New Anticoagulants for Atrial Fibrillation

Magdalena Sobieraj-Teague, M.B.B.S.,¹ Martin O’Donnell, M.B.,¹ and John Eikelboom, M.B.B.S.¹

ABSTRACT

Atrial fibrillation is already the most common clinically significant cardiac arrhythmia and a common cause of stroke. Vitamin K antagonists are very effective for the prevention of cardioembolic stroke but have numerous limitations that limit their uptake in eligible patients with AF and reduce their effectiveness in treated patients. Multiple new anticoagulants are under development as potential replacements for vitamin K antagonists. Most are small synthetic molecules that target factor IIa (e.g., dabigatran etexilate, AZD-0837) or factor Xa (e.g., rivaroxaban, apixaban, betrixaban, DU176b, idrabiotaparinux). These drugs have minimal protein binding and predictable pharmacokinetics that allow fixed dosing without laboratory monitoring and are being compared with vitamin K antagonists or aspirin in phase III clinical trials. A new vitamin K antagonist (ATI-5923) with improved pharmacological properties compared with warfarin is also being evaluated in a phase III trial. None of the new agents have as yet been approved for clinical use.

KEYWORDS: Atrial fibrillation, anticoagulants, stroke, factor Xa inhibitor, direct thrombin inhibitor

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia. The prevalence of AF increases with age, approaching 10% in those >80 years.¹ Because of progressive aging of the population, the worldwide burden of AF is expected to increase dramatically over the next 50 years.¹² The major clinical significance of AF lies in the increased risk of stroke and systemic embolism.³⁴ Compared with ischemic stroke due to other causes, strokes associated with AF tend to be more severe and are associated with a higher mortality, greater disability, and higher health-care costs.⁵⁻⁷

Currently, approved antithrombotic strategies for management of patients with AF include vitamin K antagonists (VKAs) (e.g., warfarin, acenocoumarol, phenprocoumon) and antiplatelet agents, most commonly aspirin.³⁸⁹ VKAs reduce the risk of stroke by 60 to 70% compared with placebo and by 40% compared with aspirin,³⁸⁹ and they are recommended for patients at a moderate to high risk of stroke, which accounts for >70% of patients with AF.¹⁰ Aspirin offers only a modest protection against cardioembolic stroke, reducing the risk by ~20% compared with placebo.¹¹

Despite their established efficacy, VKAs have limitations that reduce their uptake and limit their effectiveness (Table 1). VKAs have a slow onset and offset of action, a narrow therapeutic window, and a metabolism that is affected by diet, drugs, and genetic polymorphisms. Because of their variable dose-response and unpredictable anticoagulant effect, frequent laboratory monitoring and dose adjustments are necessary to ensure therapy is safe and efficacious. The requirement for international normalized ratio (INR) monitoring is inconvenient and costly for patients and health-care systems.
To a large extent, it is the limitations of VKAs that explain why only about half of eligible patients actually receive VKA therapy.10,12–17 Of those who receive VKA treatment, the INR is outside the recommended therapeutic range for 30 to 50% of the time.12,16–20 Reduced time in therapeutic range is associated with poorer outcomes, including an increased risk of ischemic stroke, higher rate of hospitalization, and increased risk of death.18,21,22

The limitations of VKAs have prompted the search for new, more effective, safer, and more convenient anticoagulant alternatives for use in AF. This article focuses on new anticoagulants that are currently under evaluation for use in patients with AF with emphasis on agents that have, or are likely to be, introduced into clinical practice in the near future.

**NEW ANTICOAGULANTS**

Table 2 lists the characteristics of an ideal anticoagulant. Although the main focus of anticoagulant drug development has been on new oral agents to replace VKAs, a novel long-acting parental agent is also being studied. The new anticoagulants are all small synthetic molecules with advantages that include minimal protein binding, predictable pharmacokinetics, and fixed dosing without the need for laboratory monitoring. The main research focus for stroke prevention in AF has been with specific inhibitors of factor Xa and factor IIa (thrombin). Inhibitors of Xa prevent thrombin generation either by directly binding to factor Xa (e.g., rivaroxaban, apixaban, betrixaban, DU176b) or indirectly catalyzing antithrombin inhibition of Xa (e.g., idraparinux, idrabiotaparinux). Oral thrombin inhibitors (e.g., dabigatran etexilate, AZD-0837) bind directly to thrombin, preventing conversion of fibrinogen to fibrin. Direct inhibitors of Xa and IIa act even when these factors are bound to fibrin or prothrombinase, meaning that these agents may have an advantage in preventing thrombus progression. ATI-5923 is a structural analog of warfarin that has improved pharmacological properties due to its small molecular size and esterase pathway metabolism. Table 3 summarizes the pharmacological characteristics of the new anticoagulants.

**ORAL THROMBIN INHIBITORS IN PHASE III TRIALS**

**Dabigatran Etxeilate**

**PHARMACOLOGY**

Dabigatran etexilate, a direct thrombin inhibitor, is an oral prodrug of the active moiety dabigatran, which binds reversibly to both clot-bound and fluid-phase thrombin inhibiting thrombus formation and thrombin-induced platelet activation.23 It has a rapid onset of action of 1 to 2 hours and a half-life of 12 to 17 hours. The bioavailability of dabigatran etexilate is ~7%.24–26 Dabigatran does not induce or inhibit cytochrome p450 (CYP), has a predictable anticoagulant response, and it has a low potential for food or drug interactions, obviating the need for laboratory monitoring.24,25 It is predominantly renally cleared, and a reduced dose is recommended in patients with creatinine clearance between 30 and 50 mL/minute. Clinical studies have excluded patients with creatinine clearance <30 mL/minute. There is no evidence that dabigatran causes liver injury, unlike its predecessor ximelagatran, the now withdrawn oral direct thrombin inhibitor.

### Table 2 Characteristics of an Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Desired Characteristic</th>
<th>Practical Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>No need for overlap with heparin</td>
</tr>
<tr>
<td>Wide therapeutic index</td>
<td>Increased safety</td>
</tr>
<tr>
<td>Minimal side effects</td>
<td>Improved compliance; less monitoring</td>
</tr>
<tr>
<td>Oral formulation</td>
<td>Convenient administration</td>
</tr>
<tr>
<td>Predictable anticoagulant response</td>
<td>Fixed-dose unmonitored treatment</td>
</tr>
<tr>
<td>No food or drug interaction</td>
<td>No need for monitoring</td>
</tr>
<tr>
<td>Availability of antidote</td>
<td>Able to reverse in case of bleeding or urgent surgery</td>
</tr>
<tr>
<td>Cost effective</td>
<td></td>
</tr>
</tbody>
</table>
**Table 3  Pharmacologic Characteristics of Emerging Anticoagulants for Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of Action</th>
<th>Dosing</th>
<th>Action Onset</th>
<th>Bioavailability</th>
<th>Half life</th>
<th>Clearance</th>
<th>Potential Interactions</th>
<th>Reversibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombin Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Direct thrombin inhibitor</td>
<td>Oral once or twice daily</td>
<td>1–2 h</td>
<td>7%</td>
<td>12–17 h</td>
<td>80% renal</td>
<td>P-gp inhibitors, quinidine, amiodarone</td>
<td>No</td>
</tr>
<tr>
<td>AZD 0837</td>
<td>Direct thrombin inhibitor</td>
<td>Oral once or twice daily</td>
<td>1 h</td>
<td>20–50%</td>
<td>9 h</td>
<td>Hepatic</td>
<td>CYP3A4 inhibitors</td>
<td>No</td>
</tr>
<tr>
<td><strong>Factor Xa Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibitor</td>
<td>Oral twice daily</td>
<td>3 h</td>
<td>80%</td>
<td>12 h</td>
<td>25% renal, 55% fecal</td>
<td>CYP3A4 inhibitors</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>Oral once or twice daily</td>
<td>3 h</td>
<td>60–80%</td>
<td>9 h</td>
<td>2/3 renal, 1/3 hepatic</td>
<td>Inhibitors of CYP3A4 and P-gp</td>
<td>No</td>
</tr>
<tr>
<td>DU 176b</td>
<td>Direct factor Xa inhibitor</td>
<td>Oral daily or twice daily</td>
<td>1–2 h</td>
<td>Not reported in humans</td>
<td>9–11 h</td>
<td>Predominantly renal</td>
<td>Not known</td>
<td>No</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Direct factor Xa inhibitor</td>
<td>Oral twice daily</td>
<td>Not reported</td>
<td>50%</td>
<td>19 h</td>
<td>Excreted in bile</td>
<td>Not known</td>
<td>No</td>
</tr>
<tr>
<td>Idraparinux and idrabiotaparinux (via ATIII)</td>
<td>Indirect factor Xa inhibitor</td>
<td>Weekly subcutaneous injection</td>
<td>1–2 h</td>
<td>100%</td>
<td>80–130 h</td>
<td>40–70% renal</td>
<td>Nil reported</td>
<td>Yes, biotinylated form reversed by IV avidin</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATI-5923</td>
<td>VKA</td>
<td>Variable, oral once daily</td>
<td>Not reported</td>
<td>Not reported</td>
<td>136 hour</td>
<td>Hepatobiliary (esterase pathway)</td>
<td>Not reported</td>
<td>Yes, vitamin K</td>
</tr>
</tbody>
</table>

VKA, vitamin K antagonist.
CLINICAL EVALUATION

On the basis of three large trials in venous thromboembolism (VTE) prevention in orthopedic surgery, Rivaroxaban is an oral direct factor Xa inhibitor. It has high oral bioavailability (60 to 80%) and rapid onset of action (3 hours). Rivaroxaban is excreted via two major routes: Two thirds is renally cleared, and a third is cleared via the fecal/biliary route. Approximately a third of the dose is excreted unchanged in the urine. The half-life in healthy young subjects is 5 to 9 hours and increases to 11 to 13 hours in the elderly as a result of decreased renal excretion. Caution is recommended in patients with moderate renal impairment (creatinine clearance [CrCl], 30 to 49 mL/minute), and rivaroxaban is contraindicated in severe renal impairment or severe liver disease. CYP3A4 and P-gp-inhibitors (e.g., ketoconazole, voriconazole, and ritonavir) reduce the metabolism of rivaroxaban, and their concomitant use in patients treated with rivaroxaban is contraindicated. Rivaroxaban has a predictable anticoagulant response negating the need for monitoring.

CLINICAL EVALUATION

Following four large trials of VTE prevention in orthopedic surgery, rivaroxaban, given at a dose of 10 mg once daily, was approved in Europe and Canada for the prevention of VTE in patients undergoing hip and knee replacement surgery.

Two phase III trials in AF are currently underway. ROCKET-AF is a randomized, double-blind, international, noninferiority trial comparing the efficacy and safety of 20 mg once-daily rivaroxaban to warfarin for prevention of stroke and systemic embolism. This study will enroll 14,000 subjects, and results are expected in 2010. The second study is a randomized, double-blind trial comparing a lower dose of rivaroxaban (15 mg once daily or 10 mg once daily for CrCl 30–49 mL/minute) daily to warfarin in 1200 subjects with AF in Japan. Recruitment began in 2007, and results are expected in 2009.

Apixaban

PHARMACOLOGY

Apixaban is an oral, selective, direct factor Xa inhibitor. Apixaban is rapidly absorbed, reaching peak plasma concentration 3 hours postingestion. It has a bioavailability of >50% and a half-life of 12 hours in healthy young volunteers. Apixaban has multiple elimination pathways, of which ~25% is renal and 55% fecal. Cytochrome P450 3A4 and sulfotransferase 1A1 appear to be the major enzymes involved in the metabolism of apixaban. Apixaban has a low potential for drug or food interactions, but potent inhibitors of CYP 3A4 (e.g., clarithromycin, ketoconazole) increase drug concentrations and may be contraindicated.

CLINICAL EVALUATION

The dose of apixaban being evaluated in AF was selected based on the results of phase II dose ranging studies in VTE prevention and treatment.
A phase IIb, randomized, multicenter, partially blind (open-label warfarin) study is currently underway in Japan and is evaluating safety and efficacy of two doses of apixaban (2.5 and 5 mg twice daily) in 250 AF subjects. This study will conclude in 2009.

Two phase III trials evaluating the efficacy and safety of apixaban in AF have been initiated. ARTIST-TOTLE is a randomized, double-blind, noninferiority trial comparing the efficacy and safety of apixaban 5 mg twice daily to warfarin for prevention of stroke and systemic embolism in patients with AF and at least one other risk factor for stroke. This trial aims to enroll 15,000 subjects, and results are expected in 2010.

AVERROES is a randomized, double-blind, superiority trial that compares apixaban, 5 mg twice daily or 2.5 mg twice daily, in those deemed to be at high risk for bleeding (meeting at least two of the following criteria: age ≥80 years, weight ≤60 kg, creatinine ≥133 μmol/L) to aspirin (81 to 324 mg) in patients with AF and at least one additional risk factor for stroke who are unsuitable or unwilling to receive VKA therapy. A total of 5,600 subjects will be enrolled, and results are expected in 2010.

**DU 176b**

**PHARMACOLOGY**

DU 176b is an oral, direct factor Xa inhibitor. DU 176b is rapidly absorbed, reaching peak plasma concentration 2 hours postingestion, has a half-life of 9 to 11 hours, and is predominantly excreted via the kidneys.

**CLINICAL EVALUATION**

A phase II, randomized, double-blind multicenter study (NCT00504556) in 2000 patients with AF and a CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes, and prior stroke or transient ischemic attack [TIA]) score ≥2 has been initiated. The trial is evaluating the safety of four fixed-dose regimens of DU-176b (30 and 60 mg daily, and 30 and 60 mg twice daily) as compared with warfarin over a 3-month period. A second phase II study (NCT00806624) is a randomized, double-blinded study evaluating the safety of two unspecified fixed dosages of DU-176b versus open-label warfarin over a 3-months treatment period in 235 subjects with AF with a CHADS2 score of ≥1.

**OTHER EMERGING ANTICOAGULANTS FOR TREATMENT OF ATRIAL FIBRILLATION**

**NEW ANTICOAGULANTS FOR ATRIAL FIBRILLATION**

**PHARMACOLOGY**

Idraparinux is a subcutaneously administered indirect inhibitor of factor Xa. It has a rapid onset of action (2 hours) and a long half-life of 80 to 130 hours allowing once-weekly dosing. It has 100% bioavailability following subcutaneous injection and a predictable anticoagulant response negating the need for monitoring of anticoagulant effect. It is excreted unchanged via the kidneys, and caution is needed in patients with renal impairment.

Idrabiotaparinux (biotinylated idraparinux) is structurally identical to idraparinux with the addition of a biotin group. The pharmacodynamic and pharmacokinetic properties of idrabiotaparinux are similar to those of idraparinux. However, unlike idraparinux, the anticoagulant activity of idrabiotaparinux can be rapidly reversed by the intravenous infusion of its antidote, Avidin, which in a clinical trial was effective in reversing the anticoagulant effect and well tolerated.

**CLINICAL EVALUATION**

Idraparinux was shown to be effective compared with standard therapy (unfractionated heparin or low molecular weight heparin, followed by a VKA) for the treatment of deep vein thrombosis (DVT) in a large phase III study but was inferior to standard treatment when evaluated for the treatment of pulmonary embolism (PE). A recently completed phase III bioequivalence study in 700 patients demonstrated that idrabiotaparinux was as effective as idraparinux for the treatment of DVT but was associated with a lower rate of major bleeding.

AMADEUS, a phase III randomized trial, compared the efficacy and safety of weekly fixed dose idraparinux with warfarin in 4576 patients with AF at moderate to high risk for stroke. Idraparinux was as effective as warfarin (0.9% versus 1.3%; p < 0.01) but had a higher risk of clinically relevant bleeding (19.7% versus 11.3%; p < 0.0001) with no difference in overall mortality. The trial was terminated early because of the increase in major bleeding. A multicenter, randomized, double-blind, noninferiority trial (BOREALIS-AF) is currently being conducted to compare idrabiotaparinux with warfarin in 9,600 patients with AF and CHADS2 score of ≥2. Results are expected in early 2011.
Table 4  Details of Phase III Randomized Trials Evaluating New Anticoagulants for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Trial Name (Trial Identifier)</th>
<th>Subject no</th>
<th>Design</th>
<th>Agent</th>
<th>Comparator</th>
<th>Population</th>
<th>No. of Sites</th>
<th>Primary Efficacy Outcome</th>
<th>Primary Safety Outcome</th>
<th>Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY (NCT00262600)</td>
<td>18,000</td>
<td>Open label (dabigatran etexilate, doses blinded, noninferiority)</td>
<td>Dabigatran etexilate, 110 or 150 mg twice daily</td>
<td>Warfarin</td>
<td>&gt;18 years old; at least one risk factor for stroke</td>
<td>962 worldwide</td>
<td>Stroke or systemic embolism</td>
<td>Major bleeding</td>
<td>Early 2009</td>
</tr>
<tr>
<td>ROCKET AF (NCT00403767)</td>
<td>14,000</td>
<td>Double blind, noninferiority</td>
<td>Rivaroxaban, 20 mg once daily</td>
<td>Warfarin</td>
<td>&gt;18 years old; history of stroke or systemic embolism or at least two risk factors for stroke</td>
<td>&gt;1100 worldwide</td>
<td>Stroke or systemic embolism</td>
<td>Major or nonmajor clinically relevant bleeding</td>
<td>June 2010</td>
</tr>
<tr>
<td>AVERROES (NCT00494871)</td>
<td>1200</td>
<td>Double blind</td>
<td>Rivaroxaban, 15 mg once daily</td>
<td>Warfarin</td>
<td>&gt;20 years old</td>
<td>&gt;160 in Japan</td>
<td>Stroke or systemic embolism</td>
<td>Major and nonmajor clinically relevant bleeding</td>
<td>December 2009</td>
</tr>
<tr>
<td>ARISTOTLE (NCT00412984)</td>
<td>15,000</td>
<td>Double blind, noninferiority</td>
<td>Apixaban, 5 mg twice daily</td>
<td>Warfarin</td>
<td>&gt;18 years old; AF or flutter; at least one other risk factor for stroke</td>
<td>&gt;1100</td>
<td>Stroke or systemic embolism</td>
<td>Major and nonmajor clinically relevant bleeding</td>
<td>November 2010</td>
</tr>
<tr>
<td>AMADEUS (NCT00412984)</td>
<td>4576</td>
<td>Open label, noninferiority</td>
<td>Idraparinux, 2.5 mg once weekly sc injection</td>
<td>VKA</td>
<td>&gt;18 years old; at least one other risk factor for stroke</td>
<td>84 worldwide</td>
<td>Stroke and systemic embolism</td>
<td>Clinically relevant bleeding</td>
<td>Stopped early</td>
</tr>
<tr>
<td>BOREALIS-AF (NCT00580216)</td>
<td>9,600</td>
<td>Double blind, noninferiority</td>
<td>Idrabiotaparinux, (biotinylated idraparinux), 3.0 mg once-weekly sc injection</td>
<td>Warfarin</td>
<td>&gt;18 years old; at least two other risk factors for stroke</td>
<td>49 worldwide</td>
<td>Stroke and systemic embolism</td>
<td>Bleeding</td>
<td>March 2011</td>
</tr>
<tr>
<td>Engage-AF (NCT00781391)</td>
<td>16,500</td>
<td>Double blind</td>
<td>DU 176b, high- and low-dose regimen</td>
<td>Warfarin</td>
<td>CHADS₂ score ≥2</td>
<td>26 in United States</td>
<td>Stroke and systemic embolism</td>
<td>Major and clinically relevant nonmajor bleeding</td>
<td>March 2011</td>
</tr>
</tbody>
</table>

See text for explanation of CHADS₂ score.
AF, atrial fibrillation; sc, subcutaneous; VKA, vitamin K antagonist.
noncompetitive inhibitor of vitamin K epoxide reductase, but it is metabolized through the esterase pathway rather then the cytochrome P450 pathway. Consequently, ATI-5923 is expected to have less variable metabolism, fewer drug and food interactions, and a more predictable anticoagulant effect than warfarin. It has a half-life of 136 hours and 100% hepatobiliary clearance. In a recent multicenter, phase II, open-label study of 66 patients with AF treated with ATI-5923 or warfarin, the mean time in therapeutic range was 71.5 and 59.3% for ATI-5923- and warfarin-treated patients, respectively, over 3 months ($p = 0.0009$).49

EmbraceAC is a phase II/III multicenter, randomized, stratified, double-blind, parallel group trial evaluating ATI-5923 versus warfarin in patients who require long-term anticoagulation including patients with AF, atrial flutter, prosthetic heart valves, VTE, or a history of myocardial infarction or cardiomyopathy. The goal of this 600-subject study is to assess whether ATI-5923 is superior to warfarin at maintaining INR values within the therapeutic range. The study will conclude in 2009.

AZD 0837
AZD-0837 is a potent oral inhibitor of thrombin being developed as a replacement for ximelagatran, which was effective for prevention of stroke in patients with AF but was withdrawn because of liver toxicity. To date, limited preclinical data have been presented but not published. AZD-0837 is rapidly acting, reaching peak concentration within 1.5 hours postingestion, has bioavailability of 20 to 55%, and a half-life of 9 hours.33 It is cleared via the liver.

Three phase II trials are underway evaluating AZD-0837 in patients with AF. NCT00684307 study is a phase II trial assessing the safety and tolerability of four different dosing regimens of AZD-0837 (450 mg, 200 mg, 300 mg, and 150 mg) compared with warfarin in 1084 patients with AF and one or more additional risk factors for stroke. Study enrollment was completed in mid-2008. NCT00623779 study is a phase II, randomized, open-label trial assessing the safety and tolerability of AZD-0837 for up to 3 months in 150 patients with AF who are unable or unwilling to take warfarin. Study enrollment concluded in December 2008. NCT00645853 study is a phase II, nonrandomized, open-label trial evaluating safety and tolerability of long-term (5 years) AZD-0837 treatment compared with warfarin in >500 AF patients at moderate to high risk of stroke. This study has completed enrollment.

Betrixaban
Betrixaban is an oral factor Xa inhibitor in early stages of clinical development. Betrixaban has an oral bioavail-

ability of 50%, a relatively long half-life of 19 hours, and is predominantly excreted unchanged in bile with minimal renal excretion. It has a low potential for drug-drug interactions.33

EXPLORE Xa, a phase II, randomized, double-blind, multicenter trial has been initiated evaluating safety, tolerability, and pilot efficacy of three blinded doses of betrixaban (40, 60, and 80 mg once daily compared with open-label warfarin in 500 patients with AF who will be treated for at least 3 months.

YM 150
YM 150 is another oral direct factor Xa inhibitor in early stages of clinical development. To date, limited data have been presented but not published. A phase II randomized, double-blind dose-finding study (NCT00448214) assessing the safety and tolerability of YM 150 in comparison to open-label warfarin in subjects with AF completed recruitment in December 2008.

CURRENT STATUS OF ANTICOAGULANT THERAPY FOR ATRIAL FIBRILLATION
VKAs are effective for the prevention of stroke and systemic embolism in patients with AF and are presently the gold standard against which new anticoagulants are being compared. There is substantial scope for improvement in the effectiveness of VKAs by increasing the proportion of eligible patients who receive treatment and by increasing the time in therapeutic range for those who receive treatment.

Of the new anticoagulants being developed as possible replacements for VKAs (Table 4), dabigatran etexilate and rivaroxaban are the most advanced and have already been approved for use to prevent VTE after major orthopedic surgery. Phase III data are available for ximelagatran and idraparinux in AF, but ximelagatran was withdrawn because of liver toxicity, and further development with idraparinux was halted because of increased bleeding. Phase III trials for dabigatran etexilate and rivaroxaban are due to be completed in 2009, apixaban in 2010, and DU-176b and idrabiotaparinux in 2011. If these agents are found to be effective and safe, then approval for clinical use can be expected to follow shortly thereafter.

CLINICAL CHALLENGES IN A FUTURE ERA OF NEW ANTICOAGULANTS
The possible approval of several new anticoagulants for long-term treatment of patients with AF who are at risk of stroke will bring a new set of challenges for physicians (Table 5). Although some of these agents are already approved for short term use in other clinical settings,
Table 5 Challenges in the Clinical Adoption of New Anticoagulants

- No validated tests to measure anticoagulation effect
- No established therapeutic range
- No antidote for most agents
- Assessment of compliance more difficult than for vitamin K antagonists
- Potential for unknown long-term adverse effects
- Balancing cost against efficacy
- Lack of head-to-head studies comparing new agents

REFERENCES

32. Weinz C, Schwartz T, Pleiss U. Metabolism and distribution of (14C) BAY 59-7939—an oral, direct factor Xa inhibitor—in rat, dog and human [abstract 196]. Drug Metab Rev 2004;36(suppl 1)
presented at: American Society of Hematology; 2008; San Francisco, CA

