many acute cardiac indications. As a result, the need for additional parenteral anticoagulants is less pressing than for new oral anticoagulants to replace warfarin. Initially, development of orally active agents was stalled because of technical difficulties; however, with advances in techniques for oral absorption, several new site-specific oral anticoagulants have now been developed and are undergoing clinical testing. Drug developers have focused mainly on 2 key targets: factor Xa and factor IIa (thrombin). The cost of developing a new anticoagulant is high. Added to these development costs, trials evaluating novel anticoagulant therapies for the prevention of major vascular events for cardiac indications are particularly expensive, because the required sample size is large, and the duration of follow-up is long. Consequently, drug development often starts with less expensive studies in the prevention of venous thrombosis, based on the premise that success in this indication predicts success for other indications.

Drugs currently under development or recently introduced into clinical practice are listed in Table 1. In the remainder of the present review, we emphasize those agents that have been or are likely to be introduced into clinical practice in cardiology. Several new parenteral compounds but no new oral agents have been approved clinically. Before discussing the new antithrombotic drugs, we briefly review the limitations and advantages of UFH and LMWH, because it is these limitations that provide opportunities for new parenteral anticoagulants. The limitations of warfarin have been reviewed extensively elsewhere5 and will not be discussed here.

**Limitations and Advantages of UFH and LMWH**

In addition to its well-known bleeding complications, UFH has biological and pharmacokinetic limitations.6 The biological limitations are immune-mediated platelet activation, which leads to heparin-induced thrombocytopenia (HIT), and an effect on bone cells that leads to heparin-induced osteoporosis. These side effects are chain length–dependent and charge-dependent. Pharmacokinetic limitations are caused by AT-independent binding of UFH to plasma proteins and to proteins released from platelets, which results in the variable anticoagulant response and, therefore, a need for anticoagulant monitoring.

Is UFH likely to become obsolete? The answer is not yet. UFH has 3 major advantages over LMWH.7 The first is that the anticoagulant effects of UFH can be rapidly and completely neutralized by protamine. On the basis of this advantage, UFH remains the anticoagulant of choice during cardio-
pulmonary bypass. Second, when used in clinical doses, UFH is not cleared by the kidneys and therefore is potentially safer than LMWH in patients with renal insufficiency. The third advantage, although theoretical, is potentially important in cardiology. UFH is effective in modulating the contact activation pathway by inactivating factor XIa and, to a lesser extent, factor XIIa through an AT-dependent mechanism (Figure). In contrast, the shorter chain length of LMWH is less effective, and pentasaccharide is ineffective in blocking these contact activation steps.6 The contact activation pathway by inactivating factor XIa and, to a lesser extent, factor XIIa through an AT-dependent mechanism (Figure). In contrast, the shorter chain length of LMWH is less effective, and pentasaccharide is ineffective in blocking these contact activation steps.6 The contact activation path-

**TABLE 1. New Anticoagulants**

<table>
<thead>
<tr>
<th>Pharmacological Target</th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IIa (thrombin)†</td>
<td>Hirudin (desirudin, lepirudin)</td>
<td>Ximelagatran</td>
</tr>
<tr>
<td></td>
<td>Bivalirudin*</td>
<td>Dabigatran*</td>
</tr>
<tr>
<td></td>
<td>Argatroban*</td>
<td>Odiparcil*</td>
</tr>
<tr>
<td>Factor Xa†</td>
<td>Fondaparinux*</td>
<td>Rivaroxaban*</td>
</tr>
<tr>
<td></td>
<td>Idraparinux‡</td>
<td>Apixaban*</td>
</tr>
<tr>
<td></td>
<td>SSR126517 (biotinylated idraparinux)</td>
<td>LY517717*</td>
</tr>
<tr>
<td></td>
<td>DX-9056a</td>
<td>YM150*</td>
</tr>
<tr>
<td></td>
<td>Otamixaban*</td>
<td>Du-176b*</td>
</tr>
<tr>
<td>Factor VIIa/TF pathway</td>
<td>Tifacogin (recombinant TFPI)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Recombinant NAPc2</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Factor VIIa</td>
<td>...</td>
</tr>
<tr>
<td>Factor IXa</td>
<td>Factor IXa aptamer*</td>
<td>TTP889</td>
</tr>
<tr>
<td>Protein C pathway</td>
<td>Protein C</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Drotrecogin (recombinant activated protein C)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>ART123 (soluble thrombomodulin)</td>
<td>...</td>
</tr>
<tr>
<td>Factor Xa/factor IIa</td>
<td>Hexadecasaccharide (SR123781A)*</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Bemiparin (ultra-LMWH)</td>
<td>...</td>
</tr>
</tbody>
</table>

TF indicates tissue factor; TFPI, tissue factor pathway inhibitor; NAPc2, nematode anticoagulant peptide; and Factor VIIa, active site blocked factor VIIa.

*Agents that are under evaluation or are approved for use for cardiology indications are identified with an asterisk.

†Many other factor Xa and factor IIa inhibitors are currently in early stages of development.

‡A biotinylated formulation of idraparinux is currently undergoing clinical trials.

Inhibition of the contact activation and tissue factor pathways by UFH and inhibition of the tissue activation pathway by LMWH and fondaparinux. Tissues factor pathway: initiation of coagulation is triggered by the tissue factor/factor VIIa complex (TF/VIIa), which activates factor IX (IX) and factor X (X). Contact activation pathway: initiation of coagulation is triggered by activation of factor XII (XIIa), which activates factor XI (XIa). Factor XIa activates factor IX, and activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (VIIIa) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. UFH targets steps in both the contact activation pathway (inactivates XIa and XIIa) and tissue factor pathway (inactivates IXa, Xa, and IIa). Fondaparinux modulates the tissue factor pathway by inactivating factor Xa. LMWH also modulates the tissue factor pathway by inactivating factor Xa and, to a lesser degree, factor IIa. LMWH exerts weak activity against the contact activation pathway. P indicates phospholipid surface; TF, tissue factor.
way contributes to thrombosis on catheter tips, stents, and filters. Most clinically relevant thrombogenic stimuli trigger coagulation through activation of the tissue factor pathway, which is blocked by inhibitors of factor Xa and thrombin. Hemostasis is also triggered by activation of the tissue factor pathway, and anticoagulant-mediated bleeding occurs as a consequence of inhibition of this pathway. In contrast, the contact activation pathway contributes to thrombosis mediated by contact with a foreign surface, and this pathway has minimal involvement in hemostasis. Therefore, by directly inhibiting the contact activation pathway (in addition to the tissue factor pathway through inhibition of factor Xa and thrombin), UFH has the potential advantage of modulating coagulation triggered by this pathway, at doses that are less likely to produce bleeding than other anticoagulants. These theoretical considerations might explain in part why early attempts to use LMWH to prevent clotting in cardiac bypass circuits were unpromising and why the risk of thrombosis of cardiac catheters is higher with fondaparinux than with UFH.7

LMWHs are prepared by depolymerization of UFH; they have a more predictable dose response and a longer-half life than UFH and are cleared principally by the renal route.3 LMWH has replaced UFH for many indications, including the management of patients with acute coronary syndromes (ACS).

UFH and LMWH are contraindicated in patients with a recent history of HIT, and LMWH is contraindicated in patients with severe renal insufficiency. The new parenteral anticoagulants can be used safely in HIT, and some are partially or entirely cleared by nonrenal mechanisms (Table 2).

New Anticoagulants

Thrombin Inhibitors

Direct thrombin inhibitors bind to thrombin and block its interaction with substrates.4 Unlike UFH, direct thrombin inhibitors inactivate fibrin-bound thrombin and fluid-phase thrombin, a theoretical advantage that is of uncertain clinical importance. Direct thrombin inhibitors lack an antidote.4

Three parenteral direct thrombin inhibitors have been licensed in North America for limited indications: hirudin is approved for treatment of patients with HIT; argatroban is approved for the treatment of HIT and for patients with or at risk of HIT who are undergoing percutaneous coronary intervention (PCI); and bivalirudin is licensed as an alternative to UFH in patients undergoing PCI.

Bivalirudin is a 20–amino acid synthetic polypeptide analog of hirudin.4 Once bound, bivalirudin is cleaved by thrombin, thereby reducing its antithrombotic activity. Bivalirudin has a plasma half-life of 25 minutes after intravenous injection and is partially cleared renally; there is no antidote for bivalirudin.4 Bivalirudin has been evaluated in patients with non–ST-segment elevation ACS who are undergoing PCI, in patients with ST-segment elevation myocardial infarction (MI) treated with streptokinase,9 and in urgent or elective PCI.10–12

Ximelagatran, the first orally active thrombin inhibitor,4 is a prodrug of the active site-directed thrombin inhibitor melagatran. After ingestion and absorption, ximelagatran undergoes rapid biotransformation to melagatran, the active agent. Melagatran is eliminated via the kidneys. Ximelagatran has a plasma half-life of 4 to 5 hours and is administered orally twice daily.4 Ximelagatran has been evaluated extensively for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF)13,14 and in patients with MI.15 Despite favorable efficacy results, ximelagatran was not approved for use in North America because of concerns regarding liver toxicity and issues related to the claim that it is noninferior to warfarin in AF patients. Nevertheless, the results of the ximelagatran studies are important because they provide solid evidence that an oral anticoagulant can be used safely and effectively without coagulation monitoring.

Dabigatran etexilate is a prodrug of dabigatran, a specific, competitive, and reversible inhibitor of thrombin.16 Dabigatran etexilate is rapidly absorbed after oral administration and converted to dabigatran. The plasma half-life is ≈8 hours after a single dose and 14 to 17 hours after multiple doses. Despite its long half-life, dabigatran etexilate is being given twice daily in a phase III trial currently under way for the prevention of stroke or systemic embolism in patients with AF. Dabigatran is cleared renally.

Odiparcil is an orally active β-D-xylodisaccharide that promotes the in vivo release of chondroitin and dermatan sulfate, which confer antithrombotic activity through activation of the AT serpin heparin cofactor II, thereby inhibiting thrombin.17 Odiparcil has been evaluated in phase 2 trials of patients with venous thromboembolism (VTE).

Factor Xa Inhibitors

Factor Xa inhibitors block factor Xa either directly, by binding to the active site of factor Xa, or indirectly, via AT.4 Unlike UFH, most factor Xa inhibitors do not have a known antidote.

Table 2. Renal Clearance of New Anticoagulants

<table>
<thead>
<tr>
<th>Type</th>
<th>Parenteral</th>
<th>Oral</th>
<th>Partial Renal</th>
<th>Predominantly Renal</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Nonrenal (≤50%)</td>
<td></td>
<td>Renal (&gt;50%)</td>
<td></td>
</tr>
<tr>
<td>Parenteral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirudin</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor Xa aptamer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Indirect (AT-Dependent) Factor Xa Inhibitors

Fondaparinux is a synthetic analog of the unique pentasaccharide sequence that mediates the interaction of UFH and LMWH with AT. Once the pentasaccharide-AT complex binds factor Xa, pentasaccharide dissociates from AT and can be reused. Thus, the indirect inhibitors are catalytic and result in AT-mediated irreversible inhibition of free factor Xa. Fondaparinux binds AT with high affinity, has excellent bioavailability after subcutaneous injection, and has a plasma half-life of 17 hours that permits once-daily administration. The drug is excreted unchanged in the urine. Dose adjustments are necessary in patients with severe renal insufficiency. Patients exposed to fondaparinux have been reported to form anti-heparin/platelet factor 4 antibodies, but fondaparinux does not bind to platelets or platelet factor 4; consequently, fondaparinux should not cause HIT. Fondaparinux has been evaluated extensively in patients with ACS and for the prevention and treatment of VTE. The anticoagulant effect of fondaparinux can be partially reversed with recombinant factor VIIa.

Indirect (AT-Dependent) Factor Xa Inhibitors

Table 3. Comparison of Indirect and Direct Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Indirect</th>
<th>Direct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitory mechanism</td>
<td>AT-dependent; catalytic</td>
<td>Non–AT-dependent; stoichiometric</td>
</tr>
<tr>
<td>Drug target</td>
<td>Free Xa</td>
<td>Free and tissue-bound Xa</td>
</tr>
<tr>
<td>Binding</td>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
</tbody>
</table>

Like fondaparinux, idraparinux is a synthetic analog of the unique pentasaccharide sequence that mediates the interaction of UFH or LMWH with AT. Idraparinux has a plasma half-life of 130 hours and is given once weekly by subcutaneous injection. Promising results were seen with idraparinux for treatment of deep vein thrombosis, but the drug was less effective than conventional therapy for the treatment of pulmonary embolism. In addition, idraparinux caused excessive bleeding when evaluated for the long-term treatment of deep vein thrombosis and for the prevention of stroke or systemic embolism in patients with AF, and it is no longer being developed. A newer, biotinylated version of idraparinux is currently being evaluated in clinical trials of patients undergoing PCI.

Factor IXa Inhibitors

Both parenteral and oral factor IXa inhibitors are under development. The most advanced parenteral factor IXa inhibitor is an RNA aptamer that binds factor IXa with high affinity and produces rapid anticoagulation. A unique aspect of the compound is its potential for rapid neutralization by a complementary oligonucleotide. This drug-antidote pair is being developed for use in cardiopulmonary bypass surgery and for other indications for which rapid anticoagulant reversal may be beneficial. An orally active direct factor IXa inhibitor (TTP889) also has been developed.

Role of New Anticoagulants by Indication: Results of Phase 3 Trials

Acute Coronary Syndrome

UFH and the LMWH enoxaparin are widely used and effective for the management of patients with ACS. Among the LMWHs, enoxaparin has been the most extensively evaluated and is the most widely used for the management of ACS, but dalteparin, nadroparin, and reviparin have also been shown to be effective. Intravenous UFH is widely used in patients with ST-segment elevation MI who are treated with fibrin-specific fibrinolytic agents, but it is not commonly used in patients treated with streptokinase. Thus, any new parenteral anticoagulants must be compared with LMWH or UFH in all patient groups with ACS except those treated with streptokinase. Several phase 3 trials of
bivalirudin and fondaparinux have been conducted and are displayed in Table 4.

**Direct Thrombin Inhibitors: Bivalirudin**

In the first phase 3 trial of bivalirudin, the Bivalirudin Angioplasty Study, 4312 patients undergoing coronary angioplasty for unstable or postinfarction angina were randomized to treatment with bivalirudin or UFH. In an updated intention-to-treat analysis, bivalirudin compared with UFH significantly reduced the frequency of the composite efficacy outcome, in-hospital death, MI, or revascularization (6.2% versus 7.9%, \( P=0.04 \)), and the frequency of bleeding (3.5% versus 9.3%, \( P<0.001 \)).

The phase 3 HERO-2 (Hirulog and Early Reperfusion or Occlusion-2) trial randomized 17 073 patients with acute ST-elevation MI to a 48-hour infusion of either fixed-dose bivalirudin after an intravenous bolus (n=8516) or adjusted-dose UFH (n=8557) in conjunction with streptokinase. The primary outcome measure was 30-day mortality, and the secondary outcome measures included reinfarction within 96 hours and bleeding. Mortality at 30 days was similar in patients randomized to bivalirudin or UFH (10.8% and 10.9%, respectively; \( P=0.85 \)). Significantly fewer reinfarctions occurred with bivalirudin than with UFH, but the rate of bleeding (including severe bleeding) was higher with bivalirudin.

Bivalirudin was evaluated in the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events) study, a phase 3 randomized trial of 6010 PCI patients who were randomly assigned to bivalirudin plus a provisional glycoprotein IIb/IIIa inhibitor (GPI), either abciximab or eptifibatide, or UFH plus GPI. The primary efficacy outcome was not significantly different in the 2 treatment groups, but rates of major bleeding were significantly lower in patients given bivalirudin than in those treated with UFH (2.4% versus 4.1%, \( P<0.001 \)).

The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) study randomized 13 819 patients with non–ST-segment elevation ACS to receive 1 of 3 treatments: bivalirudin plus provisional GPI, bivalirudin plus GPI, or intravenous UFH/enoxaparin plus GPI. Clopidogrel was added to aspirin at the discretion of the local investigator, and 57% of patients underwent PCI during study drug administration. Noninferiority was declared if the upper limit of the confidence interval of the rate of the primary outcome did not exceed 25% of the observed rate of death, MI, or unplanned revascularization in the control arm. Bivalirudin plus provisional GPI was noninferior to intravenous UFH/enoxaparin plus GPI for preventing the composite of death, MI, or unplanned revascularization for ischemia at 30 days (7.8% versus 7.3%) but was superior to intravenous UFH/enoxaparin plus GPI for clinically important bleeding, which was reduced by one half (3.0% versus 5.7%, \( P<0.001 \)).

**TABLE 4. Phase III Trials of New Anticoagulant for ACS and PCI**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>No. of Participants</th>
<th>Intervention</th>
<th>Primary Efficacy Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTACS</td>
<td>OASIS-5</td>
<td>20 078</td>
<td>Fondaparinux</td>
<td>Enoxaparin</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>HERO-2</td>
<td>17 073</td>
<td>Bivalirudin</td>
<td>UFH</td>
<td></td>
</tr>
<tr>
<td>OASIS-6</td>
<td></td>
<td>12 092</td>
<td>Fondaparinux</td>
<td>Standard care (placebo or UFH)</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>Bivalirudin Angioplasty Study</td>
<td>4312</td>
<td>Bivalirudin</td>
<td>UFH</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>REPLACE-2</td>
<td>6010</td>
<td>Bivalirudin ± GPI</td>
<td>UFH + GPI</td>
<td></td>
</tr>
<tr>
<td>ACUITY</td>
<td></td>
<td>13 819</td>
<td>Bivalirudin ± GPI</td>
<td>UFH/ enoxaparin + GPI</td>
<td></td>
</tr>
</tbody>
</table>

NSTACS indicates non–ST-segment elevation ACS; RI, reinfarction; STEMI, ST-segment elevation MI; and revasc, revascularization.

*The Bivalirudin Angioplasty Study was first reported with a per-protocol analysis. The data included in Table 3 represent a reanalysis of the study that used an intention-to-treat analysis and “contemporary definitions of adjudicated end points.”

†The primary outcome was the composite of death, MI, severe myocardial ischemia requiring urgent surgical or repeat percutaneous coronary revascularization, or in-hospital major bleeding.

‡Three primary outcomes were prespecified: composite efficacy outcome (death, MI, unplanned revascularization for ischemia); major bleeding; and a net clinical outcome (composite efficacy outcomes plus major bleeding).
din plus GPI was noninferior to intravenous UFH/exoxaparin plus GPI. The interpretation of the ACUITY trial can be questioned because of the wide noninferiority margin (25%), which does not exclude a substantial loss of antithrombotic efficacy.

The overall conclusions from the bivalirudin studies are that it is an effective anticoagulant in ACS patients, particularly for those undergoing PCI. The reports of reduced bleeding (compared with UFH) observed in the early bivalirudin studies were not confirmed in subsequent studies comparing UFH/exoxaparin with bivalirudin on a background of glycoprotein IIb/IIIa inhibition. Bivalirudin may obviate the need for a GPI during PCI and thus reduce bleeding, but a GPI may still be required in very-high-risk patients.

**Factor Xa Inhibitors: Fondaparinux**

Fondaparinux has been compared with enoxaparin in patients with non-ST-segment elevation ACS and has been compared with "standard care," comprising either intravenous UFH or placebo (no UFH), in patients with ST-segment elevation MI. The OASIS (Organization to Assess Strategies for Ischemic Syndromes)-5 study randomized 20,078 patients with non-ST-segment elevation ACS to receive fondaparinux 2.5 mg once daily or enoxaparin 1 mg per kg twice daily by subcutaneous injection for up to 8 days. At ≈1 week, a similar proportion of patients treated with fondaparinux compared with enoxaparin experienced the primary outcome of death, MI, or refractory ischemia (5.8% versus 5.7%, \(P=0.007\) for noninferiority). Fondaparinux reduced major bleeding by approximately one half (2.2% versus 4.1%, \(P<0.001\), including fatal bleeding (7 versus 22 events, \(P=0.005\)), during the first week and was associated with a 17% reduction in death (2.9% versus 3.5%, \(P=0.02\)) and a nonsignificant 23% reduction in stroke (0.7% versus 1.0%) at 30 days. More than 90% of the excess deaths that occurred in patients treated with enoxaparin occurred in patients who experienced bleeding. There was an excess of catheter-related thrombosis in fondaparinux-treated patients compared with enoxaparin-treated patients (0.9% versus 0.4%, \(P=0.001\)). Catheter thrombosis was largely avoided by the use of UFH during PCI.

The OASIS-6 study randomized 12,092 patients with ST-segment elevation MI to receive fondaparinux 2.5 mg once daily by subcutaneous injection for up to 8 days or standard care with either placebo among patients in whom UFH was believed not to be indicated (stratum 1) or intravenous UFH for 48 hours (stratum 2). At 9 days, fondaparinux compared with standard care reduced the risk of death or MI by 17% (7.4% versus 8.9%, \(P=0.003\), of death alone by 13% (6.1% versus 7.0%, \(P=0.04\), and of MI by approximately one third (1.6% versus 2.3%, \(P=0.004\)). The rate of bleeding was not increased with fondaparinux compared with the control group (1.8% versus 2.1%, \(P=0.14\)). There was no difference in total stroke (0.9% versus 1.1%) or hemorrhagic stroke (11 versus 10 events). Among patients who underwent primary PCI, there was an excess of catheter thrombosis in patients treated with fondaparinux (none of whom received UFH), and there was a nonsignificant excess of ischemic outcomes and bleeding. There were no episodes of catheter thrombosis in patients who received UFH at the time of catheterization.

The OASIS-5 results indicate that fondaparinux 2.5 mg/d is safer than enoxaparin 1 mg/kg twice daily for the management of non-ST-segment elevation ACS and is as effective during the period of drug administration. Less bleeding with fondaparinux 2.5 mg/d is associated with better long-term efficacy, including a reduction in both death and stroke. The OASIS-6 trial results are consistent with OASIS-5 and show that fondaparinux 2.5 mg/d is effective for preventing death and recurrent ischemic events in ST-segment elevation MI. The downside of fondaparinux is the increased risk of catheter thrombosis, which makes it unsuitable for use during PCI. Catheter thrombosis is likely to be caused by contact pathway activation triggered by exposure of the blood to catheters used during PCI but appears to be prevented by the use of UFH, which blocks activation of the contact activation pathway.

The reduction in bleeding with fondaparinux compared with enoxaparin in the OASIS-5 trial was unexpected. Both fondaparinux and enoxaparin exert their anticoagulant effect by activating AT, thereby accelerating the inhibition of factor Xa by AT. A percentage of the longer enoxaparin chains also inhibit thrombin in an AT-dependent manner, but the short pentasaccharide chain of fondaparinux does not inhibit thrombin. Indirect evidence suggests that the excessive bleeding with enoxaparin (over fondaparinux) is unlikely to be caused by its AT effect. Thus, UFH blocks thrombin more effectively than enoxaparin but does not cause more bleeding and argatroban do not cause more bleeding than UFH or LMWH. Randomized studies comparing fondaparinux and enoxaparin for the prevention and treatment of VTE also provide no support for the conclusion that intrinsic differences between the drugs account for differences in bleeding risk. A meta-analysis of 4 large, randomized thromboprophylaxis trials that compared fondaparinux 2.5 mg/d with enoxaparin 30 mg twice daily or 40 mg once daily in patients with hip fracture or undergoing elective hip or knee replacement surgery showed that fondaparinux significantly reduced venographic deep vein thrombosis but increased bleeding. In these trials, fondaparinux was commenced 6 hours after surgery, whereas enoxaparin was commenced more than 12 hours after surgery, so the observed effects could have been accounted for by differences in the timing of commencement of treatment after surgery rather than intrinsic differences between the drugs. In another randomized trial comparing the 2 drugs for the treatment of deep vein thrombosis, fondaparinux 5, 7.5, or 10 mg given once daily was noninferior to enoxaparin 1 mg/kg given twice daily for preventing recurrent VTE, and there was a similar risk of bleeding in the 2 treatment groups.

The more likely explanation for the reduced bleeding with fondaparinux in the OASIS-5 and -6 trials relates to differences in the intensity of the anticoagulant effect between the low dose of fondaparinux and the standard "therapeutic" dose of enoxaparin. The once-daily 2.5-mg dose of fondaparinux used in the OASIS-5 and -6 studies was the same as the dose...
that was used in earlier thromboprophylaxis trials. By contrast, the dose of enoxaparin in the OASIS-5 trial (1 mg/kg twice daily) was much higher than the dose used in orthopedic venous thromboprophylaxis trials (30 mg twice daily or 40 mg once daily). The results of the OASIS-5 and -6 studies raise the possibility that a lower anticoagulant intensity than was previously thought necessary is sufficient to prevent recurrent ischemic events and death but is much safer than the traditional (higher) intensities of enoxaparin and UFH that are currently used in the treatment of ACS.

Prevention of Arterial Thromboembolism in AF
Oral anticoagulation, targeted at an international normalized ratio (INR) of 2 to 3, is indicated for patients with AF at high risk of ischemic stroke and arterial thromboembolism.36 On the basis of a meta-analysis, warfarin is associated with a two-thirds risk reduction in ischemic stroke.37 For patients compliant with warfarin, the risk reduction may be even greater (~80%). However, warfarin has important disadvantages that include a narrow therapeutic window, multiple drug and food interactions, and the need for frequent laboratory monitoring. AF is a very exciting indication for a safe and effective novel oral anticoagulant because indefinite oral anticoagulation is indicated, and warfarin is underutilized in clinical practice for this indication.38

Direct Thrombin Inhibitors: Ximelagatran and Dabigatran
Two phase 3 trials have compared ximelagatran (36 mg twice daily) to warfarin for the prevention of cardioembolic events in patients with nonvalvular AF. The SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III study randomized 3407 patients in an open-label fashion to receive either ximelagatran or adjusted-dose warfarin (targeted to an INR of 2.0 to 3.0).13 The primary outcome, all strokes and systemic embolic events, was reported in 40 patients (1.6% per year) assigned to ximelagatran and 56 patients (2.3% per year) assigned to warfarin during a mean duration of follow-up of 21 months. Rates of major and intracranial hemorrhage were comparable in both groups, although the combination of major and minor bleeds was reduced in the ximelagatran group (25.5% compared with 29.5%; \(P=0.007\)). All-cause mortality was 3.2% per year in both groups.

The SPORTIF V trial randomized 3922 participants to receive ximelagatran 36 mg twice daily or adjusted-dose warfarin (INR 2.0 to 3.0).14 SPORTIF V was a double-blind, double-dummy trial. The primary outcome measure of all strokes (ischemic or hemorrhagic) and systemic embolic events was reported in 51 patients (1.6% per year) assigned to ximelagatran and 37 patients (1.2% per year) assigned to warfarin who were followed up for a mean of 24 months \((P=0.13)\). Rates of major bleeding were 3.1% in those receiving adjusted-dose warfarin and 2.4% in those receiving ximelagatran \((P=0.16)\). Intracranial hemorrhage occurred in 0.06% of participants in both groups. When the results of SPORTIF III and V were combined, ximelagatran was associated with a 16% relative risk reduction in the composite outcome measure of all strokes (ischemic or hemorrhagic), systemic embolic events, major bleeding, and death \((P=0.038)\). Although ximelagatran was not approved by the Food and Drug Administration, these trials demonstrate proof of principle that new oral anticoagulants that do not require coagulation monitoring have the potential to replace warfarin for prevention of stroke or systemic embolism in AF.

Dabigatran has been compared with warfarin in a phase II trial of 542 patients with nonrheumatic AF.40 During the 12-week study period, major bleeding was reported in 0.8% of the 472 patients receiving dabigatran and 0% of the 70 patients receiving warfarin. Elevated alanine aminotransferase levels (>3 times the upper limit of normal) were reported in 0.7% of patients receiving dabigatran and 0% of those receiving warfarin. On the basis of the aforementioned results, dabigatran is currently being compared with warfarin (INR 2 to 3) in a phase 3 clinical trial of 14 000 patients (Randomized Evaluation of Long-term anticoagulant therapy Y [RELY]) with nonrheumatic AF who have at least 1 additional risk factor for stroke. In this noninferiority trial, the primary outcome measure is all stroke and systemic thromboembolism.

Anti-Xa Inhibitors
Rivaroxaban is being compared with warfarin (INR 2 to 3) in a phase 3 noninferiority randomized, controlled trial in patients with AF at high risk of stroke (ie, previous ischemic stroke or at least 2 vascular risk factors). Subjects with moderate renal impairment will receive a reduced dose of rivaroxaban. The primary outcome measure is all stroke and systemic thromboembolism.

Apixaban is being compared with warfarin for the prevention of stroke or systemic embolism in patients with AF in a phase 3 noninferiority trial and is being compared with aspirin in AF patients not treated with warfarin in a phase 3 superiority trial. The primary outcome for both studies is all stroke and systemic embolism.

Acute Ischemic Stroke
Current antithrombotic guidelines do not recommend treatment doses of anticoagulants for unselected patients with acute ischemic stroke.31,42 A significant reduction in recurrent ischemic stroke has been reported with heparins in some trials, but the benefit was counterbalanced by a commensurate increase in intracranial bleeding. In other trials, no reduction in ischemic stroke was observed, but there was a consistent increase in intracranial bleeding. Therefore, ischemic stroke is a less promising indication for new anticoagulants. One approach that may deserve consideration is to target individual ischemic stroke subtypes (eg, large-vessel stroke) that may benefit more from anticoagulants than other stroke subtypes.

Conclusions
Anticoagulants in clinical use or under development modulate 1 or more steps in the coagulation pathway. The antithrombotic effect of anticoagulants is mediated by inhibition of thrombin generation, thrombin activity, or both. Factors IIa and Xa are both effective targets for anticoagulants, and to date, there is no evidence that one is better than the other, nor
is there evidence that a different anticoagulant target would be better (in terms of efficacy and safety) than factor IIa or Xa. Given these considerations, improvements of new over established anticoagulants are likely to relate to properties other than their inhibition of a specific activated clotting factor. These properties include freedom from nonhemorrhagic side effects, more favorable pharmacokinetics, a predictable dose response that obviates the need for coagulation monitoring, and more appropriate dose selection for the indication of interest. New parenteral anticoagulants are free of the complications of HIT, can be selected so that they are safe in patients with impaired renal or hepatic function, and can be administered once daily without the need for coagulation monitoring. On the basis of experience with ximelagatran, there is optimism that new effective oral anticoagulants will be developed that do not require anticoagulant monitoring. Dose selection for new anticoagulants is much more rigorous than it was for UFH and LMWH; this factor probably contributed to the improved clinical outcomes with fondaparinux in the OASIS studies and will likely contribute to the advantages of new anticoagulants.

Disclosures
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