

Stroke Prevention in Atrial Fibrillation: Pooled Analysis of SPORTIF III and V Trials

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Abstract

This article will review 2 clinical trials that recently compared the safety and efficacy of the oral direct thrombin inhibitor ximelagatran (fixed dose, 36 mg twice daily) with warfarin (adjusted dose, target international normalized ratio [INR] 2.0-3.0) in patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke. These noninferiority trials involved 7329 patients and a mean exposure to study drug of 18.5 months. The Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III (open-label, N = 3407) and V trials (double-blind, N = 3922) were designed for pooled analysis, and the data showed the efficacy of ximelagatran therapy was comparable (noninferior) with extremely well-controlled warfarin therapy in preventing stroke and systemic embolic events; the primary event rates were 1.65% per year and 1.62% per year in the warfarin and ximelagatran groups, respectively ($P = .941$). In patients with a history of stroke or transient ischemic attack (about 20% of the SPORTIF population), the event rates were 3.27% per year and 2.83% per year in the warfarin and ximelagatran groups, respectively ($P = .625$). The distribution of stroke subtypes was similar in the 2 treatment groups. Intracranial hemorrhage occurred at a rate of 0.20% per year with warfarin and 0.11% per year with ximelagatran. Combined rates of minor and major bleeding were significantly lower with ximelagatran than with warfarin (32% per year vs 39% per year; $P < .0001$). The myocardial infarction rates were the same in the pooled database (no difference between agents). The aspirin data will be the subject of two substudy papers. Oral ximelagatran administered without coagulation monitoring or dose adjustment was as effective as well-controlled, adjusted-dose warfarin for prevention of stroke and systemic embolic events and was associated with significantly less total bleeding. This oral direct thrombin inhibitor is a potentially promising treatment option for the prevention of thromboembolism.

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Oral anticoagulation is highly effective in preventing stroke in patients with atrial fibrillation (AF). Major randomized studies have shown between 60% and 80% relative risk reduction (**Figure 1**).¹⁻⁶ A meta-analysis of 5 primary prevention trials and 1 secondary prevention trial showed an aggregate relative risk reduction for ischemic stroke of 62% ($P < .001$).⁷ Much of the reported variation in efficacy in these trials may be caused by the efficiency with which patients actually took their oral medication. On-treatment analyses of these trials reveal a more than 80% relative risk reduction with warfarin.

Despite this tremendous efficacy in formal clinical studies, warfarin remains vastly underutilized in clinical practice for both primary and secondary stroke prevention. Up to two thirds of eligible patients in primary care practice are still not receiving warfarin.^{8,9} Underutilization of warfarin has been well documented in several settings^{10,11} and is especially problematic in the most elderly patients.¹² Even among individuals who are taking warfarin as directed, the possibility of undercoagulation or overcoagulation further diminishes the adequacy of the anticoagulation. One study has documented subtherapeutic international normalized ratios (INRs) in 45% of patients taking warfarin and supratherapeutic levels in 19% of these individuals, leaving only 36% of on-treatment patients adequately protected from stroke.⁸ The narrow therapeutic index of warfarin—ie, the small target INR range

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NOTE: The Food and Drug Administration (FDA) Cardiovascular & Renal Drugs Advisory Committee voted against recommending approval for ximelagatran (Exanta) for all 3 indications under review at the FDA. These indications include: prevention of stroke and other thromboembolic complications associated with atrial fibrillation; secondary prevention of venous thromboembolism (VTE) after standard treatment for an acute episode; and short-term prevention of VTE in patients undergoing knee replacement surgery. The committee agreed that the risk management plan offered by the drug's manufacturer, AstraZeneca, did not seem adequate to prevent severe liver damage. Another concern was the number of adverse cardiac events, such as myocardial infarction, possibly associated with using ximelagatran for knee replacement surgery. However, these concerns could be addressed with further safety studies. AstraZeneca is continuing discussions with the FDA.

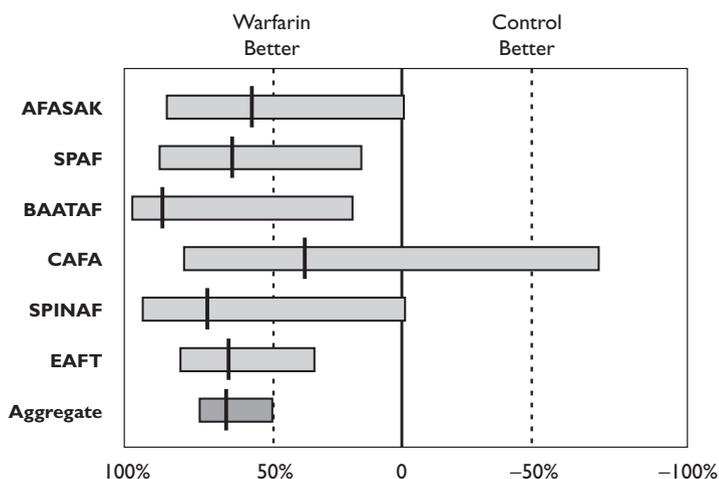
within which the patient must remain to be protected from both bleeding and clotting—has been well established.¹³⁻¹⁵ However, even scrupulous warfarin monitoring and dose adjustment provided in the controlled environment of anticoagulation clinics often fails to keep a majority of patients taking oral anticoagulants within this target INR range.⁹

Given this wide gap between the documented efficacy of warfarin and results with its actual clinical use, there is a clear need for alternative oral anticoagulants. One example of a newer drug is ximelagatran, which was the focus of the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials. Ximelagatran is an orally administered prodrug that is rapidly converted to the active direct thrombin inhibitor melagatran.¹⁶ Melagatran is a small molecule that binds directly to the active site on thrombin and prevents conversion of fibrinogen to fibrin.¹⁷ The drug has many intrinsic advantages over warfarin, including: prompt onset and offset of anticoagulation; wider therapeutic margin; more predictable pharmacokinetics; and lower potential for food, drug, or alcohol interactions.^{18,19} All of these advantages indicate that ximelagatran can be given as fixed oral dosing with no dose adjustments and no need for coagulation monitoring with INRs. Pharmacists and clinicians may note the parallels between this user-friendly profile of ximelagatran and that of other recently introduced drugs for use in clotting prophylaxis that does not require coagulation monitoring, such as low-molecular-weight heparin and indirect Xa antagonists.

Ximelagatran and SPORTIF

If all clinical trials are considered, ximelagatran has been tested in approximately 30 000 patients worldwide.²⁰ Oral ximelagatran has shown good efficacy and tolerability in the prevention of venous thromboembolic events (VTE) in patients undergoing orthopedic surgery²¹ and was recently approved for VTE prophylaxis in the European Union.²⁰ AF is one of the most common causes of embolic stroke, accounting for up to 20% of the 700 000 new and recurrent strokes that occur every year in the United States.¹ Because the risk of AF-related stroke

Figure 1. Anticoagulation in Atrial Fibrillation: Stroke Risk Reductions



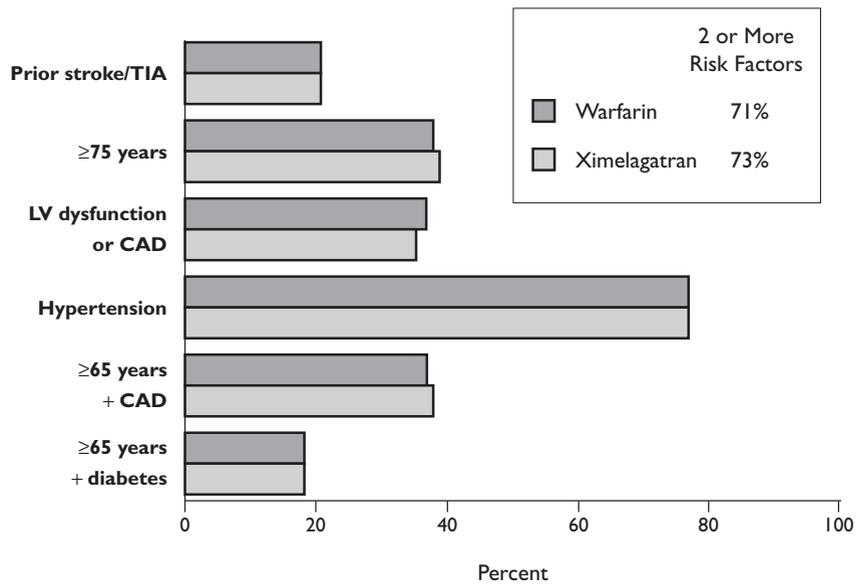
AFASAK indicates Atrial Fibrillation, Aspirin, and Anticoagulation [Peterson 1989]; SPAF, Stroke Prevention in Atrial Fibrillation [SPAF 1991]; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation [BATAAF 1990]; CAFA, Canadian Atrial Fibrillation Anticoagulation [Connolly 1991]; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation [Ezekowitz 1992]; EAFT, European Atrial Fibrillation Trial [EAFT 1993].

increases with age, the prevalence of stroke is expected to more than double during the next 20 years.^{1,22} Thus, clinicians and healthcare systems interested in stroke prevention for patients with AF will have an increasingly acute need for an oral anticoagulant that is less complicated than warfarin but, at the same time, highly efficacious.

Results from the SPORTIF trials, 2 major randomized clinical trials comparing fixed-dose ximelagatran (36 mg twice daily) with adjusted-dose warfarin (INR, 2.0-3.0), were reviewed in 7329 patients at high risk for stroke based on nonvalvular AF and other risk factors.²³ Patients enrolled in the SPORTIF trials were identified, according to current guidelines, as candidates who should be receiving warfarin therapy for stroke prevention.²⁴ The SPORTIF studies were identical in design with 1 exception: the SPORTIF III trial (N = 3407) was performed in 23 European nations and was open label, whereas the SPORTIF V trial (N = 3922) was performed in the United States and Canada and was double blind.

Because warfarin is extremely effective when used properly, the goal of the

Figure 2. Patient Characteristics in SPORTIF III and V Pooled Analysis: Stroke Risk Factors



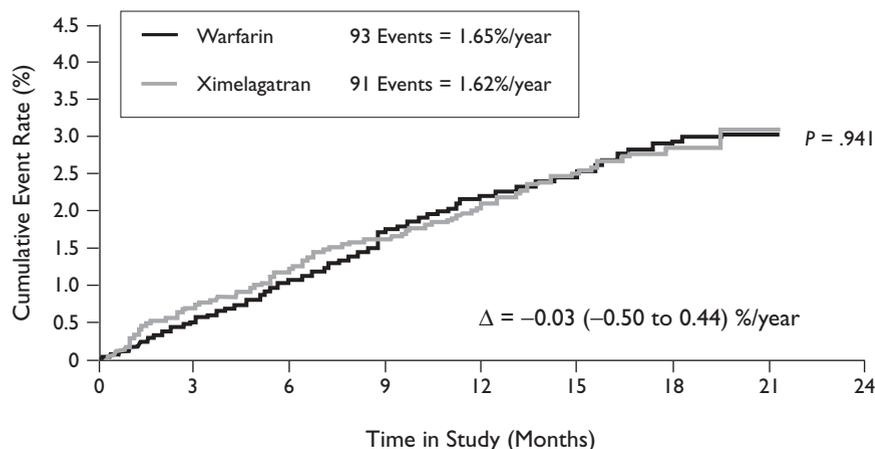
TIA indicates transient ischemic attack; LV, left ventricular; CAD, coronary artery disease.

SPORTIF study was not to prove head-to-head superiority, but, instead, to demonstrate that ximelagatran therapy was statistically no worse (ie, noninferior) than well-controlled warfarin therapy. Warfarin may not be well controlled in the general population, so the study was designed to give the warfarin arm the best possible means to independently compare warfarin to ximelagatran. The specific objective was to establish whether ximelagatran was noninferior to warfarin within a preset absolute margin of 2% per year in primary event rates.²³ SPORTIF's selection of a noninferiority statistical design is an important point that should help clinicians properly interpret the practical significance of SPORTIF's results. The study design is dictated by the fact that warfarin, when employed in strict clinical trial settings such as those created by SPORTIF, is extremely effective in preventing stroke. As just discussed, the relative risk reductions versus placebo are routinely 60% and can range up to 80% or higher in very well-controlled settings. Thus, it would be extremely difficult for any agent to demonstrate superiority over warfarin when in a highly controlled study setting. If shown to be equivalent to warfarin, how-

ever, ximelagatran might actually produce better population-level stroke reduction rates when applied in real-life clinical practice. This is because ximelagatran, unlike warfarin, may not require the tight monitoring and dose adjustment required to achieve the same level of efficacy.

The primary outcome analysis in SPORTIF III and V was that warfarin and ximelagatran were similar in efficacy in preventing all strokes (both ischemic and hemorrhagic) as well as systemic embolic events. The end points were defined based on independent and blinded adjudication. The studies used an intent-to-treat analysis, and the sensitivity analyses considered on-treatment effects and all-cause mortality. Safety evaluations focused on hemorrhages.

Previously published results of the double-blind SPORTIF III showed that 2.3% of patients taking warfarin had primary events versus 1.6% in the ximelagatran group ($P = .1$); composite end points were also similar, but the rates of combined minor and major hemorrhages were lower with ximelagatran than with warfarin (29.8% vs 25.8%, respectively; relative risk reduction, 14%; $P = .007$).²⁵ As of this arti-

Figure 3. Primary Outcome in SPORTIF III and V Pooled Analysis: Stroke and Systemic Embolic Events (Intent to Treat)

cle, the full results of SPORTIF V have not been published. This article will consider the prespecified pooled analyses of SPORTIF III and V key results with a focus on efficacy, stroke subtypes, and adverse events.

Results

Patients. The 7329 AF patients enrolled in SPORTIF III and V were considered high risk for stroke. Approximately 20% had a previous stroke or transient ischemic attack, about 40% had significant left ventricular dysfunction or congestive heart failure, and about 80% had hypertension (Figure 2). Patients typically had more than 1 risk factor for stroke in addition to their AF. In fact, nearly three quarters of SPORTIF AF patients had 2 or more additional risk factors. The distribution of these risk factors was evenly distributed between treatment groups.

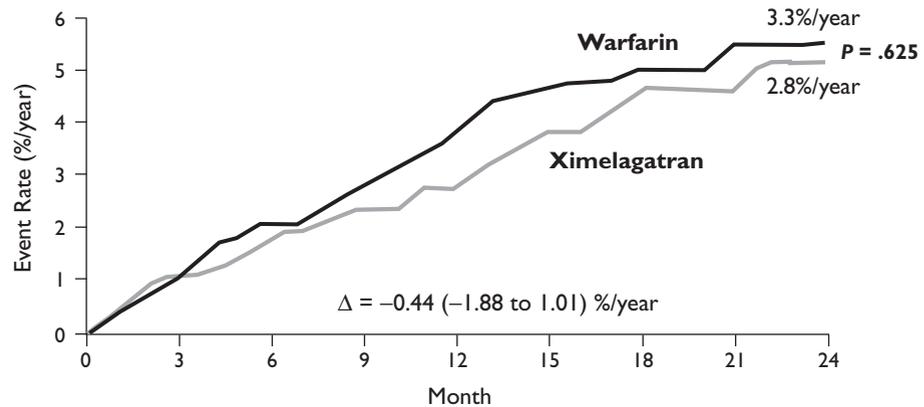
Rates of concomitant aspirin administration were 17.2% for patients receiving primary prevention and 22.7% for those receiving secondary prevention. The mean length of exposure to study drug was 18.5 months (total 11 346 patient-years' exposure). Importantly, the level of anticoagulation control in SPORTIF patients randomized to warfarin was considered excellent. Through the entire course of both studies, 67.6% of all INR values were within the 2.0 to 3.0 target therapeutic range, with 12.9% and 19.5% of readings above or below range, respectively.

This high rate of optimal anticoagulation control with warfarin indicates that the investigators were diligent in their monitoring and dose adjustment.

Treatment Efficacy. Pooled analysis from both trials of the primary intent-to-treat outcome of all stroke and systemic embolic events showed that there were 93 events in the warfarin group (1.65% per year) and 91 events in the ximelagatran group (1.62% per year) (Figure 3). This small difference of -0.03% per year had extremely tight 95% confidence intervals (CIs) of -0.50 to 0.44 , essentially confirming identical or equivalent event rates in the 2 treatment groups ($P = .941$).

Warfarin and ximelagatran were both equally effective in primary and secondary prevention. In 20% of the SPORTIF population who had had a prior transient ischemic stroke or stroke, the overall rate of stroke was—not unexpectedly—more than double that seen in those AF patients without such a history. However, the event rates in secondary prevention during these 2266 patient-years of follow-up in the 2 treatment groups were 3.27% per year in the warfarin group and 2.83% per year in the ximelagatran group (absolute difference, 0.44% per year; 95% CI, 0.98, 1.86; $P = .625$) (Figure 4). A small trend emerged after a few months favoring ximelagatran, but this was not statistically significant.

Figure 4. SPORTIF Stroke and Systemic Embolic Events (Intention to Treat): Outcomes in Primary and Secondary Prevention



Stroke Subtypes. Clinicians are especially concerned about the frequency of brain hemorrhages in elderly individuals who are being anticoagulated for stroke prevention. In fact, this concern explains much of the underutilization and undercoagulation that occurs with warfarin in clinical practice today. Because nearly 40% of SPORTIF patients were 75 years of age or older, the rates of stroke subtype are of extreme relevance.

The risks of intracranial hemorrhage in SPORTIF were only 0.19% and 0.11% (95% CI) per year in the warfarin and ximelagatran groups, respectively. The upper bounds of the 95% CI for ximelagatran was 0.23%, indicating an extremely low risk of brain hemorrhage associated with this new agent, especially when compared with the historical expectations of approximately 0.5% per year of intracranial hemorrhage for such a high-risk group.^{26,27}

The annual rates of ischemic strokes in the warfarin and ximelagatran groups were 1.46% and 1.37%, respectively. The majority of these ischemic strokes (63% in the warfarin group, 55% in the ximelagatran group) were noncardioembolic in origin, typically lacunar or large-artery atherosclerosis-related strokes. Cardioembolic strokes occurred at a rate of only 0.53% and 0.62% per year in the warfarin and ximelagatran groups, respectively, an extremely low rate considering the AF risk factor shared by all SPORTIF patients. This was another indicator of the high degree

of effectiveness of both anticoagulation therapies.

Hemorrhage. In addition to the comparative rates of intracranial hemorrhage just discussed, the rates of major and minor bleeding were also evaluated during the course of the SPORTIF trials. Bleeding was considered major when associated with a functional deficit, when hemoglobin fell by 20 g/L, when transfusion was required, or when an important anatomical site (eg, intracranial, intraspinal, intraocular, retroperitoneal, pericardial, atraumatic intra-articular) was involved. Any clinically overt bleeding that did not meet these criteria for major hemorrhage were classified as minor bleeding events.

Major bleeding occurred at an annual rate of 2.5% in the warfarin-treated group and 1.9% in the ximelagatran-treated group, a nonsignificant difference (Figure 5). However, the combined rates of major and minor bleeding events were significantly lower in the ximelagatran group (31.7% per year) than in the warfarin group (38.7% per year) ($P < .0001$).

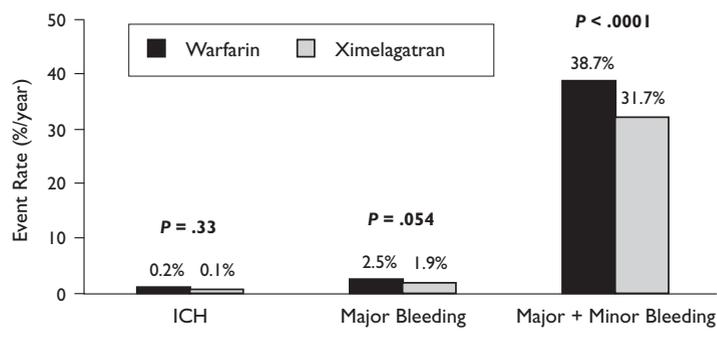
The low levels of major and minor bleeding with ximelagatran relative to warfarin indicate that the lack of a specific agent to reverse its anticoagulant effects (ie, analogous to vitamin K with warfarin) are compensated for by its inherently short half-life. This “acute reversibility by time” may be diminished in patients with poor renal func-

tion, who may require altered ximelagatran dosing. However, in general, the low rates of bleeding problems in SPORTIF indicate that the lack of reversibility with ximelagatran is not a major issue.

Liver Enzyme Elevation. Blood chemistry, hematology, urinary erythrocytes, fecal hemoglobin, and serum concentrations of hepatic transaminases, alkaline phosphatases, and bilirubin were measured monthly for the first 6 months and periodically thereafter. The only adverse effect detected was an increase in asymptomatic liver enzyme elevation in patients receiving ximelagatran. About 6.1% of patients randomized to ximelagatran had an increase in alanine aminotransferase greater than 3 times the upper limit of normal compared with a 0.8% rate in those receiving warfarin. As shown in **Figure 6**, these elevations were noted mostly during the first 2 to 6 months of the trial. In general, these liver enzyme elevations were not associated with clinical manifestations and resolved to normal whether or not treatment was stopped.

Net Clinical Benefit. An on-treatment analysis of all SPORTIF patients who were actually receiving the study drugs shows that ximelagatran provided a better net clinical benefit than warfarin (**Figure 7**). This

Figure 5. SPORTIF III and V Pooled Analysis: Hemorrhage



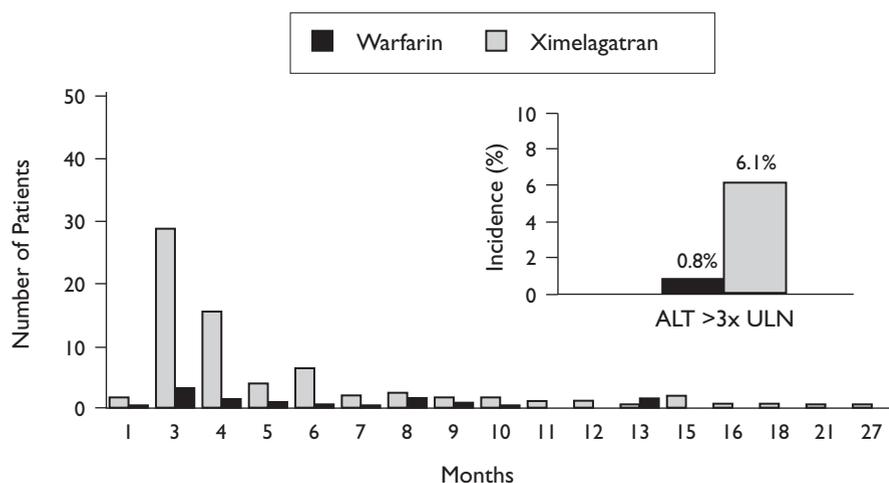
ICH indicates intracranial hemorrhage.

special composite outcome is a sum of events including stroke, systemic embolic events, major bleeding, and all-cause mortality. The 1% per year absolute risk reduction and 16% relative risk reduction in the ximelagatran group versus the warfarin group were statistically significant ($P < .038$).

Conclusion

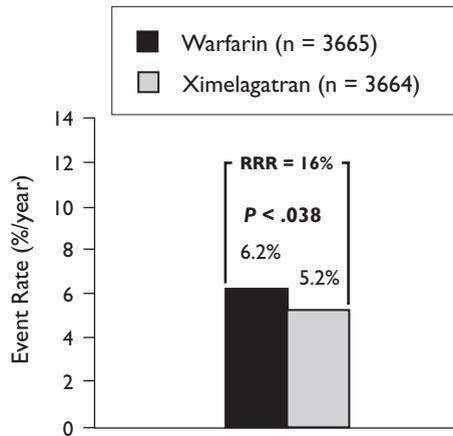
For patients with AF, both in the primary and secondary stroke prevention settings, ximelagatran could offer a viable alternative to standard dose-adjusted warfarin therapy. This oral direct thrombin inhibitor does not require coagulation monitoring and provides efficacy that is equivalent to an exceedingly well-controlled regimen of warfarin therapy.

Figure 6. SPORTIF III and V Pooled Analysis: Liver Enzyme Elevation



ALT indicates alanine aminotransferase; ULN, upper limit of normal.

Figure 7. SPORTIF III and V Pooled Analysis: Net Clinical Benefit*



*Net clinical benefit includes primary events, major bleeding, and death.

Ximelagatran also produces less bleeding than warfarin. The transient liver enzyme elevation in 6% of patients indicates that patients will require monitoring with liver function tests.

The convenience of prescribing an efficacious oral anticoagulant without the burden of monitoring and dose adjustment means that many more patients are likely to receive, and remain adherent to, the new prophylactic therapy. In particular, elderly patients with AF and 1 or 2 stroke risk factors, who in the past may have been discouraged from taking anticoagulants because of the bleeding risk, may now, with ximelagatran, be more likely to receive a prescription for effective oral stroke prophylaxis from their clinician. Long-term adherence to this new therapy may improve because of the elimination of the need for frequent trips to an anticoagulation clinic. Thus, clinicians and health systems may soon have a realistic opportunity to reduce stroke rates among a broader group of patients with AF.

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Q&A WITH DR ALBERS

Kenneth Schaecher, MD, Medical Director of Utilization Management at Intermountain Healthcare in West Valley City, Utah, interviewed Dr Albers about the work he has done with the pooled data from SPORTIF III and V. Following are highlights from their conversation.

SPORTIF: The Key Result

Dr Schaecher: Dr Albers, could you recap the key results from the pooled SPORTIF studies?

Dr Albers: The primary outcome in this trial comparing fixed-dose ximelagatran with adjusted-dose warfarin in patients with AF and stroke risk factors was the combination of strokes, both ischemic and hemorrhagic, with systemic emboli. Pooled results showed that the rate of those events was 1.62% per year taking ximelagatran and 1.65% per year taking warfarin, which are very low rates in both groups. These pooled rates show that these drugs are essentially identical in preventing major strokes and systemic emboli.

Dr Schaecher: What was the overall risk level of patients enrolled in SPORTIF?

Dr Albers: These patients were at very high risk of AF and stroke. The mean age

was 71 years, about 21% of these patients had had a previous stroke, and about 40% were older than age 75. Most patients had multiple risk factors. Nearly 80% had hypertension and many had diabetes or coronary artery disease.

Dr Schaecher: Was the SPORTIF population typical of those patients currently receiving anticoagulation therapy?

Dr Albers: Yes. In fact, the majority of these patients, before they entered the SPORTIF trial, were already receiving appropriate oral anticoagulation. So, these were high-risk candidates for stroke who did not have major risk factors for hemorrhage.

SPORTIF Study Design

Dr Schaecher: Why wasn't SPORTIF designed to show that ximelagatran was better than warfarin? Why a noninferiority trial?

Dr Albers: Warfarin is extremely effective for preventing stroke, particularly for preventing the cardioembolic strokes that occur in patients with AF. In fact, among patients who take warfarin, the relative risk reduction is more than 80%. So the issue is not trying to find a drug that is more effective than warfarin. The real issue is that warfarin

is inconvenient and significantly underutilized because of the need to do frequent coagulation monitoring and because of the food and drug interactions. The idea with SPORTIF was that ximelagatran could provide a more user-friendly approach to preventing stroke. We hoped to find, and did, in fact, find, that the drug would be extremely effective like warfarin, but also would be much more convenient to use. This implies that ximelagatran could become available to many more patients who currently are not taking advantage of the excellent efficacy of warfarin.

Dr Schaecher: So, the SPORTIF trials were designed to show that ximelagatran was equally as effective but easier and safer therapy for patients?

Dr Albers: Yes. We had also hoped to find, and did, in fact, find, that bleeding would be reduced with the new drug, but that was not one of the primary end points. Again, well-controlled warfarin has very acceptable bleeding rates, so the primary concern was not that warfarin caused too much bleeding or that warfarin was not effective enough. The problem was that warfarin was not being used optimally because of its downsides. The need for frequent monitoring as well as the food and drug interactions lead both physicians and patients to steer away from the drug. Only about half of the patients who should be taking warfarin take it.

Dr Schaecher: In SPORTIF, warfarin was very well controlled in a study setting that was very unlike the usual clinical environment. Given this, do you think that SPORTIF underestimated the amount of bleeding to be expected with warfarin?

Dr Albers: It was critical to have excellent control of warfarin therapy to ensure that we were comparing ximelagatran with optimal warfarin management. So, there was a huge effort in both SPORTIF III and V to manage warfarin therapy to the same extent as it would be in an excellent anticoagulation clinic setting. In fact, more than two thirds of all blood draws in the studies had an INR within the 2 to 3 range, which is very impressive. More than 80% of all blood draws in warfarin patients had an INR between 1.8 and 3.2. This level of anticoagulation control

is certainly much better than you would find in most practice settings. It shows warfarin at its very best. And, to answer your question, the anticoagulation control while receiving warfarin in SPORTIF III and SPORTIF V was unquestionably better than in the typical practice setting that one would encounter. So, yes, warfarin-related bleeding in actual clinical practice is probably higher.

Dr Schaecher: Is it statistically valid to pool results from an open-label study [SPORTIF III] and a double-blind study [SPORTIF V]?

Dr Albers: I think when you have hard end points in a study and an otherwise identical study design, it certainly is valid to pool the data. And the end points for these studies were very hard. We're not talking about measuring a subjective TIA [transient ischemic attack] versus no TIA. These were patients who had strokes that generally caused significant neurologic deficits. The strokes were adjudicated by blinded end-point committees for both SPORTIF III and SPORTIF V. It was the same end-point committee looking at the end points in the 2 trials. In fact, from the early design phase of these studies there was a preplanned pooled analysis.

Dr Schaecher: Why did SPORTIF III have an open-label design?

Dr Albers: SPORTIF III occurred in more than 20 countries. Practically speaking, it was not possible to do a double-blind INR control in a study of that scope. In SPORTIF V, where we were only dealing with the United States and Canada, it was possible to do a double-blind study. Using these 2 designs also provided the added opportunity to evaluate differences between an open-label and a double-blind study.

Dr Schaecher: How does the SPORTIF sample size compare with the population sizes in the core studies used to prove that warfarin was superior to aspirin in preventing AF-related stroke?

Dr Albers: The key studies that led to the acceptance of warfarin as a highly effective therapy to prevent stroke occurred in the late 1980s and early 1990s. There were 5 main studies that looked at warfarin versus control, or in some cases warfarin versus

aspirin. Those studies typically ranged from 500 to 1000 patients per study. The SPORTIF trials, III and V combined, include more than 7300 patients. So, you can see that the SPORTIF trials represent more patient experience with AF than all these other studies combined.

Monitoring Issues with Warfarin and Ximelagatran

Dr Schaecher: Ximelagatran is a twice-daily medication and it does have some liver enzyme issues that are not yet fully resolved. It's not a perfect drug. Is there any reason to suspect that ximelagatran use would drop off, or that we would start to see noncompliance with therapy similar to the noncompliance we see with warfarin in a real-world setting?

Dr Albers: Well, you're asking many different questions there. First, it's true that the drug is taken twice daily, which is a disadvantage in terms of compliance because people obviously like once-daily drugs. But the flip side of this relatively short half-life means that once you stop taking it, it rapidly leaves the system and the anticoagulation effect goes away rapidly as well. This can be an advantage versus warfarin, which can take a long time to reverse, even when using agents like vitamin K.

The pharmacokinetics of ximelagatran also allow you to initiate anticoagulation very rapidly. A few hours after you take the first pill you're anticoagulated. With warfarin you need many days for the drug to take effect.

In terms of the requirement liver function tests for ximelagatran, we think these will be relatively short term. In the studies, the liver function test abnormalities attributable to the drug typically occurred only during a period of a few months. So I believe that patients would take this medication because of this convenience, even though it is taken twice daily. In the long run, you don't have to go for the at least once per month blood draw for the INR levels.

Keep in mind, too, that when you monitor warfarin with the INR, there are frequent dose adjustments, phone calls from the physician's office or the pharmacist to the patient in terms of monitoring and making changes in the drug dosing. With the liver function test-

ing, the vast majority of the time, nearly 95% of the time, the liver function tests are not going to be elevated. Therefore, there will be no need for rapid interaction with the patient for dose adjustment.

So I agree, we still do not have a perfect drug. It would be nice to have a drug that didn't require monitoring of liver function or INR, but we don't have that at this point.

Dr Schaecher: But don't you think the likely requirement for monthly liver enzyme testing will be a deterrent for physicians wishing to prescribe this medicine?

Dr Albers: Well, physicians clearly don't like to monitor blood tests. But in high-risk patients with AF, the pros and cons of monitoring a few liver function tests is minimal compared with the impact of having a stroke.

Dr Schaecher: Some physicians might actually view the liver monitoring as an opportunity, a contact point, to make sure things are going well with the patient.

Dr Albers: These are high-risk patients with multiple cardiovascular risk factors and they should be seen on a relatively regular basis, regardless of whether they're having routine blood testing for a medication.

Controlling INRs

Dr Schaecher: Those who are not familiar with ximelagatran and coagulation testing may wonder why INRs aren't measured in the ximelagatran group.

Dr Albers: This direct thrombin inhibitor drug does not affect the INR level in the way that warfarin does. You can't reliably determine whether somebody is taking ximelagatran or not based on the INR. We do not have an ideal blood test to monitor how anticoagulated you are with the drug. In this sense, it's similar to low-molecular-weight heparin, where physicians typically prescribe the medication without having any direct monitoring of anticoagulation effect. The drugs are rapidly and reliably absorbed, and you can feel confident that if the patient is taking the drug, they're anticoagulated. So, the key question is "when did they take the last dose" rather than "what does the INR or the partial thromboplastin time indicate?"

Dr Schaecher: Do you think clinician investigators will be reluctant to administer

an oral anticoagulant as long-term preventive therapy without having a continuous surrogate measure of effectiveness such as the INR?

Dr Albers: No. They feel very comfortable using enoxaparin sodium in an inpatient setting without a prothrombin time. And they use all sorts of other medications without resorting to some blood test to tell them it's working. Physicians know some drugs require that type of feedback and other drugs don't. This one obviously doesn't require that type of blood test monitoring.

Dr Schaecher: Even so, does it make any sense to do ximelagatran levels to monitor for coagulation or as some kind of surrogate marker for effectiveness of anticoagulation?

Dr Albers: That's being looked at. We took some ximelagatran levels as part of the SPORTIF III and V trials, and some of these data are being analyzed to see if they're going to be able to explain failures, or bleeding events. But, in terms of routine practice, at this point we don't anticipate that ximelagatran levels are going to be required or particularly useful.

Reversal

Dr Schaecher: You mentioned that with warfarin we've got the ability to give vitamin K or fresh frozen plasma. Does ximelagatran have an antidote that can be used to correct its anticoagulation effect in a quick fashion?

Dr Albers: No. There's no agent to give an immediate reversal of the anticoagulation effect. With warfarin, you can reverse the effect by giving vitamin K and fresh frozen plasma, although in practice you're often looking at least 12 to 48 hours before you fully reverse the effect. Once you stop giving ximelagatran, the effect is gone on its own in 12 to 24 hours. So the time period of reversal for ximelagatran is very comparable with what you'd get with maximal intervention with warfarin. If the patient needs to be transfused because they're bleeding, you simply transfuse and stabilize them until the effect of the drug wears off, which is quite rapid.

Bleeding

Dr Schaecher: Ximelagatran was associated with significantly less bleeding than warfarin. How can this be if the rates of stroke

reduction were equivalent and patient populations were risk stratified correctly?

Dr Albers: Well, the difference you mention was attributable mainly to a difference in minor bleeding, and minor bleeds are not strokes. Some of the major bleeds are strokes, the brain hemorrhages, and there were fewer of these with ximelagatran than with warfarin. There were, in total, 6 brain hemorrhages in the pooled ximelagatran groups, and almost twice as many in the pooled warfarin groups. This difference, plus differences in other major bleeding events, led to rates of major bleeding in the pooled analysis of 2.5% per year taking warfarin, and 1.9% per year taking ximelagatran. So there was a small, absolute difference in the rate of major bleeding. With minor bleeding, however, it was a greater difference. And when you combine rates of minor and major bleeding you get a 32% rate with ximelagatran, and a 39% rate with warfarin.

This refers to the issue that we just talked about: Are these patients having trouble with bleeding because you can reverse warfarin and you can't reverse this drug? Obviously, that's not the case. Because there's actually less bleeding taking ximelagatran, and if you look at fatal bleeding, it was identical between the 2 treatments.

Dr Schaecher: Is there anything to indicate that minor bleeding is a marker or an indicator of the potential for the patient to experience a major bleed?

Dr Albers: That's a good question. Those data are being analyzed now to determine if minor bleeding was a predictor of major bleeding in the SPORTIF data set.

Dr Schaecher: Does minor bleeding ever contribute, because of patient or clinician concerns, to underanticoagulation?

Dr Albers: It's true that patients who have minor nuisance bleeds taking warfarin may complain about it, and some physicians may improperly discontinue warfarin therapy because of it. But these minor bleeds don't cause any morbidity, and, again, it's not clear that they identify patients who are going to have major bleeds. Because these patients are at risk of having strokes, I think the appropriate response is to help the patient deal with minor bleeds and to realize that they are not infrequent. About one third

of patients will complain of some type of minor bleeding event each year. But, in the big picture, it's really the strokes and the major life-threatening bleeds that you want to prevent. And unfortunately you have to accept some minor bleeds to be able to prevent the major disabling outcomes.

Patient Selection

Dr Schaecher: Based on the SPORTIF results, are there certain patient types who are likely to do better with ximelagatran versus warfarin?

Dr Albers: There were some trends, but no groups had statistically significant better outcomes with one treatment versus the other. One trend in particular involved the patients who had had a previous stroke or TIA. The trend showed lower event rates, both ischemic and hemorrhagic strokes, in those taking ximelagatran. In other words, patients who had had a previous stroke or TIA were at higher risk for having events, in general, and they seemed to do a little bit better taking ximelagatran than warfarin, but it wasn't statistically significant.

So I think basically across the board what we can say is that the drugs are very similar in their effect on preventing strokes and systemic embolism, if you monitor the warfarin

optimally. In other words, ximelagatran is likely to be comparable with optimally monitored warfarin therapy for preventing these events in basically any high-risk AF patient. And then it's going to be a question of cost analyses when we figure out how expensive the drug is, as well as the convenience for the patient.

Dr Schaecher: What are the practical implications for a managed care organization of an anticoagulant therapy that does not require therapeutic monitoring for dose adjustment?

Dr Albers: Well, they can ramp down their anticoagulation clinics. The significant resources currently put into anticoagulation clinics can then be shifted to other stroke prevention activities. Some of this shift could go to the liver function test monitoring requirement for ximelagatran, although this is likely a small cost compared with life-long, dose-adjusting, oral anticoagulation.

Dr Schaecher: I think you'll also see fewer clinician office visits for blood tests.

Dr Albers: Yes, much of the anticoagulation clinic monitoring does not involve physician visits, but those visits would also be reduced considerably if there were a switch over to the nonmonitored drug.