Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

Cardiology

UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Oral Thrombin Inhibition in the Prophylaxis Against Thromboembolism in Non-valvular Atrial Fibrillation Late-breaking results of the Fifth Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF V) Study

Originally presented by: Jonathan L. Halperin, MD

A Presentation at the Late-Breaking Clinical Trials Session of the American Heart Association Scientific Session 2003

November 9 –12, 2003 Orlando, Florida

Reported and discussed by:
GORDON MOE, M.D.

Warfarin is the standard therapy for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF). However, the requirements for coagulation monitoring, dose adjustment, and bleeding complications limit its use. The oral, direct thrombin inhibitor, ximelagatran, represents a potential alternative to warfarin in the management of patients with AF. This issue of *Cardiology Scientific Update* reviews the recently presented preliminary results of the fifth Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF V) Study, a double-blind comparison of the safety and efficacy of warfarin versus ximelagatran in patients with chronic non-valvular atrial fibrillation. It examines the impact of the results on the potential role of oral thrombin inhibition as an alternative to warfarin in the management of AF.

Atrial fibrillation (AF) is a common clinical disorder that predisposes patients to thromboembolic complications including strokes.[1] Stroke occurs at an annual rate of 4.5% in patients with AF and strokes related to AF are generally more severe than other types.[1-3] Warfarin has been shown in randomized controlled trials to reduce the incidence of stroke in patients with AF by 33% to 78%, with a modest increase in hemorrhage.[2,4-8] A meta-analysis of 5 primary prevention trials concluded that the relative risk of stroke was reduced by 67% with warfarin therapy.[5] However, the strong benefit of warfarin is negated, in part, by a significant increase in intracranial hemorrhage, especially in the elderly,[8-11] as well as the need for regular monitoring for anti-coagulation and dose adjustment.[10,12]

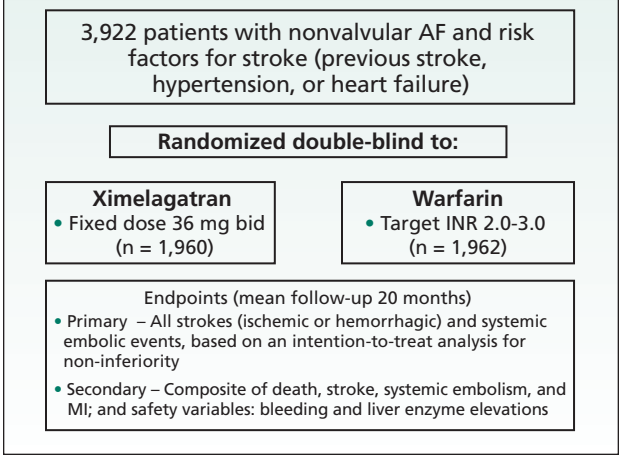
Ximelagatran is the only one of several oral direct thrombin inhibitors at an advanced stage of development for use as an anti-coagulant in the prevention and treatment of thromboembolism.[13,14] Its stable and predictable pharmacokinetic profile and low potential for drug and food interactions[14-16] offers the advantage of no requirements for frequent monitoring and dose adjustments. The Stroke Prevention using an Oral thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and SPORTIF V are two long-term phase-III studies comparing the safety and efficacy of ximelagatran 36 mg bid without coagulation monitoring versus dose-adjusted warfarin in patients with AF at risk for stroke. The rationale and design of SPORTIF III (the open-label comparison) and SPORTIF V (the double-blind comparison), as well as the main results of SPORTIF III, were published recently.[17,18] The following discussion presents the preliminary results of SPORTIF V, the double-blind comparison of the safety and efficacy of warfarin and ximelagatran in patients with non-valvular AF. Their impact on the potential role of oral thrombin inhibitors as an alternative to warfarin in the management of AF is also reviewed.

Study design

The study design of SPORTIF V has been published previously in conjunction with that of SPORTIF III.[17] The primary objective of SPORTIF III and V was to establish non-inferiority of ximelagatran relative to warfarin for prevention of all strokes and systemic embolic events in patients with AF. The principal inclusion criteria were:

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Figure 1: SPORTIF V trial design

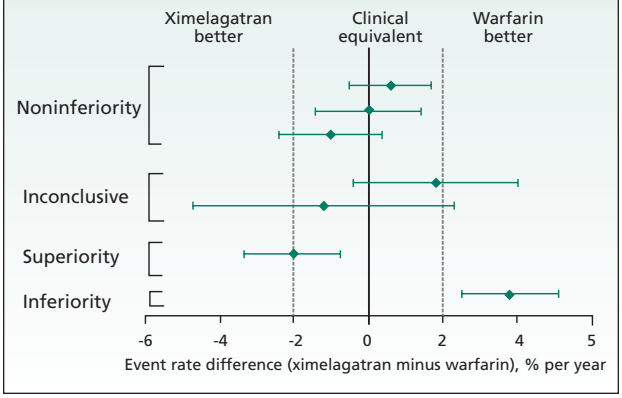


MI = myocardial infarction

- Age ≥ 18 years
- Persistent or paroxysmal AF verified by at least 2 ECG tracings, one of which was made within 2 weeks, and
- At least 1 of the following risk factors for stroke:
  - Hypertension
  - Age ≥ 75 years
  - Previous stroke, transient ischemic attacks or systemic embolization
  - Left ventricular dysfunction (ejection fraction <40% or symptomatic heart failure)
  - Age ≥ 65 years and coronary artery disease
  - Age ≥ 65 years and diabetes

The key exclusion criteria were stroke within 30 days, conditions associated with increased risk of bleeding, or the need for conventional anticoagulation. The study design of SPORTIF V is shown in Figure 1. SPORTIF V recruited 3922 patients (656 patients from Canada) from 409 sites in North America. In a double-blind protocol, patients were randomized to treatment with ximelagatran (at a fixed dose of 36 mg twice daily) or warfarin (at a dose adjusted to maintain an international normalized ratio (INR) of 2.0 – 3.0). Blinding was maintained by double-dummy study medications. In patients who received ximelagatran, sham INR values were generated using a previously validated algorithm. The primary endpoint was all stroke and systemic embolic events. Secondary endpoint composites included: death, stroke, systemic embolism, and myocardial infarction; ischemic stroke, transient ischemic attack, and systemic embolism; and bleeding and treatment discontinuations. By study design, the statistical analysis evaluated whether ximelagatran was not less effective beyond a pre-specified non-inferiority margin with a defined confidence interval (CI) (Figure 2). If the lower limit of the CI for the difference in rate (ximelagatran minus warfarin) exceeded the specified non-inferiority margin, ximelagatran would be inferior to warfarin. Conversely, an upper limit of CI less than "0" would imply superiority of ximelagatran over warfarin.

Figure 2: Hypothetical outcomes from non-inferiority analysis



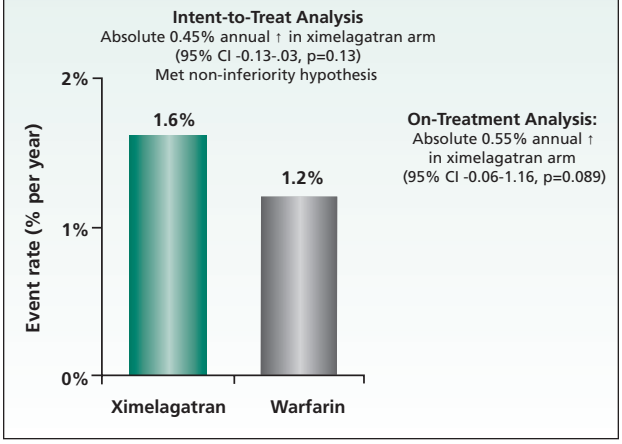
Results

The first patient in SPORTIF V was randomized in July 2000 and patient follow-up ended in March 2003. The primary results of SPORTIF V were presented recently at the American Heart Association Scientific Session. The results discussed in this *Cardiology Scientific Update* have not yet been published and, therefore, should be considered preliminary and subject to modification. The key baseline demographic data are shown in Table 1. There was no difference between the 2 groups in terms of baseline variables. Almost all patients had at least one risk factor for stroke and a significant number of patients also had left ventricular dysfunction; the majority had persistent AF. INR on warfarin was within the target range 68% of the time and

Table 1: Baseline demographics of patients in SPORTIF V (n=3922)

Mean age (years)	72
Male (%)	69
Male ≥ age 75 (%)	26
Female ≥ age 75 (%)	16
Medical history (%)	
Hypertension	81
Left ventricular dysfunction	39
Diabetes mellitus	25
Coronary artery disease	49
Previous stroke	10
Systemic (non-CNS) embolism	5
Number of risk factors (%)	
1, 2, 3, and 4	26, 31, 24, and 14
Diagnosis of AF (%)	
< 1 year, 1-5 years, > 5 years	16, 37, 47
Pattern of AF (%)	
Paroxysmal	14
Persistent	86

Figure 3: Primary endpoint, strokes (ischemic or hemorrhagic) and systemic embolic events



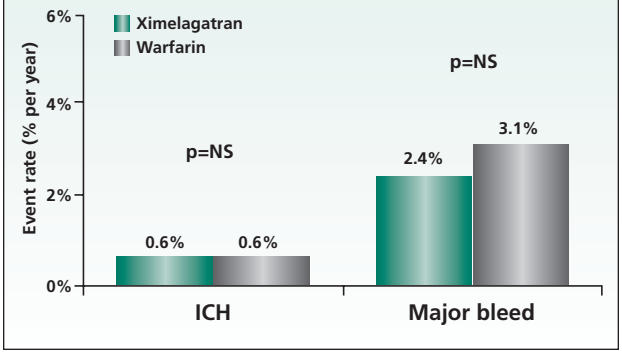
within an extended range (1.8-3.2) in 83% of the time. Results of the primary endpoint are shown in Figure 3.

There were 51 primary events of any stroke and systemic embolism in the ximelagatran group and 37 primary events in the warfarin group. By intention-to-treat (ITT) analysis, the absolute difference was +0.45% per year (ximelagatran minus warfarin) that was not statistically significant and was thought to fall within the annual 2% non-inferiority margin. When all-cause mortality was included, the absolute difference was +0.1% per year. By on-treatment analysis, the annual absolute difference was +0.55% per year, which was also not statistically significant.

When the data of SPORTIF V were combined with those of the 3410 patients from the open-label SPORTIF III study,[18] the annual event rate for the similarly-defined primary endpoint was 1.6% and 2.3% for the ximelagatran and warfarin groups, respectively, with an annual absolute difference of -0.66% (p=0.10) on ITT analysis and -0.03%, (p=0.94) for on-treatment analysis.

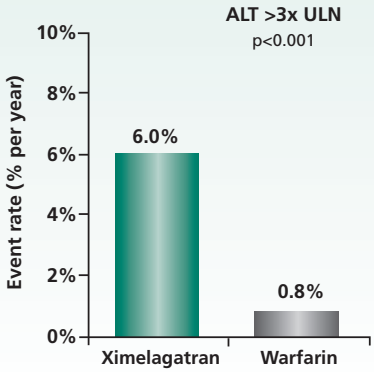
Data on bleeding complications are shown in Figure 4. Rates of intracerebral hemorrhage and major bleeding (defined as fatal, affecting a critical anatomic site, requiring blood transfusion, and a drop of hemoglobin by 2 g/dL) were low and not

Figure 4: Bleeding events



ICH = intracranial hemorrhage

Figure 5: Liver enzyme elevation



ULN = upper limit of normal

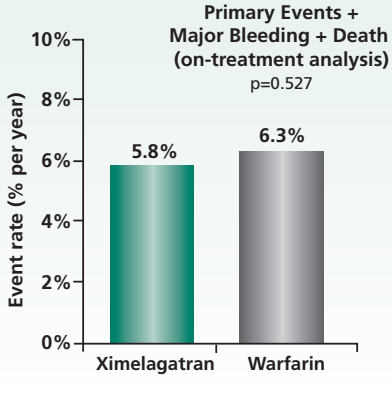
different between groups. When all bleeding was considered, the event rate was 37% and 47% for the ximelagatran and warfarin groups, respectively, with a difference that favoured ximelagatran (p<0.0001). Data on the incidence of liver function abnormalities are shown in Figure 5. The incidence of developing alanine aminotransferase (ALT) >3 times the upper limit of normal was significantly greater in the ximelagatran group. According to the investigators, these abnormalities occurred primarily in the first 2 months and normalized regardless of whether treatment was continued. One patient who received ximelagatran developed a fatal gastrointestinal hemorrhage after receiving steroid treatment for biopsy-proven hepatitis.

To assess the net clinical effect, the data on primary outcome, major bleeding, and death were combined and are shown in Figure 6. There was no significant difference between the 2 groups.

Clinical implications

SPORTIF V is the largest, randomized, double-blind, controlled trial ever conducted in patients with AF. A single dose of ximelagatran appeared to be as effective as warfarin in preventing

Figure 6: Net clinical effect



stroke and systemic embolism. This non-inferiority of ximelagatran was also reported in the open-label SPORTIF III trial that has already been published.[18] Importantly, in SPORTIF V, ximelagatran was compared with a "well-managed" conventional systemic anticoagulation protocol using warfarin that resulted in therapeutic INRs. This might also account, in part, for the low primary event rate in the warfarin group, which was strikingly similar to that in warfarin-treated AF patients in the meta-analysis of warfarin trials.[5]

In community clinical practice, the control of INR using warfarin is very likely to be less optimal than that reported in clinical trials. This is due, in part, to the expense and inconvenience associated with the use of warfarin, which often results in its under-treatment.[4,5,7] The primary outcome results of SPORTIF V are clinically relevant, suggesting that ximelagatran has the potential to be an alternative to warfarin in terms of *efficacy* in patients with non-valvular AF. However, several issues regarding the interpretation of the results warrant further discussion.

First, even though the point estimate of the primary endpoint of SPORTIF V, fell (with the corresponding CI) within the non-inferiority margin, it actually went in the opposite direction to that in SPORTIF III, where the point estimates of the primary event favoured ximelagatran.

Second, the number of primary events in SPORTIF V (37 in warfarin and 51 in ximelagatran) was very small, which complicates the interpretation for non-inferiority. For example, in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) that was also presented in the same meeting, non-inferiority was established with approximately 1000 primary events in each treatment arm.

The results of SPORTIF V also raise concerns for *safety*. Although ximelagatran compared favourably with warfarin in terms of the occurrence of intracerebral hemorrhage and major bleeds, the excess of liver function abnormalities in patients treated with ximelagatran raises important concerns. Indeed, an excess of liver function abnormalities were also observed in SPORTIF III (6% versus 1%, $p<0.0001$) and also in SPORTIF II, an earlier dose-guiding, safety study.[14] It is conceivable that this excess of liver function abnormalities may even become more clinically relevant in community clinical practice where patients are likely to be monitored in a less intensive fashion than in clinical trials.

Conclusion

Oral thrombin inhibition using ximelagatran represents a promising alternative approach to warfarin in the management of patients with chronic non-valvular AF. However, although uncertainty remains regarding the efficacy and safety of this approach, hopefully, this will be clarified with the publication of the results from SPORTIF V and other ongoing trials of oral thrombin inhibition in other conditions.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-88.
2. Connolly SJ. Preventing stroke in patients with atrial fibrillation: current treatments and new concepts. *Am Heart J* 2003;145:418-23.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147: 1561-64.
4. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993;342:1255-62.
5. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-57.
6. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;18: 349-55.
7. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992;327:1406-12.
8. 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.
9. Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *Ann Intern Med* 1996;156:409-16.
10. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to develop guidelines for the management of patients with atrial fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Eur Heart J* 2001;22:1852-923.
11. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S-21S.
12. Hirsh J, Dalen J, Guyatt G. The sixth (2000) ACCP guidelines for antithrombotic therapy for prevention and treatment of thrombosis. American College of Chest Physicians. *Chest* 2001;119:1S-2S.
13. Hrebickova L, Nawarskas JJ, Anderson JR. Ximelagatran: a new oral anticoagulant. *Heart Dis* 2003;5:397-408.
14. Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol* 2003;41:1445-51.
15. Bredberg E, Andersson TB, Frison L, et al. Ximelagatran, an oral direct thrombin inhibitor, has a low potential for cytochrome P450-mediated drug-drug interactions. *Clin Pharmacokinet* 2003;42:765-77.
16. Johansson LC, Frison L, Logren U, Fager G, Gustafsson D, Eriksson UG. Influence of age on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor. *Clin Pharmacokinet* 2003;42:381-92.
17. Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003;146:431-38.
18. Olsson SB. 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;362:1691-98.

Dr. Moe discloses that St. Michael's Hospital received research grants from AstraZeneca for participating in SPORTIF V. This issue of Cardiology Scientific Update was not financially supported by AstraZeneca or any other agencies.