

Preventing Stroke in Atrial Fibrillation: The SPORTIF Programme

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Key Words

Stroke prevention · Oral direct thrombin inhibitors · Oral vitamin K antagonists · Ximelagatran · Warfarin · Non-valvular atrial fibrillation · SPORTIF III · SPORTIF V

Abstract

Atrial fibrillation (AF) is the most common cardiac risk factor for stroke. Oral anticoagulants such as the vitamin K antagonist warfarin have been proven effective in reducing the risk of stroke in AF. Warfarin, however, has many disadvantages including the need for coagulation monitoring, a narrow therapeutic index, inter-/intra-patient variability and food–drug interactions. As a result, warfarin is underused in clinical practice and a viable alternative is needed. Ximelagatran, the first oral direct thrombin inhibitor, is given as a fixed dose, does not have a narrow therapeutic index, has low potential for drug interactions, has no significant food interactions and does not require coagulation monitoring. Ximelagatran has been evaluated in the Stroke Prevention using an Oral direct Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trial programme, the largest clinical trials of antithrombotic therapy for stroke prevention in AF to date. The phase III trials, SPORTIF III and V, compared ximelagatran (36 mg twice daily) with well-controlled warfarin (international normalized ratio 2.0–3.0) in a combined population of more than 7,000 moderate- to high-risk AF patients. Data from SPORTIF III show an absolute reduction in stroke and systemic embolic events

with ximelagatran compared with warfarin at 21 months (1.6 vs. 2.3% per year, respectively; $p = 0.10$). Preliminary data from SPORTIF V appear to further support non-inferiority between the two agents. On-treatment analysis of the rate of major bleeding events shows an absolute, nonsignificant reduction in the event rate per year with ximelagatran versus warfarin in both studies. The results of SPORTIF III and V demonstrate that a fixed oral dose of ximelagatran, without coagulation monitoring, is comparable to dose-adjusted warfarin in preventing stroke and other thromboembolic complications among moderate- to high-risk AF patients and has a lower rate of both major and minor bleeding. With its positive benefit-risk ratio, ximelagatran may increase the population of eligible patients for anticoagulation with AF and maximize the potential of anticoagulation in the prevention of stroke.

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Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Recent estimates using data from the Framingham Heart Study suggest that men and women older than 40 years have a 1:3 risk of developing AF during their lifetime [1]. The incidence of AF increases rapidly with age so that the lifetime risk is similar in those aged older than 80 years [1]. Furthermore, AF confers an independent risk of stroke that is greater than that of cor-

onary heart disease (CHD) or hypertension [2], such that 15% of all strokes occur in people with AF [3].

Risk factors for stroke in AF include previous stroke, hypertension, heart failure (HF), increasing age, diabetes and coronary artery disease (CAD) [4]. In addition, evidence suggests that women with AF and CHD have a higher risk of stroke and of mortality than men [5]. The risk of stroke in AF increases dramatically with age: half of all AF-associated strokes occur in patients older than 75 years, and in the Framingham Heart Study, the risk of stroke attributable to AF increased from 1.5% in those aged 50–59 years to 23.5% for those aged 80–89 years [2]. The prevalence of AF is predicted to increase 2.5-fold between 2000 and 2050 [6], reflecting the ageing population. Therefore the management of AF to prevent thromboembolism and consequent death and disability will assume growing importance, particularly in high-risk populations.

Prevention of Stroke in Atrial Fibrillation: Current Issues

Current treatment guidelines recommend the use of oral anticoagulation therapy in AF to prevent thromboembolism in patients older than 75 years of age, in patients older than 65 years with risk factors such as diabetes, hypertension or CAD, and in patients of any age with other risk factors such as HF, hypertension or prior stroke (table 1) [7, 8]. The efficacy of the vitamin K antagonists – particularly warfarin – for reducing the risk of stroke in AF is well established. A meta-analysis of the use of dose-adjusted warfarin in primary and secondary prevention trials found that warfarin reduced the risk of stroke by 62% (95% CI, 48–72%) and the risk of all-cause mortality by 26% (95% CI, 4–43%) compared with placebo [3]. In the same analysis, aspirin was less effective, reducing the risk of stroke by 22% compared with placebo.

Despite compelling evidence from randomized, controlled clinical trials for the efficacy of warfarin in patients with AF who are most at risk of stroke, warfarin is underused in clinical practice. Studies from around the world highlight that warfarin is underused among eligible patients, and that patients are rarely treated in accordance with guidelines. In the USA, for example, estimates of the proportion of patients treated according to guidelines range from 44 [9] to 79% [10]. Studies in the UK show that in 1994, only 20% of appropriate patients received warfarin [11], and by 1998, this proportion had

Table 1. Risk stratification and anticoagulation in non-valvular atrial fibrillation. Adapted from Lip GY, et al. *Br Med J* 2002; 325: 1022–1025 [8].

Assess risk, and reassess regularly

- 1 High risk (annual risk of CVA = 8–12%)
 - All patients with previous transient ischaemic attack or CVA
 - All patients aged ≥ 75 with diabetes and/or hypertension
 - All patients with clinical evidence of valve disease, heart failure, thyroid disease and/or impaired left ventricular function on echocardiography¹
- 2 Moderate risk (annual risk of CVA = 4%)
 - All patients aged <65 with the clinical risk factors diabetes, hypertension, peripheral arterial disease or ischaemic heart disease
 - All patients aged >65 who are not in the high-risk group
- 3 Low risk (annual risk of CVA $<1\%$)
 - All other patients <65 with no history of embolism, hypertension, diabetes or other clinical risk factors

Treatment

High risk: give anticoagulation (vitamin K antagonists, dose-adjusted to attain INR 2.0–3.0) if no contraindications and possible in practice

Moderate risk: either anticoagulation or aspirin 75–300 mg

In view of insufficient clear-cut evidence, treatment may be decided on individual cases. Referral and echocardiography may help.

Low risk: give aspirin 75–300 mg daily

CVA = Cerebrovascular accident.

¹ Echocardiography – not needed for routine risk assessment but refines clinical risk stratification in case of impaired left ventricular function and valve disease. A large atrium per se is not an independent risk factor on multivariate analysis.

only increased marginally to 23% [12]. A study of patients in general practice in the UK found that the target international normalized ratio (INR) for warfarin recommended by the British Society for Haematology was only being achieved in 41% of patients [13]. Furthermore, in groups at the highest risk of stroke, such as those older than 75 years, there is evidence that the use of warfarin is even lower [14].

Why is warfarin not more widely used? There are a number of factors associated with warfarin that limit its use in those patients who could benefit. Warfarin has unpredictable activity and is associated with serious safety issues, including a risk of major bleeding that necessitates regular coagulation monitoring. There is an annual rate of severe bleeding of 1.2% in patients treated with warfarin [3]. Warfarin has a narrow therapeutic index whereby the risk of bleeding increases substantially as the INR in-

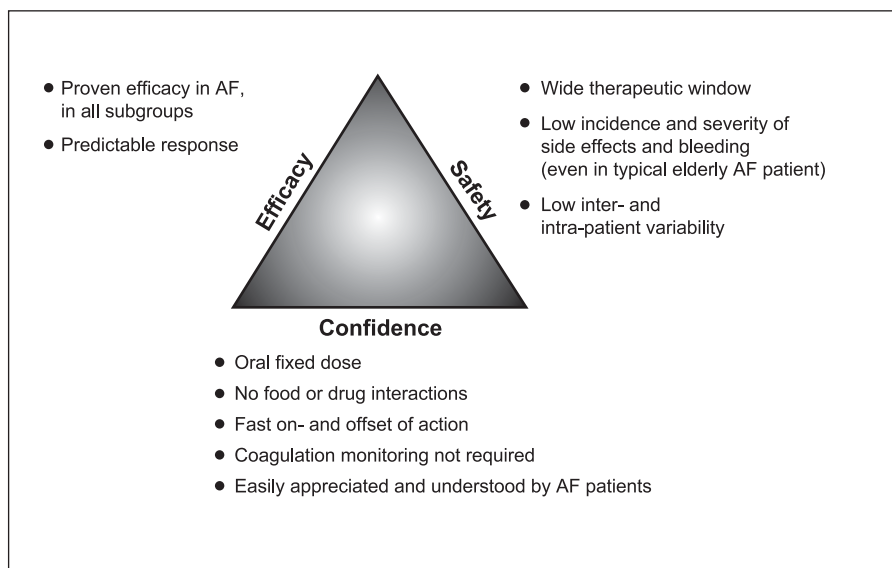


Fig. 1. Ideal characteristics of an antithrombotic agent in AF.

creases above the target of 2.0–3.0, but the risk of stroke increases below this range [15]. Furthermore, age is one of the most powerful predictors of bleeding complications with warfarin [16] – meaning that the risk of bleeding is highest in those most at risk of stroke. Warfarin is associated with numerous food and drug interactions [17], with the result that patients with comorbidities (and in some cases a consequent increased risk of stroke) may be excluded from the benefits of prophylactic anticoagulant therapy. These limitations and the need for regular monitoring of warfarin’s coagulation effect mean that many physicians and patients are reluctant to start treatment. This had led to wide variation (and disagreement) among UK consultants regarding the best treatment strategies for AF [18, 19].

The Need for New Treatment Options

With the limitations of current oral anticoagulants, how can thromboprophylaxis in AF be optimized, and what is required for the ‘ideal’ antithrombotic agent? Figure 1 summarizes what might be considered as ideal characteristics for a new antithrombotic agent in AF. Not only is a drug required with proven efficacy in all subgroups of AF patients and with a predictable response, it also needs to have the convenience of an oral fixed dose, a lack of food or drug interactions, no requirement for coagulation monitoring, and a fast on- and offset of action. It is also important that the treatment is appreciated and un-

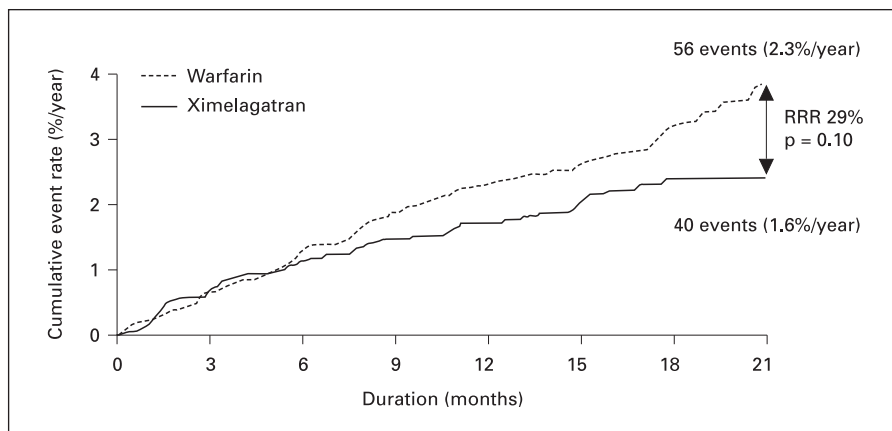
derstood by patients with AF, as many patients do not know why they are taking warfarin, let alone the importance of taking it regularly and the need for INR monitoring [20]. Finally, it is essential that the agent is well tolerated, does not have a narrow therapeutic window, has a low incidence and severity of side effects and bleeding, and has low inter- and intra-patient variability.

Does such an ideal agent exist? Ximelagatran, the first oral agent in the new class of direct thrombin inhibitors, may potentially be such an antithrombotic agent for AF, as supported by data from the Stroke Prevention using an ORal direct Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trial programme. The SPORTIF programme investigated the efficacy and safety of ximelagatran for prevention of stroke in AF, and is the largest such study of antithrombotic therapy for stroke prevention in AF yet undertaken [21].

SPORTIF III and V: Study Design

The phase III trials of ximelagatran, SPORTIF III and V, compared ximelagatran with warfarin in patients with non-valvular AF and one or more risk factors for stroke [21]. The objective was to demonstrate the non-inferiority of ximelagatran compared with warfarin. Both were randomized, multi-centre, parallel-group studies that were identical in design except that SPORTIF V was double blinded whereas SPORTIF III was open label, and SPORTIF V was conducted at 409 sites in North Amer-

Fig. 2. Cumulative event rate of stroke and systemic embolism in SPORTIF III (intention-to-treat analysis). RRR = Relative risk reduction. Reproduced with permission from Elsevier [22].



ica, while SPORTIF III took place in 259 sites in Europe, Asia and Australasia [21]. While the trials were run independently, their similar designs allowed a pre-defined pooling of results [21]. Patients were randomized to receive ximelagatran (36 mg twice daily) or dose-adjusted warfarin (INR 2.0–3.0), for a minimum per-patient exposure of 12 months [21]. The mean duration of treatment was 17 months in SPORTIF III (n = 3,407) and 20 months in SPORTIF V (n = 3,922), with primary analysis based on intention to treat [21]. The primary end point in both studies was the incidence of stroke and systemic embolic events [21].

Considering the combined population from both studies, approximately 90% had persistent AF and the population overall was at substantially higher risk of stroke [21]. The majority (~70%) were males and the mean age was 71 ± 8.9 years. Almost 80% were hypertensive and 25% had had a prior stroke or transient ischaemic attack. More than 70% of patients had two or more of the following risk factors for stroke in addition to AF: prior stroke; age greater than 75 years; left ventricular dysfunction or congestive heart failure; hypertension; and age greater than 65 years with CAD or diabetes.

An important aspect of the SPORTIF trials was the quality of warfarin control. The proportion of patients receiving warfarin who were within the target INR range of 2.0–3.0 was 66 and 68% in SPORTIF III [22] and SPORTIF V [23], increasing to 81 and 83%, respectively, within an INR range of 1.8–3.2. This is a substantially higher degree of dose control than is seen in clinical practice [13] or in many previous trials [24], and allows a comparison of ximelagatran with well-controlled warfarin.

SPORTIF III and V: Efficacy Results

Published results from the open-label SPORTIF III trial indicate that ximelagatran is at least as effective as warfarin in the prevention of stroke in AF [22]. In the intent-to-treat analysis there was a nonsignificant absolute reduction in the cumulative event rates for the primary end points of stroke and systemic embolism at 21 months in the ximelagatran compared with the warfarin group (1.6 vs. 2.3% per year, respectively; $p = 0.10$), equivalent to a relative risk reduction of 29% (fig. 2) [22]. The publication of detailed results from SPORTIF V and from a pre-planned pooled analysis of SPORTIF III and V is pending. However, preliminary data from SPORTIF V appear to further support non-inferiority between the two agents, showing no significant difference in primary events between the two treatment groups at 24 months: 1.6% per year in the ximelagatran group vs. 1.2% per year with warfarin ($p = 0.13$) [23].

SPORTIF III and V: Safety

On-treatment analysis of the rate of major bleeding events in SPORTIF III and V shows an absolute, non-significant reduction in the event rate per year with ximelagatran versus warfarin in both studies (fig. 3) [22, 23]. However, ximelagatran produced a statistically significant reduction in the composite end point of major and minor bleeds compared with warfarin [22, 23].

An increased incidence of elevated liver enzyme levels (defined as an alanine transaminase rate of three times the upper limit of normal) was seen in the ximelagatran group compared with the warfarin group in both trials: in

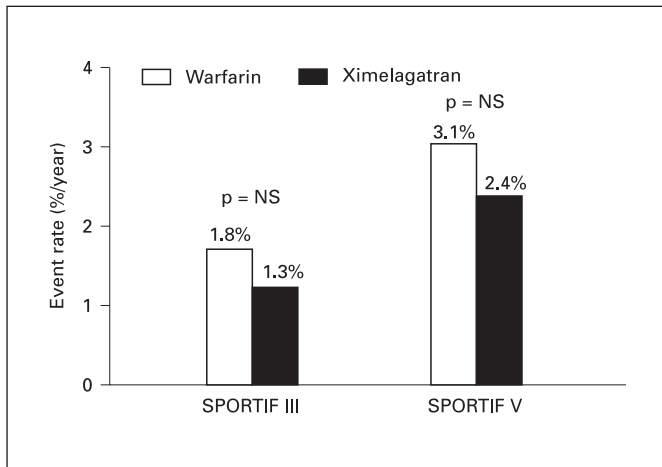


Fig. 3. Major bleeding events in SPORTIF III and V (on-treatment analysis) [22, 23]. NS = Nonsignificant. Adapted from Albers GW, on behalf of the SPORTIF Investigators. American Academy of Neurology 2004 [26].

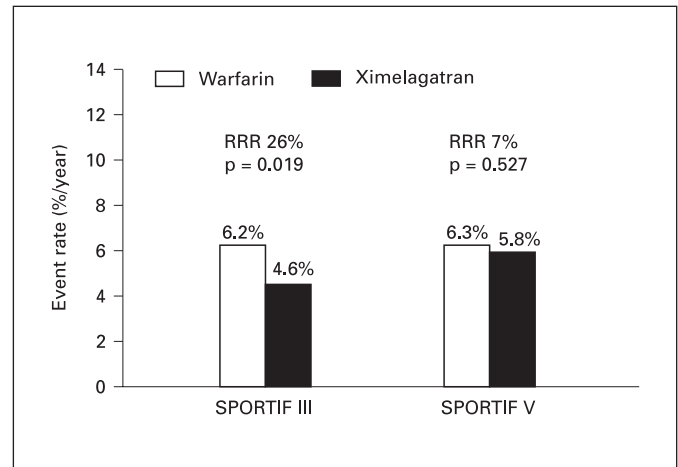


Fig. 4. Net clinical benefit in SPORTIF III and V, calculated as relative risk reduction in cumulative events of stroke and systemic embolism, major bleeding and death [22, 25]. Adapted from Halperin JL, for the Executive Steering Committee on behalf of the SPORTIF V investigators. American Heart Association 2003 [25].

SPORTIF III the incidence was approximately 6 vs. 1%, respectively [22], with similar results in SPORTIF V (6 vs. 0.8%) [23]. These occurred in the first 6 months of treatment and typically tended to be transient and to resolve spontaneously, whether or not the drug was continued or discontinued. Based on these findings and similar liver enzyme changes reported from other ximelagatran trials in venous and arterial thrombosis, it is likely that liver function testing will be required when a patient is started on ximelagatran therapy.

SPORTIF III and V: Net Clinical Benefit

What do the results of SPORTIF III and V mean to our patients? What is the net clinical benefit to the patient in terms of prior events, risk of bleeding and mortality? The net clinical benefit demonstrated by ximelagatran compared with warfarin can be calculated in terms of the composite effect on primary events (stroke and systemic embolism), major bleeding events and mortality (fig. 4). Results from SPORTIF III demonstrated that treatment with ximelagatran in high-risk patients with AF results in a statistically significant reduction in stroke and systemic embolism, major bleeding events and mortality of 26% compared with warfarin (4.6 vs. 6.2% per year; $p = 0.019$) [22]. Preliminary results from SPORTIF V show a nonsignificant relative risk reduction of 7% with ximelagatran compared with warfarin (5.8 vs. 6.3% per year; $p = 0.527$) [25].

Conclusions

Warfarin, a treatment with proven efficacy in the prevention of stroke in AF, is associated with significant safety issues and inconveniences, including the need for frequent coagulation monitoring and numerous food– and drug–drug interactions. Because of the limitations of warfarin, it is underused in clinical practice and many patients do not receive appropriate or effective prophylaxis. Trials with ximelagatran, the first oral direct thrombin inhibitor, suggest that this agent may offer a promising alternative to warfarin. The results from SPORTIF V support previous findings from SPORTIF III in demonstrating the comparable efficacy of ximelagatran and well-controlled warfarin in the prevention of stroke in AF. In addition, they confirm the lower risk of bleeding conferred by ximelagatran. Results from SPORTIF III and V suggest that ximelagatran offers a net clinical benefit in terms of prevention of primary events, bleeding and mortality that is superior to warfarin. Together with the convenience of fixed oral dosing and elimination of the need for coagulation monitoring, SPORTIF III and V demonstrate the potential of ximelagatran as a new option to improve treatment outcomes in AF through consistent and predictable anticoagulation, and, crucially, to increase the proportion of patients eligible for prophylactic anticoagulant therapy.

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