New Possibilities in Anticoagulant Management of Atrial Fibrillation

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Warfarin therapy achieving an International Normalized Ratio between 2 and 3 has been shown to be effective in preventing stroke. However, warfarin administration is problematic because of its variable dose, interaction with numerous foods and drugs, narrow therapeutic range, need for chronic anticoagulation monitoring, and long onset and offset of action, which all contribute to the significant underuse of warfarin in patients with atrial fibrillation at risk for stroke despite clear indication for its use. This has led to new approaches. Studies with idraparinux (AMADEUS), a factor 10a inhibitor, and with aspirin and clopidogrel (ACTIVE), both platelet inhibitors, are on-going. Studies with ximelagatran (Stroke Prevention by Oral Thrombin Inhibition in Atrial Fibrillation [SPORTIF] trials III and V), an oral direct thrombin inhibitor, have been completed. They compared ximelagatran with warfarin in patients with nonvalvular atrial fibrillation at risk for stroke. The studies demonstrated that ximelagatran is not inferior to warfarin. Moreover, ximelagatran has rapid onset and offset of action, fixed oral dosing without the need for anticoagulation monitoring, low potential for food and drug interactions, and a therapeutic margin wider than that of warfarin. We anticipate further studies to demonstrate definitively that the small percentage of patients (0.5%) with elevation of both alanine aminotransferase (ALT) and bilirubin levels can be managed safely, thereby making ximelagatran a promising option for preventing thromboembolism in patients with atrial fibrillation at risk for stroke.

[Rev Cardiovasc Med. *2004;5(suppl 5):S30-S38*]

Key words: Anticoagulation • Atrial fibrillation • Stroke • Systemic embolism • Warfarin • Ximelagatran

It is estimated that atrial fibrillation currently affects about 2.4 million Americans, and that by 2050, the number will be about 5.6 million.[1] Two principal clinical problems are associated with atrial fibrillation.[2] One is that if the ventricular response rate is not adequately controlled, patients may develop a tachycardia-mediated cardiomyopathy. The other problem is the risk of stroke. Patients with atrial fibrillation have a fivefold increased risk of stroke compared

Table 1
Atrial Fibrillation and Stroke: 30-Year Study from the Framingham Study Patient Cohort

Age group	Previous AF, %	Stroke per 1000 pyO	Stroke per 1000 pyAF	Incidence Density Ratio	Population Attributable Risk, %*
60-69	1.8	4.5	21.2	4.7	7.3
70-79	4.7	9.0	48.9	5.4	16.5
80-89	10.2	14.3	71.4	5.0	30.8

*Adjusted for blood pressure.
AF, atrial fibrillation; pyAF, patient years in patients with atrial fibrillation; pyO, patient years in patients without atrial fibrillation.
Data from Wolf et al.[3]

with those in sinus rhythm (Table 1).[3] Moreover, as patients get older, the prevalence of atrial fibrillation increases, roughly doubling with each decade beginning with the fifth decade; so 2%-3% of people in their 60s, 5%-6% of people in their 70s, and 8%-10% of people in their 80s have atrial fibrillation (Table 1).[1,3,4] Moreover, the population attributable risk also increases with age (Table 1), so almost one-third of patients in their 80s who present with a stroke have atrial fibrillation.[3] There is also a 14.7% to 58% incidence of so-called silent strokes, ie, strokes in which there are no manifestations of motor or sensory deficit, in patients with atrial fibrillation at risk for stroke, but untreated with warfarin.[5-8] Such strokes are associated with senile dementia or Alzheimer's disease. Clearly, prevention of stroke in patients with atrial fibrillation is a key management goal.

Risk Factors for Stroke

A series of primary prevention trials comparing warfarin versus placebo in patients with atrial fibrillation have demonstrated that warfarin therapy provides a 68% stroke risk reduction on an intention-to-treat analysis,[9] and an 83% risk reduction on an on-treatment analysis.[10] The latter essentially means that if warfarin is given to a patient with atrial fibrillation, and an International Normalized Ratio (INR) in the therapeutic range (2-3, target 2.5) is maintained, that patient's risk of stroke is reduced to the same level as the risk that would be present if he or she was in sinus rhythm. But as we learned from the Atrial Fibrillation Investigators analysis,[9] not all patients with atrial fibrillation have the same risk for stroke. Risk for stroke may be stratified by several factors (Table 2), including a prior thromboembolic stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure or poor left ventricular function, and age ≥ 65.[11] It may further be stratified into mild, moderate, and severe categories.[11] Other risks, such as coronary artery disease, gender, thyrotoxicosis, rheumatic mitral valve disease, and hypertrophic cardiomyopathy, are important to consider.[11] Importantly, a meta-analysis of data from several clinical trials indicates that paroxysmal (intermittent) atrial fibrillation carries the same risk for stroke as persistent or permanent atrial fibrillation.[12] It is thought that patients under age 65 with lone atrial fibrillation, ie, atrial fibrillation in the absence of structural heart disease, have a very low risk for stroke such that when weighing the benefits and risks of warfarin therapy per se, there is no benefit to treatment with warfarin.[11,13] However, the opposite is true in the presence of risk factors for stroke.[11,13]

How does one translate these risks derived from group data to the individual patient? There are now schemes available to do this. The CHADS2 score helps predict stroke risk in patients with atrial fibrillation using risk factors of congestive heart failure, hypertension, age ≥ 75, diabetes, and history of a prior stroke or transient ischemic attack.[14] Also, the Framingham study has developed an absolute assessment of stroke risk (a stroke risk score) derived from the Framingham patient cohort of individuals with new-onset atrial fibrillation. It is based on the following five risk factors: advancing age, female gender, increasing systolic blood pressure, prior stroke or transient ischemic attack, and diabetes mellitus.[15] These schemes should be helpful in risk stratification for stroke in individual patients with atrial fibrillation.

Table 2
Atrial Fibrillation: Risk Factors for Stroke

	Relative Risk
Prior stroke or TIA	2.5
Hypertension	1.6
Diabetes	1.7
CHF	1.4
Age ≥ 65 years	1.4 every 10 years
Poor LV function	2.0

CHF, congestive heart failure; LV, left ventricular; TIA, transient ischemic attack.
Data from Atrial Fibrillation Investigators.[9]

Oral Anticoagulant Therapy

Warfarin is very effective as prophylaxis against stroke in patients with atrial fibrillation. However, its use is associated with well-recognized problems[16,17] that contribute to management difficulty as well as its underuse. First is the delayed onset and offset of action. For instance, it may take a mean of 5 weeks to establish a stable dose of warfarin to achieve and maintain an INR in the therapeutic range (2-3); if the INR gets inappropriately high, reversibility of warfarin's effect is slow. Moreover, the dose response to warfarin is unpredictable, so that the appropriate dose varies widely from patient to patient. Also, there are numerous drug–drug interactions and drug–food interactions that often confound management with warfarin. All this occurs in the face of warfarin's well-recognized narrow therapeutic range. Thus, it is no surprise that anticoagulation monitoring for patients taking warfarin is mandatory and problematic. Moreover, these problems are among the reasons study after study has demonstrated that warfarin is underused in patients with atrial fibrillation who do not have a relative or absolute contraindication to warfarin, but who do have stroke risks.[18-20] In addition, it is the elderly who get warfarin least, but need it most.[19]

Several factors may be involved in the apparent underuse of warfarin among elderly patients. In addition to the problems with warfarin use cited earlier, there is concern of additional risk of bleeding,[11] particularly as a result of falls, frailty, or accidental overdosing. Although the relative risk of ischemic stroke increases by 1.4 per decade beginning at age 65 years, so does the relative risk of intracranial bleeding while taking warfarin.[21] This had led to a recommendation in the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines[11] for a lower INR target (range 1.6-2.5, target 2.0) for the primary prevention of ischemic stroke and systemic embolism in patients older than 75 years who are considered at increased risk of bleeding complications, but have no frank contraindications to oral anticoagulant therapy (a class II recommendation). However, it is important to emphasize that because the base rate of ischemic stroke is considerably greater than the risk of intracranial bleeding, the risk of ischemic stroke in the absence of warfarin therapy is considerably greater than the risk of intracranial bleeding while receiving warfarin.[21] An additional perspective is that although there is no increased therapeutic benefit associated with an INR > 3, an increased risk for bleeding does not occur until the INR reaches 3.9-4.0.[21,22]

Finally, of patients who do take warfarin, less than two-thirds have an INR in the therapeutic range at any one time and, most often, less than half the patients have an INR in the therapeutic range at any given time.[11,23] The latter is quite important because when the INR falls below 2, there is a very steep rise in the odds ratio for stroke, so that the risk of stroke doubles with an INR of 1.7.[24]

Aspirin in Patients with Atrial Fibrillation at Risk for Stroke

Among the several studies that have compared aspirin with warfarin, it is clear that warfarin is far superior to aspirin in diminishing the risk of stroke.[11,25] Moreover, of the several studies that have compared aspirin with placebo, only the Stroke Prevention in Atrial Fibrillation (SPAF) I trial demonstrated a relative risk reduction in stroke with aspirin.[26] That study not only is an outlier, driving the meta-analyses of the several trials comparing aspirin with placebo, but the data from the SPAF I trial demonstrate an internal inconsistency between patients in group I (patients eligible for warfarin) and patients in group II (patients with a relative or absolute contraindication to warfarin), both of which compared aspirin with placebo (Figure 1). Analysis of these data throws yet more doubt on the efficacy of aspirin as an effective treatment for prevention of stroke in patients with atrial fibrillation.[27] For the most part, this is reflected in the guidelines regarding the type of anticoagulation therapy that is recommended for patients with atrial fibrillation who are at risk for stroke.[11] Moreover, not only do we know that aspirin is a poor second-best to warfarin in preventing stroke in patients with atrial fibrillation at risk for stroke, but, also, should a stroke occur on aspirin, it is usually more severe, and is associated both with a higher in-hospital mortality and 30-day mortality when compared with warfarin therapy that maintains an INR in the therapeutic range.[22] In short, the data clearly indicate that aspirin not only is insufficiently effective in preventing stroke compared with warfarin, but, also, should a stroke occur, its consequences are likely to be far more severe.

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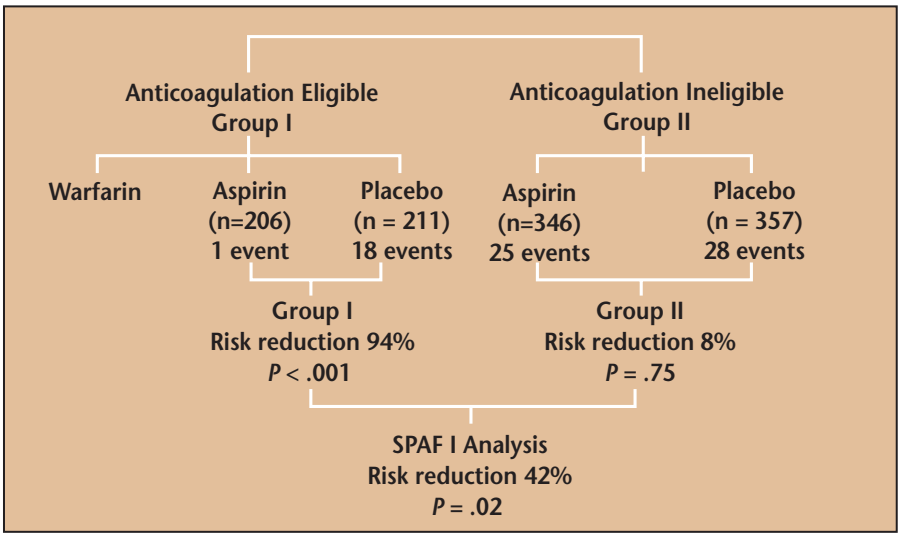

Figure 1. *Aspirin eligible atrial fibrillation patients: outcome of patients randomized to aspirin versus placebo in group I of the SPAF I trial. In group I, there was only one event (stroke) in patients receiving aspirin versus 18 events in the placebo group. This was highly statistically significant. However, in group II, there were 25 events in patients receiving aspirin versus 28 events in patients receiving placebo. This was not statistically significant. Thus, there was internal inconsistency. When the data from both groups were combined, the data were significant, but this was driven by what appears to be the outlier data from group I. See text for discussion. Modified from SPAF Investigators.*[27]

Does Maintenance of Sinus Rhythm in Patients With a History of Atrial Fibrillation and Risk Factors for Stroke Eliminate the Risk of Stroke?

One of the putative advantages of pursuing a rhythm control strategy (ie, attempting to maintain sinus rhythm) in patients with atrial fibrillation at risk for stroke is that with the absence of atrial fibrillation, the cause of clot formation in the left atrium is eliminated. Therefore, it has been a clinical assumption that there is no longer any need for oral anticoagulation with warfarin. Several factors have clearly affected this assumption. First are the data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial examining the relationship of ischemic stroke to INR and the presence of atrial fibrillation.[28] Of note, there was no significant difference in the incidence of stroke in the rate control versus the rhythm control arms (Table 3). However, of the strokes that occurred in the rhythm control arm, 57% occurred in patients not taking warfarin, and 22% occurred in patients whose INR was less than 2. It is probable that these data are in part explained by an important incidence of so-called silent or asymptomatic atrial fibrillation.[29-32] There is now a large body of evidence indicating that there is an important incidence of asymptomatic atrial fibrillation in patients with a history of atrial fibrillation who were thought to be in sinus rhythm. For instance, in a recent study by Israel and colleagues[32] in patients with a history of atrial fibrillation in whom atrial fibrillation recurred, in more than one-third (38%), the atrial fibrillation was both asymptomatic and of greater than 48 hours duration. Moreover, 16% of the patients developed asymptomatic atrial fibrillation of greater than 48 hours duration, even after documentation of freedom from atrial fibrillation for 3 months. Data such as those from the AFFIRM trial and from the several trials demonstrating asymptomatic atrial fibrillation have led to the widely accepted conclusion that patients with atrial fibrillation and risk factors for stroke should receive anticoagulation indefinitely, even when sinus rhythm appears to be restored and maintained.[28] The point is that success rates of maintaining continuous sinus rhythm in patients with a history of atrial fibrillation are often grossly overestimated, with potential serious consequences for the patient.

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New Antithrombotics for Atrial Fibrillation

Because of the well-accepted need for clinically effective anticoagulation in patients with atrial fibrillation at risk for stroke, and because of the limitations of warfarin therapy outlined earlier, until now, there has been an unmet need to provide still better oral anticoagulants. Presently, there are three trials comparing warfarin with new approaches to prevent stroke in patients with atrial fibrillation. Two are ongoing: The AMADEUS trial[33] is a multicenter, randomized open-label, noninferiority study comparing warfarin with idraparinux (a pentasaccharide that is a factor Xa–specific blocker) administered subcutaneously on a weekly basis. The other is the ACTIVE (Atrial fibrillation Clopidogrel Trial

with Irbesartan for prevention of Vascular Events) trial[34] comparing the antiplatelet agents aspirin plus clopidogrel with either warfarin (ACTIVE W: warfarin therapy indicated) or with aspirin alone (ACTIVE A: warfarin therapy not indicated) in patients with atrial fibrillation at risk for stroke. A third series of trials, Stroke Prevention by Oral Thrombin Inhibition in Atrial Fibrillation (SPORTIF) has been completed.[35,36] SPORTIF compared ximelagatran, an oral direct thrombin inhibitor, with warfarin in patients with nonvalvular atrial fibrillation and one or more additional risk factors for stroke.

Table 3
AFFIRM Trial: Relationship of Ischemic Stroke, International Normalized Ratio (INR), and Atrial Fibrillation (AF)

	Rate Control n (%)	Rhythm Control n (%)
Ischemic stroke	77 (5.5)	80 (7.1)
INR ≥ 2.0	23 (31)	16 (21)
INR < 2.0	27 (36)	17 (22)
Not taking warfarin	25 (33)	44 (57)
AF at time of event	42 (69)	25 (37)

Event rates derived from Kaplan-Meier analysis; $P = .79$.
Data from Wyse et al.[28]

The SPORTIF Trials

Ximelagatran

Ximelagatran is a prodrug that is rapidly absorbed and converted to melagatran, which is a potent, direct, reversible thrombin inhibitor that binds both free and clot-bound thrombin.[37-40] The drug is characterized by rapid onset and offset of action; its peak concentration (C_{max}) is at about 2 hours, and its half-life is 4-5 hours, similar to that of low molecular weight heparins. Ximelagatran is about 80% renally excreted and is not metabolized, and there is no interaction with the cytochrome P-450 enzyme system. The drug has low plasma protein binding and a low potential for food/drug/alcohol interactions. The only interaction presently identified is an almost twofold increase in the absorption of ximelagatran with erythromycin.[41] In retrospective studies with patients in all the ximelagatran trials who were also taking both ximelagatran and erythromycin (just under 300 patients), there was no difference in outcome or incidence of bleeding in these patients compared with other patients taking ximelagatran or with patients taking warfarin.[41] Moreover, this just-under-twofold increase is well within the variability of absorption (three- to fourfold) of ximelagatran in people taking 36 mg twice daily. Ximelagatran has fixed dosing, a predictable response, requires no coagulation monitoring, and has had no age, race, or gender differences observed to date. Finally, clinical data demonstrate efficacy with twice-daily dosing.

SPORTIF Design

The SPORTIF trials compared fixed-dose ximelagatran (36 mg twice daily) with adjusted-dose warfarin (INR 2-3) in patients with nonvalvular atrial fibrillation and one or more additional risk factors for stroke.[35,36] The objective was to establish whether ximelagatran was noninferior to warfarin within a prespecified absolute difference of 2% per year for the difference in rates of primary events. SPORTIF III, a randomized, but open-label trial in 3,407 patients, was performed in 23 nations, mostly in Europe and the Pacific Rim. SPORTIF V was performed in 3,922 patients in the United States and Canada, and was a double-blind, double-dummy study with appropriate sham INRs performed. The design of both trials was the same and included patients with atrial fibrillation and one or more additional risk factors for stroke. Treatment allocation was randomized, and there were multiple levels of blinded event assessment. Minimal exposure was 12 months per patient, with at least 4000 patient-years of follow-up in aggregate, and an accumulation of 80 primary events. The primary outcome was prevention of all strokes (ischemic or hemorrhagic) and systemic embolic events based on an intention-to-treat analysis. The secondary end point was the same as the primary end point except that it was an on-treatment analysis. Other end points included safety, and a prespecified pooled analysis of the SPORTIF III and V trials.

SPORTIF Patient Characteristics

The SPORTIF III and V trials were very well balanced for stroke risk factors, including prior stroke/transient ischemic attack, age greater than or equal to 75 years, left ventricular dysfunction or congestive heart failure, hypertension, age greater than or equal to 65 years with coronary artery disease, or age greater than or equal to 65 years with diabetes (Figure 2). In SPORTIF III, 70% of the patients on warfarin and 68% of the patients on ximela-

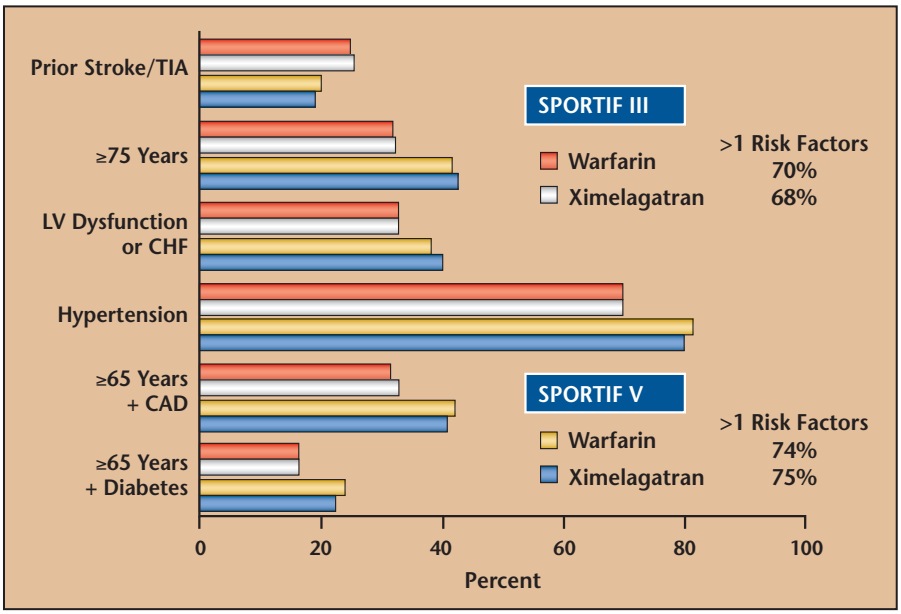


Figure 2. *SPORTIF III and V: patient characteristics and risk factors for stroke. CAD, coronary artery disease; CHF, congestive heart failure; LV, left ventricular; TIA, transient ischemic attack. Data from SPORTIF III Investigators[35] and SPORTIF V Investigators.[36]*

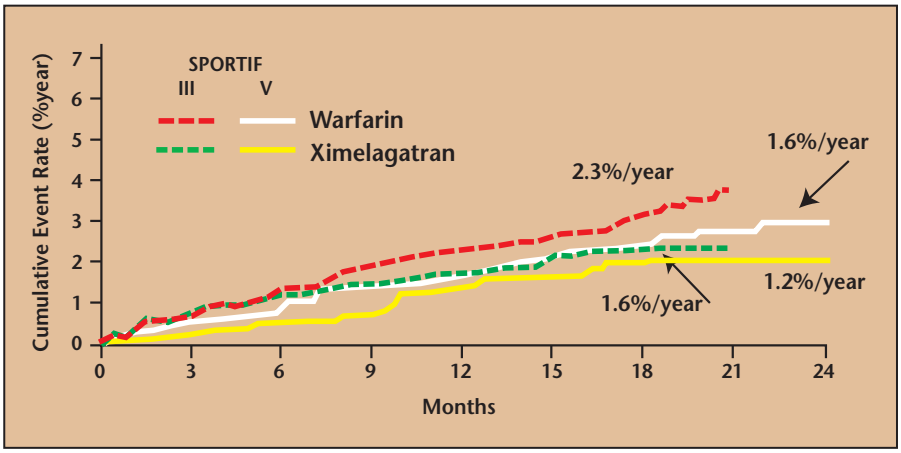
gatran had 2 or more risk factors for stroke. In SPORTIF V, 74% of the patients on warfarin and 75% of the patients on ximelagatran had 2 or more risk factors for stroke. The percentage of patients taking warfarin who achieved a therapeutic INR in this trial was really quite good compared with previously reported results: 66% of the patients in SPORTIF III and 68% in SPORTIF V had an INR between 2 and 3.

SPORTIF Results

In both SPORTIF III and SPORTIF V, the primary outcome of stroke and systemic embolism was 1.6% per year, with the results being virtually superimposable from each study (Figure 3). In SPORTIF III, the incidence of stroke and systemic embolism on warfarin was 2.3% per year, and in SPORTIF V it was 1.2% per year (Figure 3). When comparing ximelagatran with warfarin in SPORTIF III and SPORTIF V, there was no significant difference in the primary outcome (P = .10 and 0.13, respectively), with the prespecified "meta-analysis" P value being 0.94 (Figure 4). Clearly, ximelagatran was not inferior to warfarin. Moreover, in terms of hemorrhage in SPORTIF III and SPORTIF V, there was no significant difference in intracranial hemorrhage or major bleeding between warfarin and ximelagatran, but in terms of major and minor bleeding, in both SPORTIF III and V, ximelagatran was significantly better (P = .007 and .001, respectively). When examining the on-treatment analysis of major bleeding, the pooled data indicated a trend toward an advantage for ximelagatran (P = .054). When examining the net clinical benefit (defined as the number of primary events plus major bleeding plus death) in an on-treatment analysis, the relative risk reduction on ximelagatran was 16% compared with warfarin (P = .038).

In the SPORTIF trials (and actually in all the long-term trials with ximelagatran), there was about a 6% incidence of elevation to greater than or equal to 3 times the upper limit of normal of alanine aminotransferase (ALT) levels. In both trials, these elevations occurred primarily in the first 6 months. When combining the data from both trials, of 3,364 patients who received ximelagatran, 224 had an elevated ALT level that was greater than 3 times the upper limit of normal (6.1%) (Table 4).[42,43] The cause of this incidence of elevated ALT levels is unclear at this time. In the 96 patients who were continued on treatment, the ALT level normalized in 92, returned to less than 2

Figure 3. *The SPORTIF program: primary outcome (stroke or systemic embolism) intention-to-treat analysis. There was no significant difference in outcomes between ximelagatran and warfarin treatment. Data from SPORTIF V Investigators.[36]*



times the upper limit of normal in 3, and was greater than 2 times the upper limit of normal both pre- and poststudy in 1. Of the 128 patients who discontinued treatment, ALT normalized in 112, returned to less than 2 times the upper limit of normal in 6, and was greater than 2 times the upper limit of normal both pre- and poststudy in 3; 7 patients died, 4 of unrelated disease.

Of the other 3, one died of a perforated duodenal ulcer about 1 month after starting a course of prednisone therapy administered because of elevated ALT levels; the second developed fulminant hepatitis B and died of hepatic failure; the third died of bleeding from a Bilroth II anastomosis. These 3 deaths and the association of bilirubin elevated to greater than 2 times the upper limit of normal along with elevated ALT levels in 0.5% of all patients exposed to ximelagatran, versus 0.08% in the comparator, in all the clinical trials with ximelagatran, raised safety concerns at the USFDA, which importantly influenced their decision not to grant approval for initiation of ximelagatran therapy at this time in the United States. At the time of this writing, further studies are anticipated to demonstrate that ximelagatran is safe, and that elevations in ALT and bilirubin levels can be effectively and safely managed, thereby allowing the many advantages for oral anticoagulation therapy with this drug to be realized.

Clinical Implications of the SPORTIF Trials

As the first oral direct thrombin inhibitor, ximelagatran would offer a new approach to anticoagulation, including 1) fixed oral dosing, with no titration required; 2) predictable pharmacokinetics, proven in a broad range of patients; 3) rapid onset and offset of anticoagulation; 4) no coagulation monitoring, with predictable, stable, and reproducible anticoagulant effect; 5) a therapeutic margin wider than warfarin's; and 6) consistent pharmacodynamics not affected by food, alcohol, or the cytochrome P-450 enzyme system, with resultant low potential for food or drug interactions. If the safety of the drug can be satisfactorily demonstrated to the USFDA, so that it will be approved for clinical use in the treatment of patients with atrial fibrillation at risk for stroke, the above advantages of ximelagatran likely will lead to a sea change in the anticoagulation treatment of patients with atrial fibrillation at risk for stroke.

Finally, it is important to emphasize that ximelagatran was not studied

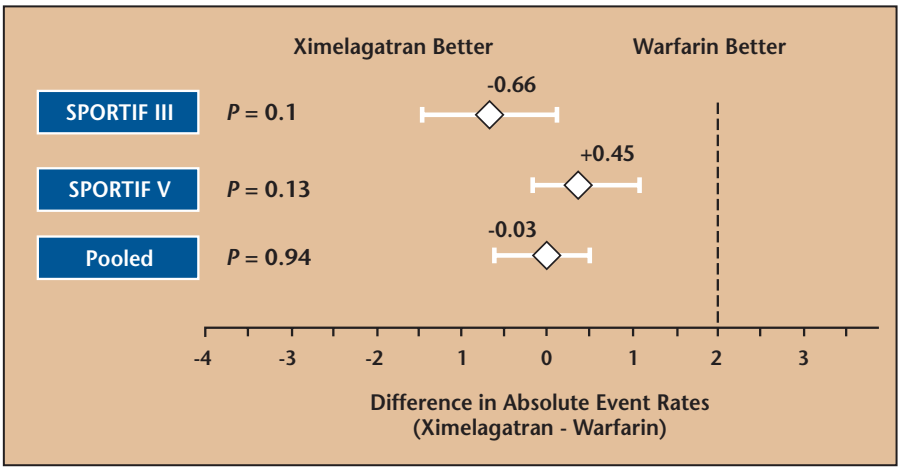


Figure 4. *SPORTIF program primary analyses: intention-to-treat analysis. Note that the data comparing ximelagatran with warfarin were well within the prespecified margin of 2% per year for the difference in primary event rates. Data from SPORTIF V Investigators.*[36]

Table 4
SPORTIF Programs: Outcome of Alanine Aminotransferase (ALT) Elevation (> 3 Times the Upper Limit of Normal [ULN])

Status after 1st ALT elevation (> 3 × ULN)	SPORTIF III n = 1704	SPORTIF V n = 1960	Pooled n = 3664
Incidence ALT (> 3 × ULN)	107	117	224
Continued on treatment	59	37	96
Normalized	57	35	92
Returned to ≤ 2 × ULN	1	2	3
> 2 × ULN (pre- and poststudy)	1	—	1
Discontinued treatment	48	80	128
Normalized	43	69	112
Returned to ≤ 2 × ULN	2	4	6
> 2 × ULN (pre- and poststudy)	—	3	3
Died	3	4	7

Data from AstraZeneca[42] and the SPORTIF III Investigators.[43]

in the following patient groups: precardioversion patients, patients with prosthetic heart valves, pregnant patients, and patients with a creatinine clearance less than 30 mL/min. Data in these groups will have to be accumulated before it can be determined whether ximelagatran can be used both safely and effectively in these patient populations.

SPORTIF III and V Conclusions

We await the anticipated new studies of long-term treatment with ximelagatran to demonstrate that elevations of ALT and bilirubin levels, which occurred in 0.5% of all patients who took ximelagatran in every long-term clinical trial are clinically manageable without the expectation of significant fatal hepatotoxicity. Should that be demonstrated, the data from SPORTIF III and V then will permit the conclusion that in high-risk patients with nonvalvular atrial fibrillation, ximelagatran represents a promising treatment option for the prevention of thromboembolism in patients at risk for stroke. Ximelagatran offers fixed oral dosing without coagulation monitoring, its effectiveness is comparable to well-controlled warfarin in preventing stroke and systemic embolic events, and it causes less bleeding than warfarin. ■

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Main Points

- Warfarin is very effective as prophylaxis against stroke in patients with atrial fibrillation. However, its use is associated with well-recognized problems, which is why studies have demonstrated that warfarin is underused in patients with atrial fibrillation who do not have a relative or absolute contraindication to the drug, but who do have stroke risks.
- Aspirin not only is insufficiently effective in preventing stroke compared with warfarin, but also, should a stroke occur, its consequences are likely to be far more severe than with warfarin when a therapeutic INR is achieved.
- Data from several trials demonstrating asymptomatic atrial fibrillation have led to the widely accepted conclusion that patients with atrial fibrillation and risk factors for stroke should receive anticoagulation indefinitely, even when sinus rhythm appears to be restored and maintained.
- Ximelagatran has fixed dosing and a predictable response, requires no coagulation monitoring, and has had no age, race, or gender differences observed to date. Clinical data demonstrate efficacy with twice-daily dosing.
- The SPORTIF trials demonstrated that ximelagatran was comparable in efficacy to warfarin. Moreover, in terms of hemorrhage in SPORTIF III and SPORTIF V, there was no significant difference in intracranial hemorrhage or major bleeding between warfarin and ximelagatran, but in terms of major and minor bleeding, in both SPORTIF III and V, ximelagatran was significantly better (P = .007 and .001, respectively). When examining the on-treatment analysis of major bleeding, the pooled data indicated a trend toward an advantage for ximelagatran (P = .054).
- We await the anticipated studies to demonstrate definitively that elevation of alanine aminotransferase (ALT) and bilirubin levels, which occur in a small percentage of patients taking ximelagatran long-term, can be safely managed. It can be anticipated that careful monitoring of ALT and bilirubin levels for the first 6 to 8 months of therapy will be necessary.

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Acknowledgment
Dr. Waldo's research is supported in part by Grants RO1 HL38408 and RO1 HL074189 from the National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD.