

Novel Antithrombotic Therapies for the Prevention of Stroke in Patients With Atrial Fibrillation

Martin O'Donnell, MB; and Jeffrey I. Weitz, MD

Abstract

Atrial fibrillation (AF), the most common type of arrhythmia in adults, is a major risk factor for stroke. The prevalence of AF increases with age, occurring in 1% of persons <60 years of age and in almost 10% of those >80 years of age. Recent studies show that treatment strategies that combine control of ventricular rate with antithrombotic therapy are as effective as strategies aimed at restoring sinus rhythm. Current antithrombotic therapy regimens in patients with AF involve chronic anticoagulation with dose-adjusted vitamin K antagonists unless patients have a contraindication to these agents or are at low risk for stroke. Patients with AF at low risk for stroke may benefit from aspirin. Although vitamin K antagonists are effective, their use is problematic, highlighting the need for new antithrombotic strategies.

This article will (a) provide an overview of the clinical trials that form the basis for current antithrombotic guidelines in patients with AF, (b) highlight the limitations of current antithrombotic drugs used for stroke prevention, (c) briefly review the pharmacology of new antithrombotic drugs under evaluation in AF, (d) describe ongoing trials with new antiplatelet therapies and idraparinux, and completed studies with ximelagatran in patients with AF, and (e) provide clinical perspective into the potential role of new antithrombotic drugs in AF.

(*Am J Manag Care.* 2004;10:S72-S82)

Atrial fibrillation (AF), the most common arrhythmia in adults, accounts for about one third of hospital admissions for cardiac arrhythmias.¹ The prevalence of AF increases with age, increasing from 1% in those <60 years of age to almost 10% in persons >80 years of age.²⁻⁶ When adjustments are made for age, AF is more common in men than in women.⁷ Thus, the

incidence of AF in men ranges from 0.2% per year for men 30 to 39 years of age to 2.3% per year for men between the ages of 80 and 89 years.^{8,9} In women, the age-adjusted incidence is half that in men.⁷

A predisposing condition is found in 90% of patients with AF.^{10,11} These include cardiac and noncardiac causes. The most common cardiac conditions associated with AF are hypertension, rheumatic mitral valve disease, coronary artery disease, and congestive heart failure (CHF).¹² Noncardiac causes include hyperthyroidism, hypoxic pulmonary conditions, surgery, and alcohol intoxication.¹² The 10% of patients without a predisposing cause are said to have lone AF.

Patients with AF may present with symptoms ranging from palpitations associated with a feeling of malaise to those of hemodynamic compromise. However, the most feared complication of AF is thromboembolism, which can present as a stroke or systemic embolic event.¹² Compared with age-matched controls, patients with nonvalvular AF have a 2- to 7-fold increased risk of stroke with the absolute risk of stroke ranging from 1% to about 5% per year depending on the absence or presence of clinical risk factors.^{3,9,13-15} Factors that increase the risk of stroke include patient age of ≥ 75 years, CHF, hypertension (systolic or diastolic), diabetes mellitus, and past history of a cardioembolic event (transient ischemic attack, stroke, or systemic embolism).^{16,17} In patients presenting with acute ischemic stroke, AF is found in up to 20%, and its presence is associated with a 2-fold increase in mortality.¹⁸

Because of the risk of thromboembolism in patients with AF, a major part of treatment is the use of measures to reduce the

Because of the risk of thromboembolism in patients with AF, a major part of treatment is the use of measures to reduce the

risk of stroke. One obvious question is whether conversion to sinus rhythm lowers the risk of thromboembolism in patients with AF. Recently, 4 studies have addressed this question by examining whether rate control or rhythm control provides more effective protection against thromboembolic events, reduces mortality, and offers better relief of symptoms or improved quality of life.¹⁹⁻²² All 4 of these studies focused mainly on patients >65 years of age with at least 1 risk factor for stroke. The largest study, the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial,¹⁹ 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.¹⁹

The primary end point, 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; $P=.008$). Rates of stroke were 8.9% and 7.4% in the rhythm control and rate control groups, respectively ($P<.2$), and >70% of strokes in both groups occurred in patients who had stopped anticoagulant therapy, or in those whose international normalized ratio (INR) was <2.0.¹⁹ Thus, patients in the AFFIRM trial¹⁹ showed no improvement in mortality or morbidity with aggressive rhythm control; findings that have been confirmed in 3 smaller randomized clinical trials.²⁰⁻²² These data indicate that a strategy that combines rate control with antithrombotic therapy is as effective as rhythm control in most patients with AF.

At present, options for antithrombotic therapy in patients with AF are limited to aspirin and/or vitamin K antagonists, the most common of which is warfarin.¹⁷ However, this is likely to change in the near future as the role of new antithrombotic regimens is established in patients with AF. These novel regimens include a combination

of antiplatelet drugs, aspirin plus clopidogrel, ximelagatran, the first oral direct thrombin inhibitor, and idraparinux, a parenteral, long-acting synthetic pentasaccharide.²³ This paper will (a) provide an overview of the clinical trials that form the basis for current antithrombotic guidelines in patients with AF, (b) highlight the limitations of current antithrombotic drugs, (c) briefly review the pharmacology of new antithrombotic drugs, (d) describe ongoing trials with new antiplatelet therapies and idraparinux, and completed studies with ximelagatran in AF patients, and (e) provide clinical perspective into the potential role of new antithrombotic drugs for patients with AF.

Current Status of Antithrombotic Therapy in AF

Meta-analyses of primary prevention studies indicate that warfarin is more effective than placebo for prevention of stroke and systemic embolism in AF patients (odds ratio [OR], 0.31; 95% CI, 0.19-0.48; $P<.001$), but is associated with a trend for an increased risk of major bleeding (OR, 1.9; 95% CI, 0.89-4.00; $P=.1$).²² Compared with placebo for primary prevention, aspirin also reduces the risk of stroke and systemic embolism (OR, 0.68; 95% CI, 0.46-1.02; $P=.06$), without clear evidence of an increased risk of major bleeding (OR, 0.82; 95% CI, 0.37-1.78; $P>.2$).²² When warfarin is compared with aspirin, warfarin produces a greater reduction in stroke and systemic embolism (OR, 0.66; 95% CI, 0.45-0.99; $P=.04$), without conclusive evidence of more major bleeding (OR, 1.61; 95% CI, 0.75-3.44; $P>.2$).²² For primary prevention, adjusting the dose of warfarin to produce an INR of 2.0 to 3.0 appears to be more effective than low-dose warfarin regimens that target an INR of 1.1 to 1.6 (OR, 0.52; 95% CI, 0.25-1.08; $P=.08$), even when low-dose warfarin is combined with aspirin (OR, 0.44; 95% CI, 0.14-1.39; $P=.16$).²²

Two trials evaluated warfarin or aspirin for secondary prevention, enrolling AF patients who already had suffered a stroke or transient ischemic attack.^{24,25} In the largest trial,²⁴ patients were stratified according to their eligibility for warfarin

Table 1. Annual Risk of Stroke in National Stroke Registry of Atrial Fibrillation (NRAF) Applied to Different Stroke Risk-Stratification Schemes

	AFI	SPAF	CHADS ₂
Risk factor classification	<i>Low risk</i> = no risk factors <i>Moderate risk</i> = age >65 years <i>High risk</i> = prior ischemic event, hypertension and DM	<i>Low risk</i> = no risk factors <i>Moderate risk</i> = hypertension <i>High risk</i> = prior ischemic event, women >75 years, recent CHF or LVF 25%, SBP >160 mm Hg	1 point for each of the following: recent CHF, hypertension, age ≥75 years, or DM 2 points for prior cerebral ischemic event
NRAF stroke rate (%) per 100 patient-years (95% confidence interval)⁶¹			
Low	—	1.5 (0.5-2.8)	0 1.9 (1.2-3.0) 1 2.8 (2.0-3.8)
Moderate	2.2 (1.1-3.5)	3.3 (1.7-5.2)	2 4.0 (3.1-5.1) 3 5.9 (4.6-7.3)
High	5.4 (4.2-6.5)	5.7 (4.4-7.0)	4 8.5 (6.3-11.1) 5 12.5 (8.2-17.5) 6 18.2 (10.5-27.4)

AFI indicates 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; LVF, left ventricular function; SBP, systolic blood pressure.
Source: Reference 61.

treatment. Among warfarin-eligible patients, warfarin was more effective than aspirin (OR, 0.38; 95% CI, 0.22-0.66; *P*=.001), but produced more major bleeding than placebo (OR, 4.1; 95% CI, 1.2-14.0; *P*=.029).²⁴ When aspirin was compared with placebo in warfarin-ineligible patients, there was no difference in efficacy or safety.²⁴ The other secondary prevention trial compared 2 different intensities of warfarin therapy.²⁵ This trial was stopped prematurely because there was more major bleeding in the higher-intensity warfarin group (target INR, 2.2-3.5) than in those randomized to low-intensity warfarin (INR, 1.5-2.1; OR, 14.2; 95% CI, 0.78-2.57; *P*=.07).²⁵ The evidence that higher-intensity warfarin reduced the incidence of stroke was inconclusive (OR, 0.55; 95% CI, 0.5-6.2; *P* >.2).²⁵ Based on all of these observations, it is recommended that for primary or secondary prevention, patients with AF should receive warfarin in doses adjusted to achieve an INR of 2.0 to 3.0, unless they have a contraindication to its use or are at low risk of stroke.¹⁷

Schemes developed for risk stratification are outlined in **Table 1**. Aspirin may be useful in those at low risk of stroke.

Less information is available about the need for anticoagulation in patients with AF who spontaneously convert to sinus rhythm. Because up to 50% of such patients revert to AF, particularly those with underlying cardiac disease, continuing anticoagulation is appropriate for most.²² However, long-term anticoagulation may not be necessary in young patients with no underlying cardiac disease.¹⁷

Although warfarin and aspirin are the mainstays of antithrombotic therapy in AF, both drugs have limitations. These limitations have prompted clinical trials with new antithrombotic drugs.

Limitations of Current Antithrombotic Therapy in AF

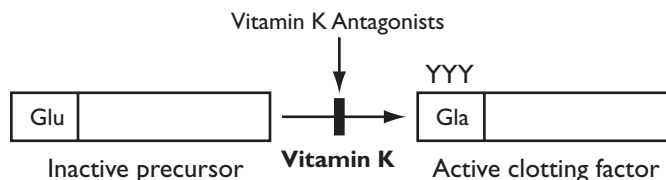
As a class, vitamin K antagonists, such as warfarin, act as anticoagulants by interfer-

ing with the reduction of vitamin K to its 2,3-epoxide form.²⁶⁻²⁸ Reduced vitamin K is an essential cofactor for post-translational γ -carboxylation of glutamine residues found on the amino terminals of vitamin K-dependent coagulation factors (Figure 1).²⁹⁻³² Carboxylation of these glutamine residues, which generates the so-called Gla-domain, endows these clotting factors with the capacity to bind to negatively charged phospholipid surfaces.^{33,34} Without this step, these clotting factors are nonfunctional.^{31,32} Because the vitamin K-dependent clotting factors are involved in the extrinsic (factor VII), intrinsic (factor IX), and common pathways of coagulation (factor X and prothrombin), vitamin K antagonists have profound inhibitory effects on thrombin generation.²⁶ However, the antithrombotic effect of vitamin K antagonists requires reduction in the functional levels of factor X and prothrombin, a process that takes 3 to 5 days to achieve.^{26,35} Thus, a slow onset of action is 1 limitation of these drugs (Table 2).

Another drawback of vitamin K antagonists is their narrow therapeutic window. Optimal efficacy and safety of vitamin K antagonists in patients with AF requires an INR of 2.0 to 3.0.¹⁷ An INR <2.0 is associated with an increased risk of stroke,³⁶ and strokes tend to be more debilitating when the INR is subtherapeutic.³⁷ Conversely, the risk of hemorrhage increases with an INR over 3.0, particularly when the INR exceeds 4.0.³⁶ Because vitamin K antagonists have a narrow therapeutic window, the INR must be monitored to ensure that it remains within the desired range.²⁶ This is both inconvenient for patients and physicians, and costly for the healthcare system.

Dosing of vitamin K antagonists is problematic, a feature that compounds the need for coagulation monitoring.²⁶ Multiple drugs influence the pharmacodynamics of vitamin K antagonists, whereas others such as aspirin or nonsteroidal anti-inflammatory agents increase the risk of bleeding by interfering with platelet function.^{38,39} Variable intake of dietary vitamin K and excessive alcohol intake also can affect the anticoagulant response to vitamin K antagonists.^{38,39} In addition, genetic variations in cytochrome P450 isoenzymes can influence dosage

Figure 1. Mechanism of Action of Vitamin K Antagonists



Vitamin K is essential for post-translational γ -carboxylation of glutamic acid (Glu) residues on vitamin K-dependent clotting factors, thereby generating the Gla-domain. This modification renders these clotting factors functionally active by endowing them with the capacity to bind to negatively charged phospholipid surfaces. By blocking this step, vitamin K antagonists reduce the levels of functional vitamin K-dependent clotting factors.

requirements by enhancing or reducing the metabolism of vitamin K antagonists.²⁶

Although vitamin K can be used to reverse the anticoagulant effects of vitamin K antagonists, complete reversal can take ≥ 24 hours.²⁶ When urgent reversal is needed, plasma, prothrombin concentrates, or recombinant factor VIIa must be given in conjunction with vitamin K.²⁶ It is estimated that up to half of warfarin-eligible patients with AF do not receive anticoagulation therapy, reflecting, at least in part, the limitations of vitamin K antagonists.⁴⁰ Anticoagulant use is lowest in elderly patients, the group that has the highest risk of stroke.⁴¹ Furthermore, community-based studies indicate that those receiving warfarin have INR values within the therapeutic range less than half of the time.⁴² These observations have prompted the development of ximelagatran and idraparinux, new agents that have mechanisms of action distinct from that of vitamin K antagonists and produce such a predictable anticoagulant response that coagulation monitoring is unnecessary (Table 2).

Although it represents a more convenient and safer alternative to vitamin K antagonists, aspirin does not confer the same degree of protection against stroke as warfarin in patients with AF.⁴³ Thus, a meta-analysis of studies comparing aspirin with vitamin K antagonists reveals a significant 36% reduction with vitamin K antagonists.⁴³

Table 2. Comparison of Vitamin K Antagonists with Ximelagatran

Delivery	Vitamin K Antagonist	Ximelagatran	Idraparinux
	Oral	Oral	Subcutaneous
Mechanism of action	Attenuate thrombin generation by reducing levels of vitamin K–dependent clotting factors	Binds thrombin and blocks its activity	Catalyzes factor Xa inhibition by antithrombin
Onset of action	Delayed 3-5 days	Rapid; peak drug levels in 2 hours	Rapid; peak drug levels in 3-6 hours
Drug interactions	Multiple	None	None
Food interactions	Influenced by vitamin K content in diet	None	None
Need for coagulation monitoring	Yes	No	No
Dosing	Variable and dictated by INR results	Fixed	Fixed
Antidote	Vitamin K	None	None
Drug-induced elevation in serum transaminases	Rare	Occurs in about 6% of patients	None

INR indicates international normalized ratio.

One unanswered question is whether aspirin in combination with clopidogrel is more effective than aspirin alone for stroke prevention in patients with AF.

Pharmacology of New Antithrombotic Drugs for AF

New antithrombotic strategies for stroke prevention in patients with AF focus on the use of novel anticoagulants, ximelagatran or idraparinux, or more potent antiplatelet therapy with a combination of aspirin plus clopidogrel.

Ximelagatran. The first oral direct thrombin inhibitor, ximelagatran is a prodrug of melagatran.⁴⁴ Ximelagatran is absorbed from the gastrointestinal tract with bioavailability of 20%.⁴⁴ Plasma levels of ximelagatran peak about 30 minutes after drug ingestion.⁴⁴ Although ximelagatran has no intrinsic anticoagulant activity, it is rapidly transformed to melagatran, a small molecule that targets the

active site of thrombin and blocks the enzyme’s catalytic activity. Plasma levels of melagatran peak at 2 hours, and the drug has a half-life of 4 to 5 hours in patients. Because melagatran has a short half-life, ximelagatran is given twice daily.⁴⁴

Melagatran is primarily eliminated via the kidneys.^{44,45} Consequently, its half-life is prolonged in patients with a creatinine clearance less than 30 mL/min.⁴⁵ In most patients, however, ximelagatran can be given in fixed doses. There are no known drug or food interactions. 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.

Idraparinux. A synthetic analog of the pentasaccharide sequence in heparin and low-molecular-weight heparin (LMWH) that mediates their interaction with antithrom-

bin, idraparinux catalyzes the inhibition of factor Xa by antithrombin.⁴⁶ Idraparinux only targets factor Xa, because, unlike heparin or LMWH, idraparinux is too short to bridge antithrombin to thrombin.^{46,47} Like other heparin derivatives, idraparinux must be given parenterally.^{46,47} After subcutaneous administration, idraparinux has a plasma half-life of 80 hours.⁴⁶ Consequently, the drug can be administered subcutaneously once weekly.⁴⁸ In contrast, fondaparinux, the first-generation synthetic pentasaccharide, has a half-life of 17 hours.^{47,49} The longer half-life of idraparinux relative to fondaparinux reflects the fact that idraparinux binds more tightly to antithrombin because it is more sulfated than the natural pentasaccharide.^{46,47} Idraparinux produces a predictable anticoagulant response, thereby obviating the need for coagulation monitoring (Table 2).

Aspirin Plus Clopidogrel Combination.

As antiplatelet drugs, aspirin and clopidogrel target distinct pathways involved in platelet activation and aggregation.⁵⁰ Aspirin irreversibly acetylates and inhibits cyclooxygenase, the enzyme that catalyzes the first step in the synthesis of thromboxane A₂, a potent platelet agonist (Figure 2).⁵¹ In contrast, clopidogrel irreversibly inhibits P2Y₁₂, 1 of the 3 types of adenosine diphosphate (ADP) receptors found on platelets. Blocking this receptor attenuates platelet aggregation in response to ADP released from activated platelets.⁵²

Both drugs are well absorbed from the gastrointestinal tract and are given once daily.⁵⁰ The antiplatelet effect of aspirin is evident within 1 to 4 hours of administration. In contrast, the inhibitory effects of clopidogrel on platelet aggregation are dose dependent and, unless a loading dose is given, take 4 to 7 days to reach a steady state.⁵² The delayed effect of clopidogrel indicates that the drug must be metabolized to active intermediates; clopidogrel itself is inactive.^{50,52}

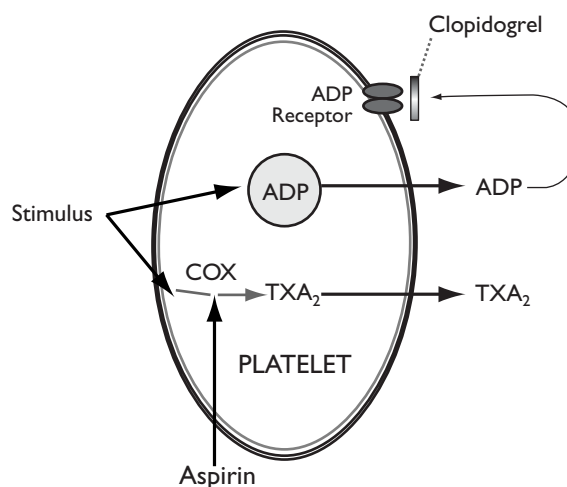
Because both aspirin and clopidogrel have irreversible effects on platelet aggregation, restoration of normal platelet function is delayed for 5 to 7 days when the drugs are stopped. When given in combination, the

dose of aspirin usually is 81 mg daily, whereas clopidogrel is given once daily at a dose of 75 mg.⁵⁰

The rationale behind the use of combination antiplatelet therapy by patients with AF comes from 2 sources.⁵³⁻⁵⁵ First, the European Stroke Prevention Study-II (ESPS II) evaluated a long-acting formulation of dipyridole, another platelet inhibitor, both alone and in combination with aspirin, in 6660 patients who had had an ischemic stroke or transient ischemic attack.⁵³ Compared with placebo, aspirin and dipyridole alone reduced the risk of stroke by 18% ($P=.013$) and 16% ($P=.04$), respectively, whereas the combination produced a risk reduction of 37% ($P<.001$). In a subgroup analysis of patients with AF, there was a trend for an additive benefit with combined antiplatelet therapy.⁵⁵

The combination of aspirin plus clopidogrel was evaluated in the Clopidogrel in Unstable Angina for Prevention of Recurrent Events (CURE) trial.⁵⁴ This study randomized 12 562 patients with non-ST-elevation acute coronary syndromes to aspirin alone or the combination of aspirin plus clopidogrel. Overall, combination antiplatelet therapy

Figure 2. Mechanism of Action of Aspirin and Clopidogrel



By irreversibly acetylating cyclooxygenase (COX), aspirin blocks the synthesis of thromboxane A₂ (TXA₂), a potent platelet agonist released from activated platelets. In contrast, clopidogrel irreversibly inhibits P2Y₁₂, an important adenosine diphosphate (ADP) receptor, thereby attenuating platelet activation in response to released ADP.

py resulted in a 22% risk reduction in recurrent ischemic events and a reduction in stroke ($P < .001$). Compared with aspirin alone, combination antiplatelet treatment was associated with a 1.4-fold increase in major bleeding (2.7% and 3.7%, respectively; $P = .001$), but no significant increase in life-threatening bleeding.⁵⁴ Together these studies suggest that using combinations of antiplatelet drugs with complementary mechanisms of action increases efficacy and only modestly compromises safety.

Clinical Trial With New Antithrombotic Drugs in AF

Two completed phase 3 trials have compared ximelagatran with warfarin in patients with AF.^{56,57} A phase 3 study comparing once-weekly subcutaneous idraparinix with warfarin has recently started.⁵⁸ Likewise, a trial evaluating the aspirin plus clopidogrel combination in patients with AF has also been initiated.⁵⁹

Ximelagatran. Two phase 3 trials have compared unmonitored oral ximelagatran (36 mg twice daily) with dose-adjusted warfarin (target INR, 2.5; range, 2.0-3.0) in patients with nonvalvular AF and at least 1 additional risk factor for stroke.^{56,57} The Stroke Prevention Using the Oral Thrombin Inhibitor in Patients with nonvalvular AF (SPORTIF)-III trial⁵⁶ used an open-label design with blinded end-point adjudication, whereas SPORTIF-V⁵⁷ was a double-blind, double-dummy trial using a sham INR to maintain blinding. Outcome measures were the same in both trials; the primary efficacy outcome was a combination of all strokes (both ischemic and hemorrhagic) and systemic embolic events, whereas the primary safety end point was bleeding, which was classified as major or minor. Both studies were designed as noninferiority trials to demonstrate that ximelagatran was no less effective or safe than warfarin.^{56,57}

In SPORTIF-III, which enrolled 3407 patients, the primary efficacy outcome occurred in 40 subjects randomized to ximelagatran and 56 of those given warfarin for rates of stroke and systemic embolic events of 1.6% and 2.3% per annum, respectively, based on an intention-to-treat analysis and a mean duration of follow-up of 21 months.⁵⁶

The rate of major bleeding was similar with ximelagatran and warfarin (1.3% and 1.8% per annum, respectively), but the rate of major plus minor bleeding was lower with ximelagatran than with warfarin (25.5% and 29.5% per annum, respectively; $P = .003$). All-cause mortality was 3.2% per annum in both treatment groups.⁵⁶

Based on preliminary data from the SPORTIF-V trial, which enrolled 3922 patients, there were 51 strokes or systemic embolic events in patients randomized to ximelagatran and 37 in those given warfarin for event rates of 1.6% and 1.2% per annum, respectively ($P = .13$).⁵⁷ Rates of major bleeding were similar in patients given ximelagatran or warfarin (2.4% and 3.1% per annum, respectively; $P = .16$), whereas the rate of major plus minor bleeding was lower with ximelagatran than with warfarin (37% and 47% per annum, respectively; $P < .001$). Intracranial hemorrhage occurred in 0.06% of participants in each treatment group.⁵⁷

When the results of SPORTIF-III and SPORTIF-V are combined, the absolute difference in the rate of stroke and systemic embolic events is 0.03% lower in those given ximelagatran, a difference that is not significant ($P = .94$).⁵⁷ Rates of major bleeding with ximelagatran and warfarin are 1.9% and 2.5% per year ($P = .054$). Using a composite end point of all strokes, systemic embolic events, major bleeding, and death, ximelagatran produced a 16% relative risk reduction compared with warfarin ($P = .038$).

Based on the results of the SPORTIF-III and SPORTIF-V trials, unmonitored ximelagatran appears to be as effective and safe as dose-adjusted warfarin. It is noteworthy that warfarin control in the 2 SPORTIF trials was excellent; 81% and 83% of INR values were within the expanded therapeutic INR range of 1.8 to 3.2 in SPORTIF-III and SPORTIF-V, respectively.^{56,57} 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 warfarin may not be as good.^{26,42} It is in this setting that ximelagatran may have a competitive edge.

Idraparinix. In an ongoing open-label phase 3 study, unmonitored idraparinix

(given subcutaneously once weekly) is being compared with dose-adjusted warfarin (target INR, 2.5; range, 2.0-3.0) in patients with AF with at least 1 additional risk factor for stroke.⁵⁸ The study is designed as a noninferiority trial.

Aspirin Plus Clopidogrel Combination.

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 14 000.⁵⁹ Patients are enrolled in 1 of 2 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 patients with AF with a contraindication to warfarin or who refuse anticoagulant therapy. In patients eligible for anticoagulants, the ACTIVE-W trial, which is powered for noninferiority, compares the combination of aspirin plus clopidogrel with dose-adjusted warfarin (target INR, 2.5; range, 2.0-3.0). Both trials use the same end points; the primary efficacy end point is a composite of all strokes, systemic embolic events, and cardiovascular deaths, whereas the primary safety end point is bleeding, which is divided into major and minor bleeding.⁵⁹

Conclusions and Future Directions

Stroke is the most feared complication of AF. With recent studies demonstrating that strategies that combine rate control with anticoagulant therapy are as effective as the costly and difficult task of maintaining sinus rhythm, more patients will require antithrombotic therapy. At present, the options for antithrombotic therapy are limited. Vitamin K antagonists 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, vitamin K antagonists 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 do not require monitoring.

Is ximelagatran a suitable alternative to vitamin K antagonists 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 vitamin K antagonists. The results of the SPORTIF-III and -V trials indicate that unmonitored ximelagatran therapy is as effective and 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.

Based on all the studies evaluating long-term ximelagatran, approximately 6% of patients develop an increase in alanine aminotransferase.⁵⁷ The increase in transaminase is associated with a concomitant increase in bilirubin in only 0.4% of subjects. Typically, the increase in transaminases occurs after 6 weeks to 4 months of ximelagatran treatment. Usually, it is asymptomatic, and reversible in 2 to 4 weeks, even if ximelagatran is continued.⁵⁷ Although this complication does not appear to result in long-term hepatic problems, more information is needed. At the very least, patients will require blood tests to monitor levels of alanine aminotransferase. If the level is >5-fold higher than the upper limit of normal, ximelagatran therapy will have to be stopped. Ximelagatran can be continued in those with less marked elevations in alanine aminotransferase, but these patients will need weekly monitoring to ensure that their liver enzymes return to normal. Thus, patients given ximelagatran will require monitoring of liver function tests. In contrast, the coagulation monitoring and consequent dose adjustments that are the hallmark of warfarin therapy are unnecessary with ximelagatran.

Another potential drawback of ximelagatran is the lack of an antidote. This is unlikely to be a problem, however, because the drug has a short half-life.

If cost is the only determinant of value, this may limit the use of ximelagatran. The

drug will be more expensive than warfarin, even factoring the cost of the coagulation monitoring that is required with warfarin. If cost is an issue, ximelagatran may be best reserved for patients who are difficult to control with warfarin, or in those who have limited access to a coagulation laboratory. Further, ximelagatran may have some ability to offset medical costs of strokes and bleeds if used in the clinical practice setting.

The role of idraparinux in the management of AF is uncertain. As a parenteral agent, it is less convenient than orally active anticoagulants. However, once-weekly subcutaneous injections might be useful in patients who are noncompliant with their medications, or in those with impaired absorption from the gastrointestinal tract. 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.⁶⁰ Furthermore, repeated doses of factor VIIa may be needed because idraparinux has such a long half-life. Given these potential limitations, the results of the ongoing clinical trial are needed to establish the potential role of idraparinux in the management of patients with AF.

Aspirin is easier to give than vitamin K antagonists, but it is less effective than vitamin K antagonists 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. If the aspirin plus clopidogrel combination is as effective and safe as warfarin, this combination may prove

simpler to use than ximelagatran, although cost will remain an issue.

New antithrombotic drugs have the potential to simplify management of patients with AF. Ximelagatran is likely to be the first available alternative to warfarin. Although its role in the management of patients with AF remains to be established, ximelagatran has the potential to increase the use of anticoagulation therapy in patients with AF, thereby reducing morbidity and mortality from stroke.

Acknowledgments

Dr O'Donnell is the recipient of a Research Fellowship Award from the Heart and Stroke Foundation of Canada. Dr Weitz is a Career Investigator of the Heart and Stroke Foundation of Canada and holds the Heart and Stroke Foundation of Ontario/J.F. Mustard Chair in Cardiovascular Research and the Canada Research Chair (Tier 1) in Thrombosis from the Government of Canada.

.....
REFERENCES

1. **Bialy D, Lehmann MH, Schumacher DN, Steinman RT, Meissner MD.** Hospitalization for arrhythmias in the United States: importance of atrial fibrillation. *J Am Coll Cardiol.* 1992;19(suppl):41A.
2. **Ostrander LD Jr, Brandt RL, Kjelsberg MO, Epstein FH.** Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan. *Circulation.* 1965;31:888-898.
3. **Flegel KM, Shipley MJ, Rose G.** Risk of stroke in non-rheumatic atrial fibrillation. *Lancet.* 1987;1:526-529.
4. **Wolf PA, Abbott RD, Kannel WB.** Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke.* 1991;22:983-988.
5. **Furberg CD, Psaty BM, Manolio TA, et al.** Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol.* 1994;74:236-241.
6. **Go AS, Hylek EM, Phillips KA, et al.** Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA.* 2001;285:2370-2375.
7. **Psaty BM, Manolio TA, Kuller LH, et al.** Incidence of and risk factors for atrial fibrillation in older adults. *Circulation.* 1997;96:2455-2461.
8. **Wolf PA, Abbott RD, Kannel WB.** Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med.* 1987;147:1561-1564.
9. **Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE.** The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med.* 1995;98:476-484.
10. **Brand FN, Abbott RD, Kannel WB, Wolf PA.** Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham study. *JAMA.* 1985;254:3449-3453.

11. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med*. 1987;317:669-674.
12. Snow V, Weiss KB, LeFevre M, Kannel WB. Management of newly detected atrial fibrillation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med*. 2003;139:1009-1017.
13. Wolf PA, Dawber TR, Thomas HE Jr, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology*. 1978;28:973-977.
14. Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation*. 1999;99:3028-3035.
15. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol*. 2000;35:183-187.
16. van Walraven C, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med*. 2003;163:936-943.
17. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest*. 2001;119:194S-206S.
18. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke*. 1996;27:1765-1769.
19. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825-1833.
20. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834-1840.
21. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789-1794.
22. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med*. 2003;139:1018-1033.
23. Weitz JI, Hirsh J. New anticoagulant drugs. *Chest*. 2001;119(1 suppl):95S-107S.
24. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342:1255-1262.
25. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolic Secondary Prevention Cooperative Study Group. *Stroke*. 2000;31:817-821.
26. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimum therapeutic range. *Chest*. 2001;119(suppl):8S-21S.
27. Whitton DS, Sadowski JA, Suttie JW. Mechanisms of coumarin action: significance of vitamin K epoxide reductase inhibition. *Biochemistry*. 1978;17:1371-1377.
28. Fasco MJ, Hildebrandt EF, Suttie JW. Evidence that warfarin anticoagulant action involves two distinct reductase activities. *J Biol Chem*. 1982;257:11210-11212.
29. Stenflo J, Fernlund P, Egan W, Roepstorff P. Vitamin K dependent modifications of glutamic acid residues in prothrombin. *Proc Natl Acad Sci USA*. 1974;71:2730-2733.
30. Nelsestuen GL, Zytovicz TH, Howard JB. The mode of action of vitamin K. Identification of gamma-carboxyglutamic acid as a component of prothrombin. *J Biol Chem*. 1974;249:6347-6350.
31. Friedman PA, Rosenberg RD, Hauschka PV, Fitz-James A. A spectrum of partially carboxylated prothrombins in the plasmas of coumarin-treated patients. *Biochim Biophys Acta*. 1977;494:271-276.
32. Malhotra OP, Nesheim ME, Mann KG. The kinetics of activation of normal and gamma-carboxyglutamic acid-deficient prothrombins. *J Biol Chem*. 1985;260:279-287.
33. Nelsestuen GL. Role of gamma-carboxyglutamic acid. An unusual protein transition required for the calcium-dependent binding of prothrombin to phospholipid. *J Biol Chem*. 1976;251:5648-5656.
34. Borowski M, Furie BC, Bauminger S, Furie B. Prothrombin requires two sequential metal-dependent conformational transitions to bind phospholipid. Conformation-specific antibodies directed against the phospholipid-binding site on prothrombin. *J Biol Chem*. 1986;261:14969-14975.
35. Wessler S, Gitel SN. Warfarin. From bedside to bench. *N Engl J Med*. 1984;311:645-652.
36. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med*. 1996;335:540-546.
37. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-1026.
38. Hylek E, Heiman H, Skates S, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA*. 1998;279:657-662.
39. Wells PS, Holbrook AM, Crowther MR, Hirsch J. Interactions of warfarin with drugs and food. *Ann Intern Med*. 1994;121:676-683.
40. Perez I, Melbourn A, Kalra L. Use of antithrombotic measures for stroke prevention in atrial fibrillation. *Heart*. 1999;82:570-574.
41. White RH, McBurnie MA, Manolio T, et al. Oral anticoagulation in patients with atrial fibrillation: adherence with guidelines in an elderly cohort. *Am J Med*. 1999;106:165-171.
42. Samsa GP, Matchar DB, Goldstein LB, et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med*. 2000;160:967-973.
43. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131:492-501.
44. Gustafsson D, Nystrom J, Carlsson S, et al. The direct thrombin inhibitor melagatran and its oral prodrug H 376/95: intestinal absorption properties, biochemical and pharmacodynamic effects. *Thromb Res*. 2001;101:171-181.

45. Eriksson UG, Gustafsson D, Mandema J, et al. Pharmacokinetics of H376/95, in orthopedic surgery patients treated to prevent deep vein thrombosis and pulmonary embolism. *Blood*. 2000;96:93B.
46. Herbert JM, Heralut JP, Bernat A, et al. Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting synthetic pentasaccharide. *Blood*. 1998;91:4197-4205.
47. Koopman MM, Buller HR. Short- and long-acting synthetic pentasaccharides. *J Intern Med*. 2003;254:335-342.
48. PERSIST Investigators. A novel long-acting synthetic factor Xa inhibitor (idraparinux sodium) to replace warfarin for secondary prevention in DVT: a phase II evaluation. *J Thromb Haemost*. 2004;2:47-53.
49. Samama MM, Gerotziapas GT. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb Res*. 2003;109:1-11.
50. Patrono C, Collier B, Dalen JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side-effects. *Chest*. 2001;119:39S-63S.
51. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med*. 1994;330:1287-1294.
52. Savi P, Heilmann E, Nurden P, et al. Clopidogrel: an antithrombotic drug acting on the ADP-dependent activation pathway of human platelets. *Clin Appl Thromb Hemost*. 1996;2:35-42.
53. Diener HC, Forbes C, Riekkinen PJ, et al. European Stroke Prevention Study II: efficacy and safety data. *J Neurol Sci*. 1997;151:S27-S61.
54. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
55. Diener HC, Lowenthal A. Letter to the Editor. *J Neurol Sci*. 1997;153:112.
56. Olsson SB; Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.
57. SPORTIF V. American Heart Association Scientific Sessions 2003. *Circulation*. 2003;108:E9051.
58. A safety and efficacy trial evaluating the use of SanOrg34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation. Available at: <http://clinicaltrials.gov/show/NCT00070655>. Accessed: January 16, 2004.
59. Connolly SJ. Preventing stroke in patients with atrial fibrillation: current treatments and new concepts. *Am Heart J*. 2003;145:418-423.
60. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation*. 2002;106:2550-2554.
61. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.