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
To a large extent, it is the limitations of VKAs that explain why only about half of eligible patients actually receive VKA therapy.\textsuperscript{10,12–17} Of those who receive VKA treatment, the INR is outside the recommended therapeutic range for 30 to 50% of the time.\textsuperscript{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.\textsuperscript{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 been, 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 Etexilate

PHARMACOLOGY

Dabigatran etexilate, a direct thrombin inhibitor, is an oral produg of the active moiety dabigatran, which binds reversibly to both clot-bound and fluid-phase thrombin inhibiting thrombus formation and thrombin-induced platelet activation.\textsuperscript{23} It has a rapid onset of action of 1 to 2 hours and a half-life of 17 to 19 hours. The bioavailability of dabigatran etexilate is ~7%.\textsuperscript{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.\textsuperscript{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.

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Table 1 Limitations of Vitamin K Antagonists

- Slow onset and offset of action
- Narrow therapeutic index
- Variable and unpredictable anticoagulant effect due to
  - Genetic polymorphisms of CYP2C9\textsuperscript{*} and VKORC1\textsuperscript{y} genes
  - Multiple food and drug interactions
  - Concurrent disease
- Need for monitoring of anticoagulant effect and dose adjustments

\*Cytochrome P450 (CYP2C9).
\textsuperscript{y}Vitamin K epoxide reductase complex subunit 1 (VKORC1).

Table 2 Characteristics of an Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Desired Characteristic</th>
<th>Practical Advantage</th>
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<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>Accessibility</td>
</tr>
<tr>
<td>Table 3 Pharmacologic Characteristics of Emerging Anticoagulants for Atrial Fibrillation</td>
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<tr>
<td>----------------------------------</td>
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<tr>
<td></td>
<td>Mode of Action</td>
</tr>
<tr>
<td><strong>Thrombin Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td>AZD 0837</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td><strong>Factor Xa Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>DU 176b</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Idraparinux and idrabiotaparinux</td>
<td>Indirect factor Xa inhibitor (via ATIII)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>ATI-5923</td>
<td>VKA</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, dabigatran etexilate is approved in Europe, the United Kingdom, and Canada for prevention of VTE following hip and knee replacement surgery. The dosage used in these trials was dabigatran etexilate, 150 or 220 mg, once daily.

One phase II trial (Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation [PETRO]) has evaluated dabigatran etexilate in AF. The main objective of this study was to determine the dose-related incidence of bleeding to guide dose selection for the subsequent phase III trial. The 502 patients were randomized to receive blinded doses of 50 mg, 150 mg, or 300 mg of dabigatran etexilate twice daily, alone or in combination with 81 mg or 325 mg of aspirin or open-label warfarin for 12 weeks. Of the patients assigned to dabigatran etexilate, the treatment was withdrawn in 7% due to adverse events. A further 3% had their assigned dose halved because of renal impairment. Concomitant aspirin was stopped in the 300 mg dabigatran etexilate group following four episodes of major hemorrhage (this is the only group in which major bleeding was observed). Two episodes of stroke were reported, both in the dabigatran etexilate 50 mg twice-daily group. Based on the results of PETRO, a 150 mg twice-daily dose as well as a slightly lower 110 mg twice-daily dose was chosen for further evaluation in the phase III trial.

An extended follow-up of participants in PETRO to assess the long-term effects of dabigatran on liver function is ongoing (PETRO-Ex). A large phase III randomized controlled trial (Randomized Evaluation of Long-Term Anticoagulant Therapy [RE-LY]), which completed recruitment of more than 18,000 participants, will determine whether long-term anticoagulation with dabigatran etexilate (110 mg or 150 mg twice daily) is noninferior to open-label warfarin in patients with AF. Final study results are expected in 2009. The RELY-ABLE trial (Long-Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed RE-LY Trial) is an extension of the RE-LY trial, which began in December 2008 and aims to evaluate longer term safety of dabigatran etexilate in 8000 patients.

ORAL FACTOR XA INHIBITORS IN PHASE III TRIALS

Rivaroxaban

PHARMACOLOGY

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 are 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.

Apixaban

PHARMACOLOGY

Apixaban is an oral, selective, direct factor Xa inhibitor. Apixaban is rapidly absorbed, reaching peak plasma concentrations 3 hours postdosing. 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. ARISTOTLE 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.42

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.

Engage-AF is a phase III, randomized, double-blind study assessing safety and efficacy of two different dose regimens of DU-176b (high and low dose) versus warfarin in subjects with AF and a CHADS2 score ≥2 (NCT00781391). The expected duration of the study is 24 months, and results are expected in 2011.

OTHER EMERGING ANTIMICROBIALS FOR TREATMENT OF ATRIAL FIBRILLATION
ATI-5923 is a novel warfarin analogue with improved pharmacological properties. It is a selective,
<table>
<thead>
<tr>
<th>Trial Name</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</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</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>ROCKET AF</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>ROCKET AF</td>
<td>5600</td>
<td>Double blind, superiority</td>
<td>Apixaban, 5 mg twice daily</td>
<td>Aspirin (81–324 mg CHADS2 score ≥1)</td>
<td>&gt;50 years old</td>
<td>Stroke or systemic embolism</td>
<td>Major and nonmajor clinically relevant bleeding</td>
<td>April 2010</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</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>ROCKET AF</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>ROCKET AF</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</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 CHAD2 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 than 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 ($p = 0.0009$).

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 post ingestion, has bioavailability of 20 to 55%, and a half-life of 9 hours. 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.

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,
their long-term use in large numbers of patients with AF will raise questions concerning laboratory monitoring in selected clinical settings, reversal of anticoagulant effect, and long-term safety.

The new anticoagulants generally have a predictable anticoagulant response that allows for convenient, fixed-dose, and unmonitored treatment. However, there will be specific circumstances in which laboratory assessment of the anticoagulant effect will be important for clinical decision making. In the case of apparent treatment failure, assessment of adequacy of anticoagulant effect might help in the assessment of compliance with treatment and decision making about future antithrombotic treatment. There will also be instances where quantifying the anticoagulant effect may be important, such as patients with reduced renal or hepatic function, patients with extremities of body weight, and those receiving concomitant medications that may affect anticoagulant response. Likewise, in patients presenting with bleeding complications, assessment of the intensity of anticoagulation is likely to have management implications. Most of the new anticoagulants in advanced clinical development do not have a defined therapeutic range or established protocols for laboratory monitoring of anticoagulant effect, but these will need to be developed as new anticoagulants become available.

Of the new anticoagulants, only idrabiotaparinux and ATI-5923 have specific reversal agents. For the remainder of the new anticoagulants, there are no clinical data evaluating the effectiveness of coagulation factors or hemostatic agents such as recombinant factor VIIa to reverse their anticoagulant effect, although there is some animal data and anecdotal human experience on the use of such agents. For new anticoagulants with short half-lives, the issue of reversal is less important than for longer acting agents. However, in the setting of major bleeding or emergency surgery, acute reversal of anticoagulant effect will still be important. Finally, given the chronic nature of AF and the often indefinite duration of treatment, long-term safety evaluation of the new anticoagulants will be essential.

**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 agents

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