Emerging therapies for stroke prevention in atrial fibrillation

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Atrial fibrillation (AF) is a major risk factor for stroke. Recent studies show that treatment strategies which combine control of ventricular rate with antithrombotic therapy are as effective as those strategies aimed at restoring sinus rhythm. Current antithrombotic therapy regimens in patients with AF involve chronic anticoagulation with dose-adjusted vitamin K antagonists (VKAs), unless patients have a contraindication to these agents or are at low risk for stroke. AF patients at low risk for stroke may benefit from aspirin. Although VKAs are effective, their use is problematic, highlighting the need for new antithrombotic strategies. This paper will (i) provide an overview of the clinical trials that form the basis for current antithrombotic guidelines in patients with AF, (ii) highlight the limitations of current antithrombotic drugs used for stroke prevention, (iii) review the pharmacology of new antithrombotic drugs under evaluation in AF, (iv) describe ongoing trials with new antiplatelet therapies and idraparinux, and completed studies with ximelagatran in patients with AF, (v) discuss the role of non-pharmacological techniques to reduce the risk of stroke in AF patients, and (vi) provide clinical perspective into the potential role of new antithrombotic drugs in AF.

KEYWORDS
Anticoagulants; Antiplatelets; Atrial fibrillation; Surgery; Vitamin K antagonists; Ximelagatran

Introduction

Patients with atrial fibrillation (AF) may present with symptoms ranging from palpitations to those of haemodynamic compromise. AF accounts for about one-third of hospital admissions for cardiac arrhythmias.\textsuperscript{1} Predisposing cardiac and non-cardiac conditions are found in 90\% of patients with AF.\textsuperscript{2,1} The most common cardiac conditions associated with AF are hypertension, rheumatic mitral valve disease, coronary artery disease, and congestive heart failure (CHF).\textsuperscript{2} Non-cardiac causes include hyperthyroidism, hypoxic pulmonary conditions, surgery, and alcohol intoxication.\textsuperscript{3} The 10\% of patients without a predisposing cause are said to have lone AF.

The most feared complication of AF, however, is thromboembolism, which can present as a stroke or systemic embolic event.\textsuperscript{4} Compared with age-matched controls, patients with non-valvular AF have a two- to seven-fold increased risk of stroke, with the absolute risk of stroke ranging from 1 to \(\sim\)15\% per year, depending on the absence or presence of clinical risk factors.\textsuperscript{5–11} Factors that increase the risk of stroke in AF patients include an age of \(\geq\)75, CHF, hypertension (systolic or diastolic), diabetes mellitus, and past history of a cardioembolic event (transient ischaemic attack, stroke, or systemic embolism).\textsuperscript{10,11} AF is found in up to 20\% of patients presenting with acute ischaemic stroke, and its presence is associated with a two-fold increase in mortality.\textsuperscript{12}
Rate or rhythm control?

A major part of the treatment of patients with AF is the use of measures to reduce the risk of thromboembolism. One obvious question is whether conversion to sinus rhythm lowers the risk of thromboembolism in patients with AF. This question has been addressed recently in four studies, examining whether rate or rhythm control provides more effective protection against thromboembolic events, reduces mortality, and offers better relief of symptoms or improved quality of life in patients of at least 65 years of age with a minimum of one additional risk factor for stroke.13–16 The largest study, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,13 randomized 4060 such patients to rate or rhythm control. Anticoagulation was continued indefinitely in the rate control group and was encouraged in the rhythm control group, but could be stopped if sinus rhythm was maintained for at least 4, but preferably 6 consecutive weeks. The prevalence of sinus rhythm in the rhythm control group was 82, 73, and 63% at 1, 3, and 5 years, respectively, whereas its prevalence in the rate control group was 35% at 5 years.13

The primary outcome measure, overall mortality at 5 years, was 23.8 and 21.3% in the rhythm control and rate control groups, respectively [hazard ratio, 1.15; 95% confidence interval (CI), 0.99–1.24; *P* = 0.08].13 The rates of stroke were 8.9% in the rhythm control group and 7.4% in the rate control group (*P*, 0.2). In both groups, >70% of strokes occurred in patients who had stopped anticoagulant therapy, or in those where the international normalized ratio (INR) was <2.0. This trial, therefore, suggests that there is no increased benefit in terms of mortality or morbidity with aggressive rhythm control relative to rate control; findings that have been confirmed in the three smaller randomized clinical trials.14–16 In summary, therefore, treatment strategies that combine rate control with antithrombotic therapy are as effective as rhythm control in most patients with AF, and that even when rhythm control is employed, reversion to AF is sufficiently common to warrant continued anticoagulation therapy.

Current antithrombotic therapy

On the basis of the available data, the current recommended options for antithrombotic therapy for both primary or secondary prevention in patients with AF are limited to chronic anticoagulation with dose-adjusted vitamin K antagonists (VKAs), such as warfarin, dose-adjusted to an INR of 2.0–3.0, and/or, in patients at low risk for stroke, aspirin.11,17,18 Although aspirin represents a more convenient and safer alternative to VKAs, it does not confer the same degree of protection against stroke as warfarin in patients with AF.19 A meta-analysis of studies comparing aspirin with VKAs reveals a significant, 36% greater risk reduction with VKAs.19 Risk stratification schemes are outlined in Table 1.20–23

Less information is available about the need for anticoagulation in AF patients who spontaneously revert to sinus rhythm. Because up to 50% of such patients will revert to AF, particularly those with underlying cardiac disease, anticoagulation therapy is considered appropriate for most of these patients.16 In young patients without underlying cardiac disease, however, long-term anticoagulation may not be required.11,17,18

Limitations of VKAs

Slow onset of action

As a class, VKAs act as anticoagulants by interfering with the reduction of vitamin K to its 2,3-epoxide form.24–26 Reduced vitamin K is an essential cofactor

<table>
<thead>
<tr>
<th>Risk factor classification</th>
<th>AFIT20</th>
<th>SPAF21,22</th>
<th>CHADS23</th>
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<tbody>
<tr>
<td>Low risk = no risk factors</td>
<td>Moderate risk = age &gt;65 years</td>
<td>Moderate risk = hypertension</td>
<td>1 point for each of the following:</td>
</tr>
<tr>
<td>High risk = prior ischaemic event, hypertension, and DM</td>
<td>High risk = prior ischaemic event, women &gt;75 years, recent CHF or LV 25%, SBP &gt; 160 mmHg</td>
<td>recent CHF, hypertension, age &gt;75 years, or DM</td>
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</tr>
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| NRAF Stroke rate per 100 patient years [% (95% CI)23 |
| Low | 1.5 (0.5–2.8) | 0: 1.9 (1.2–3.0) |
| Moderate | 2.2 (1.1–3.5) | 1: 2.8 (2.0–3.8) |
| High | 5.4 (4.2–6.5) | 2: 4.0 (3.1–5.1) |

AFIT, Atrial Fibrillation Investigators; SPAF, Stroke Prevention in Atrial Fibrillation trial; CHADS2, Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke; DM, diabetes mellitus; CHF, congestive heart failure; LV, left ventricular function; SBP, systolic blood pressure; NRAF, non-rheumatic atrial fibrillation.
for post-translational γ-carboxylation of glutamic acid residues found on the amino terminals of vitamin K-dependent coagulation factors (Figure 1).27–30 Carboxylation of these glutamic acid residues, which generates the so-called Gla domain, endows these clotting factors with the capacity to bind to negatively charged phospholipid surfaces in a calcium-dependent fashion.31,32 Without this modification, the vitamin K-dependent clotting factors are non-functional.29,30 Because the vitamin K-dependent clotting factors are involved in the extrinsic pathway (factor VII), intrinsic pathway (factor IX), and the common pathway of coagulation (factor X and prothrombin), VKAs have profound inhibitory effects on thrombin generation.24 To exert their antithrombotic effect, VKAs must reduce the functional levels of factor X and prothrombin, a process which takes 3–5 days to achieve.24,33 Thus, a slow onset of action is a limitation of these drugs (Table 2).

**Narrow therapeutic window**

Optimal efficacy and safety of VKAs in patients with AF require an INR of 2.0–3.0.17 Subtherapeutic INR values of <2.0 are associated with an increased risk of stroke,34 which also tend to be more debilitating than those that occur in patients whose INR is within the optimal therapeutic range.35 Conversely, the risk of major haemorrhage increases with an INR >3.0.34 Because VKAs have such a narrow therapeutic window, the INR must be monitored regularly to ensure that it remains within the desired range.11,17,18 This is inconvenient for both patients and physicians, and costly for the healthcare system.

**Interactions**

The pharmacodynamics of VKAs are influenced by multiple interactions with concomitantly prescribed drugs.36,37 Variable intake of dietary vitamin K and excessive alcohol consumption can also affect the anticoagulant response to VKAs.37 In addition, genetic variations in cytochrome P450 isoenzymes can influence dosage requirements by enhancing or reducing the metabolism of VKAs.11,24 These features also demand that VKA administration be dose-adjusted according to the INR with continual coagulation monitoring.24 In addition, although vitamin K can be used to reverse the anticoagulant effects of VKAs, complete reversal can take 24 h or longer.11,24 When urgent reversal is needed, plasma, prothrombin concentrates, or recombinant factor VIIa must be given in conjunction with vitamin K.

**Alternative pharmacological approaches**

A reflection, at least in part, of the limitations of VKAs is that at least 50% of eligible patients do not currently receive appropriate anticoagulation therapy.38 Indeed, use of anticoagulant therapy is lowest in elderly patients
with AF, the group at highest risk for stroke. Furthermore, community-based studies indicate that those receiving warfarin have INR values within the therapeutic range less than half of the time. These limitations have highlighted the need for new antithrombotic strategies and have prompted clinical trials with new treatment regimens or novel antithrombotic drugs that have mechanisms of action distinct from that of the VKAs and produce a predictable anticoagulant response, thereby rendering coagulation monitoring unnecessary (Table 2).

Such novel treatment regimens include the combination of two antiplatelet drugs, aspirin plus clopidogrel; idraparinux, a parenteral, long-acting synthetic pentasaccharide; and ximelagatran, an oral direct thrombin inhibitor. In addition, new non-pharmacological methods are becoming available. These include catheter ablation therapy to eliminate the arrhythmogenic foci that trigger AF or to modify atrioventricular (AV) node conduction; the use of implanted cardiac devices capable of atrial sensing and defibrillation; and surgery designed to prevent the conduction of arrhythmogenic impulses from the atria to the AV node.

**Aspirin plus clopidogrel**

As antiplatelet drugs, aspirin and clopidogrel target distinct pathways involved in platelet activation and aggregation. Aspirin irreversibly acetylates and inhibits cyclooxygenase (COX), the enzyme that catalyzes the first step in the synthesis of thromboxane A₂ (TXA₂), a potent platelet agonist (Figure 2). In contrast, clopidogrel irreversibly inhibits P₂Y₁₂, one of the three types of adenosine diphosphate (ADP) receptors found on platelets. Blocking this receptor attenuates platelet aggregation in response to ADP released from activated platelets.

Both drugs are well absorbed from the gastrointestinal tract and are given once daily. While the antiplatelet effect of aspirin is evident within 1–4 h of administration, the inhibitory effects of clopidogrel on platelet aggregation are dose dependent and, unless a loading dose is given, take 4–7 days to reach a steady-state. This delayed effect reflects the fact that clopidogrel itself is inactive and is metabolized to active intermediates. When aspirin is given alone for stroke prevention in patients with AF, the recommended dose is 325 mg once daily. In contrast, when given in combination, the dose of aspirin is usually 81 mg daily, whereas clopidogrel is given once daily at a dose of 75 mg. As both drugs have irreversible effects on platelet aggregation, restoration of normal platelet function upon their withdrawal is delayed for 5–7 days.

The rationale behind the use of combination antiplatelet therapy in patients with AF comes from the European Stroke Prevention Study II (ESPIS II). This trial evaluated a long-acting formulation of dipyridamole, another platelet inhibitor, either alone or in combination with

<table>
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<tr>
<th>Table 2</th>
<th>Comparison of VKAs with ximelagatran and idraparinux</th>
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<tbody>
<tr>
<td><strong>Delivery</strong></td>
<td>VKAs</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Delayed for 3–5 days</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Multiple</td>
</tr>
<tr>
<td><strong>Food interactions</strong></td>
<td>Influenced by vitamin K content in diet</td>
</tr>
<tr>
<td><strong>Need for coagulation monitoring</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Variable and dictated by INR results</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Vitamin K</td>
</tr>
<tr>
<td><strong>Drug-induced elevation in serum transaminases</strong></td>
<td>Rare</td>
</tr>
</tbody>
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INR, international normalized ratio.
aspirin, in 6660 patients who had a previous ischaemic stroke or transient ischaemic attack. Compared with placebo, aspirin and dipiridamole alone reduced the risk of recurrent stroke by 18% ($P = 0.013$) and 16% ($P = 0.04$), respectively, whereas the combination produced a risk reduction of 37% ($P < 0.001$). In a subgroup analysis of patients with AF, there was a trend for an additive benefit with combined antiplatelet therapy.47

In contrast, the recently published Management of Atherothrombosis with Clopidogrel in High-Risk Patients with recent Transient Attack or Ischaemic Stroke (MATCH) trial, which compared clopidogrel alone with the combination of clopidogrel plus aspirin, in 7599 patients who had a previous ischaemic stroke or transient ischaemic attack failed to demonstrate superiority of the dual antiplatelet regimen.48 Compared with clopidogrel alone, aspirin plus clopidogrel did not reduce the rate of recurrent ischaemic stroke over 18 months’ follow-up. Furthermore, the rate of life-threatening bleeding was higher with the combination of aspirin plus clopidogrel than it was with aspirin alone (2.6 and 1.3%, respectively; $P < 0.0001$).49 It is important to note, however, that very few patients with a cardioembolic stroke (<3%) were recruited into this trial.

A trial evaluating an aspirin plus clopidogrel combination has been initiated in patients with AF. The ongoing Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trial uses a partial factorial design and has a target sample size of 14 000 patients.49 Patients are enrolled in one of two studies depending on whether they are candidates for anticoagulant therapy. The ACTIVE-A trial is a superiority trial comparing the combination of aspirin plus clopidogrel with aspirin alone in AF patients with a contraindication to warfarin or who refuse anticoagulant therapy. In patients eligible for anticoagulants, the ACTIVE-W trial, which is powered to demonstrate non-inferiority, compares the combination of aspirin plus clopidogrel with dose-adjusted warfarin (target INR, 2.5; range, 2.0–3.0). In both trials, the primary outcome measure is a composite of all strokes, systemic embolic events, myocardial infarction and cardiovascular deaths, whereas the primary safety outcome measure is major and/or minor bleeding.49

### Idraparinux

Idraparinux, a synthetic analogue of the pentasaccharide sequence in heparin and low-molecular-weight heparin (LMWH) which mediates their interaction with antithrombin, catalyzes the inhibition of factor Xa by antithrombin.50 Unlike heparin or LMWH, idraparinux specifically targets factor Xa as it is too short to bridge antithrombin to thrombin.50,51 As with other heparin derivatives, idraparinux must be given parenterally but, as it has a plasma half-life of 80 h after subcutaneous administration,50,51 it can be administered once weekly.52 The longer half-life of idraparinux relative to fondaparinux, the first generation synthetic pentasaccharide that has a half-life of 17 h,51,53 reflects the fact that idraparinux binds more tightly to antithrombin than the natural pentasaccharide.50,51

Idraparinux also produces a predictable anticoagulant response, thereby obviating the need for coagulation monitoring (Table 2).

The AMADEUS study is an ongoing open-label Phase III trial which will enrol over 7000 patients, comparing subcutaneous idraparinux (given subcutaneously once weekly without coagulation monitoring) with dose-adjusted warfarin (target INR, 2.5; range, 2.0–3.0) in patients with AF and at least one additional risk factor for stroke.54 Designed as a non-inferiority trial, the primary efficacy outcome measure is a composite of all strokes (ischaemic and haemorrhagic) and systemic embolic events. The primary safety endpoint is major and minor bleeding.

### Ximelagatran

Ximelagatran, an oral direct thrombin inhibitor, is a prodrug of melagatran.42 After oral administration, ximelagatran is absorbed from the gastrointestinal tract with a bioavailability of 20% and plasma levels peak at approximately 30 min after drug ingestion.42 Although ximelagatran has no intrinsic anticoagulant activity, it is rapidly transformed to melagatran, a small molecule which targets the active site of thrombin and blocks the enzyme’s catalytic activity. Plasma levels of melagatran peak at 2 h after drug ingestion. The drug has a half-life of 4–5 h in patients and must, therefore, be administered twice daily.42

Melagatran is eliminated primarily via the kidneys.42,55 Consequently, its half-life is prolonged in patients with a creatinine clearance < 30 mL/min.45 However, dosing requirements do not vary with age, gender,56 ethnicity,57 obesity,58 or food59 or alcohol60 intake and, therefore, ximelagatran can be given in fixed doses to most patients. Oral ximelagatran also exhibits a low potential for interaction with other medications.61–65 Ximelagatran produces such a predictable anticoagulant response that coagulation monitoring is unnecessary, making it an attractive candidate to evaluate as an alternative to warfarin in patients with AF.

Two completed Phase III trials have compared ximelagatran (36 mg twice daily), administered without coagulation monitoring, with dose-adjusted warfarin (target INR, 2.5; range, 2.0–3.0) in patients with non-valvular AF and at least one additional risk factor for stroke.56–68a The Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with Non-valvular AF III (SPORTIF III) trial used an open-label design with blinded endpoint adjudication, whereas SPORTIF V was a double-blind, double-dummy trial using a sham INR scheme to maintain blinding.66 Outcome measures were the same in both trials; the primary efficacy outcome was a combination of all strokes (ischaemic and haemorrhagic) and systemic embolic events, whereas the primary safety endpoint was bleeding, which was classified as major or minor. Both studies were designed as non-inferiority trials to demonstrate that ximelagatran was at least as effective and tolerated as warfarin.66
warfarin. On the basis of a mean duration of follow-up of 21 months, and by intention-to-treat analysis, annual rates of stroke and systemic embolic events were 1.6% in the ximelagatran-treated patients and 2.3% in the warfarin group. The rate of major bleeding was similar in the ximelagatran and warfarin groups (1.3 and 1.8% per annum, respectively), but the rate of major plus minor bleeding was significantly lower with ximelagatran than with warfarin (25.5 and 29.5% per annum, respectively; \(P = 0.003\)). All-cause mortality was 3.2% per annum in both treatment groups.67

In the SPORTIF V trial, which enrolled 3922 patients, 51 strokes or systemic embolic events occurred in patients randomized to ximelagatran and in 37 patients receiving dose-adjusted warfarin, equating to event rates of 1.6 and 1.2% per annum, respectively \((P = 0.13)\). Rates of major bleeding were similar in patients receiving either ximelagatran or warfarin (2.4 and 3.1% per annum, respectively; \(P = 0.15\)), whereas the rate of major plus minor bleeding was lower with ximelagatran than with warfarin (37 and 47% per annum, respectively; \(P < 0.001\)). Intracranial haemorrhage occurred in 0.06% of participants in each treatment group.68

In a pre-specified analysis of the pooled data from SPORTIF III and SPORTIF V, the absolute difference in the rate of stroke and systemic embolic events was 0.03% lower in those given ximelagatran relative to those receiving warfarin \((P = 0.94)\). Rates of major bleeding with ximelagatran and warfarin were 1.9 and 2.5% per annum, respectively \((P = 0.054)\). Using a composite endpoint of all strokes, systemic embolic events, major bleeding, and death, ximelagatran produced a 16% relative risk reduction compared with warfarin \((P = 0.038)\).

On the basis of the results of the SPORTIF III and SPORTIF V trials, ximelagatran, with no need for coagulation monitoring, appears to be as effective and safe as dose-adjusted warfarin. It is noteworthy that warfarin control in the two SPORTIF trials was excellent; 81 and 83% of INR values were within the expanded therapeutic INR range of 1.8–3.2 in SPORTIF III and SPORTIF V, respectively.67,68 Thus, these trials compare ximelagatran with near optimally controlled warfarin. In the community, where warfarin is unlikely to be as well controlled, the efficacy and safety of ximelagatran may have a competitive edge.

Non-pharmacological treatments for AF

Non-pharmacological treatment modalities to reduce the risk of stroke in patients with AF include catheter ablation therapy, device therapy, and surgery. These treatments usually are reserved for younger patients with sustained AF whose symptoms are not well controlled with medications, particularly those at high risk for stroke. Surgical procedures also can be considered in AF patients undergoing cardiac surgery for other reasons.

Catheter ablation therapy

Types of ablation therapy for AF include AV node ablation and pulmonary vein isolation, both of which can be undertaken percutaneously. AV node ablation or modification represent palliative procedures that cause complete or high-grade heart block. A permanent pacemaker is needed after AV node ablation. Neither procedure eliminates AF or prevents its recurrence. Consequently, patients undergoing these procedures require long-term anticoagulation for stroke prevention.

Pulmonary vein isolation avoids AV block and therefore permanent pacing. This procedure is based on the observation that AF is often triggered by ectopic rhythm disturbances that arise in the pulmonary veins and can be mapped to small areas of less than a few millimetres.71–74 These areas can then be focally ablated or isolated by means of linear ablation lesions. If successful, this procedure can eliminate AF, thereby obviating the need for anticoagulant therapy.72–74

Device therapy

Implantable cardiac defibrillators (ICDs) can be used to deliver an electric shock to terminate AF. Both atrial and dual chamber defibrillators have been evaluated in AF patients and appear promising therapies in carefully selected patients with recurrent episodes of drug-resistant symptomatic AF.75 The influence of these devices on the risk of systemic embolism is uncertain.

Surgery

The usual surgical procedure for AF treatment is known as the Maze procedure, an operation that can be performed via a midline sternotomy or using minimally invasive techniques.76–79 This procedure involves precise incisions into the right and left atria aimed at surgically isolating the pulmonary veins from the atria, dividing the left and right atria into several dead-end corridors in continuity with the sinus node and removing the left atrial appendage. The goal of this type of surgery is to confine the electrical impulses which trigger AF and prevent them from reaching the AV node. In the partial Maze procedure, incisions are made only in the left atria.80,81 Recent modifications of this type of surgery use alternative energy sources in place of surgical incisions to confine the electrical impulses in the atria. These include radiofrequency,82 cryotherapy,83 and microwave84 ablation techniques.

Conclusions and future directions

Stroke remains the most feared complication of AF. Recent studies have demonstrated that the combination of rate control with anticoagulant therapy is as effective as more costly and difficult strategies aimed at maintaining sinus rhythm. Furthermore, even when rate control strategies are employed, recurrent AF occurs with sufficient frequency to warrant ongoing antithrombotic therapy. Thus, more patients with AF will require antithrombotic therapy. Currently, however, the options for antithrombotic therapy are limited. VKAs are highly effective at reducing the risk of stroke, but these drugs are
difficult to administer because they have a narrow therapeutic window and their activity is influenced by dietary vitamin K intake and by a multitude of drugs. Because of these problems, VKAs are underused in the AF population and, when given, the level of anticoagulation is often outside the therapeutic range, thereby increasing the risk of complications. Therefore, there is clearly a need for new anticoagulants that have similar efficacy, but are easier to administer.

Of the new anticoagulants under investigation in AF, ximelagatran is at the most advanced stage of development. On the basis of the data available to date, ximelagatran is a suitable alternative to VKAs in patients with AF? With oral bioavailability, a predictable anticoagulant response to fixed doses, and no need for coagulation monitoring, ximelagatran is easier to administer than VKAs. The results of the SPORTIF III and V trials indicate that ximelagatran therapy without coagulation monitoring is as effective and as safe as dose-adjusted warfarin in patients with AF who are at risk for stroke. Given these data and its ease of use, what potential barriers prevent ximelagatran from replacing warfarin in patients with AF? Issues that still need to be addressed with ximelagatran include elevation of liver enzymes, its most common side effect; the lack of an antidote; and cost.

On the basis of all the studies evaluating long-term ximelagatran, 7.9% of patients develop an increase in alanine aminotransferase over three times the upper limit of normal. Typically, the increase occurs 1–6 months after initiation of ximelagatran treatment and is usually asymptomatic and reversible. The increase in alanine aminotransferase was associated with a concomitant increase in bilirubin over three times the upper limit of normal in 0.5% of subjects in these studies. Although the observed elevations do not appear to result in permanent hepatic injury, more long-term information is needed. During the initial treatment period with ximelagatran, alanine aminotransferase levels will need to be tested regularly. Although regular testing of hepatic enzymes will be required for all patients treated long-term, ximelagatran obviates the coagulation monitoring and subsequent dose adjustments that are a hallmark of warfarin therapy. The lack of an antidote for ximelagatran is unlikely to be a problem as the drug has a short half-life. Economic analyses are needed to determine whether ximelagatran will offset medical costs of strokes and bleeds when used in the clinical practice setting.

The role of idraparinux in the management of AF will be defined by the ongoing AMADEUS trial. As a parenteral agent, idraparinux is less convenient than orally active anticoagulants. However, once-weekly subcutaneous injections might be preferable to warfarin because idraparinux does not require coagulation monitoring. Idraparinux does not appear to increase serum transaminase levels; consequently, liver function test monitoring is unlikely to be necessary with this agent. There is no antidote for idraparinux; unlike heparin or LMWH, protamine sulfate does not neutralize the anticoagulant effect of idraparinux. Because of the lack of an antidote and its long half-life, reversal will be difficult in idraparinux-treated patients who require urgent medical or surgical interventions, or in those who present with major bleeding. Although recombinant factor VIIa reverses the anticoagulant effects of fondaparinux, this agent is expensive and may have procoagulant effects. Furthermore, repeated doses of factor VIIa may be needed because idraparinux has such a long half-life.

Aspirin is easier to give than VKAs, but it is less effective at reducing the risk of stroke in patients with AF. The combination of aspirin plus clopidogrel is widely used in patients with acute coronary syndromes where it is more effective than aspirin alone. This combination also may be more effective than aspirin in patients with AF. If this is true, aspirin plus clopidogrel may replace aspirin alone in patients with AF at low risk for stroke or in those who are ineligible for anticoagulant therapy. It remains to be established whether aspirin plus clopidogrel is as effective and safe as warfarin in AF patients at higher risk for stroke.

New antithrombotic drugs have the potential to simplify management of patients with AF. Ximelagatran is likely to be the first available alternative to warfarin. Studies with idraparinux are underway and trials evaluating orally active factor Xa inhibitors are likely to follow soon. The availability of these new agents has the potential to increase the use of anticoagulation therapy in patients with AF, thereby reducing morbidity and mortality from stroke.

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References

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