REVIEW

Direct thrombin inhibitors: novel antithrombotics on the horizon in the thromboprophylactic management of atrial fibrillation

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Antithrombotic agents have verified efficacy in reducing the thromboembolic risk associated with atrial fibrillation. This article focuses on the emergence of a new oral direct thrombin inhibitor, ximelagatran, into the arena of atrial fibrillation thromboprophylaxis. This review does not cover atrial fibrillation in the context of valvular heart disease. The efficacy of aspirin and warfarin will be discussed briefly.

prevention and 2.5%/year for secondary prevention (numbers needed to treat of 66 and 40 respectively).

ORAL ANTICOAGULANT THERAPY: EVIDENCE FOR WARFARIN

Warfarin, which was introduced 60 years ago, is the current mainstay of oral antithrombotic therapy for AF. However, despite its confirmed superior efficacy as compared with aspirin, warfarin therapy can be problematic with some patients swinging between bleeding and clotting.^{4 10}

Table 2 summarises five randomised controlled trials of warfarin compared with control or placebo for the prevention of stroke in patients with NVAf. All of these trials were stopped early because of strongly positive results in favour of warfarin.^{11 12 19–21} Meta-analysis of the five primary prevention trials showed that the relative risk of stroke was reduced by 67% (from 4.5%/year to 1.6%/year; 95% CI 50% to 79% $p < 0.001$) but with an increased risk of major bleeding from 1.0% to 1.3%.²² The European atrial fibrillation trial, which compared warfarin, aspirin and placebo in NVAf patients with recent transient ischaemic attacks or minor ischaemic stroke, mirrored these results with a relative risk reduction of 66% with warfarin ($p < 0.001$).²³ The absolute reduction in strokes was much greater (80/year/1000 compared with 31/year/1000) because the baseline stroke rate in the study population was higher.²³

ASPIRIN COMPARED WITH WARFARIN

Table 3 shows the results of five randomised trials comparing aspirin with warfarin for primary prevention of stroke in NVAf; meta-analysis found that warfarin reduces the risk of stroke compared with aspirin by 36% (95% CI 14% to 52%).^{11 13 18 23–25} Low intensity warfarin alone or in combination with aspirin is significantly less effective than adjusted dose warfarin in this patient population.²⁶

Several professional bodies have issued guidelines to assist physicians in managing AF. Most have recommended adjusted dose warfarin (international normalised ratio (INR), 2.0–3.0) for patients at increased risk of future stroke.^{27–30}

Abbreviations: AF, atrial fibrillation; NVAf, non-valvular atrial fibrillation; SPORTIF, stroke prevention using an oral thrombin inhibitor in atrial fibrillation; TIA, transient ischaemic attack; ALAT, alanine aminotransferase

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice¹ because of an increasingly aging population coupled with improved survival of patients with cardiac disease. The median age of patients presenting with AF is 75 years; with 84% older than 65 years.² Consequently in medical circles, AF is increasingly being recognised as the “modern global epidemic” resulting in a huge burden on health resources; about 1 in 100 of the population have AF and the rate rises to greater than 1 in 10 in the elderly.³

AF is far from being a “benign arrhythmia” and is associated with increased morbidity and mortality. The Framingham study showed an increased incidence of stroke in AF patients with annual incidence being similar to patients with rheumatic and non-rheumatic AF.^{4 5} It is associated with doubling of overall morbidity and mortality from cardiovascular disease⁶ and has now become the leading cause of embolic stroke.⁷ Patients with non-valvular atrial fibrillation (NVAf) have a 5.6-fold greater risk for embolism and those with AF of rheumatic valvular origin have a 17.6-fold greater risk as compared with healthy controls.⁸ This quantifies as increased risk of about 5% per year for primary events and 12% per year for recurrent events.^{9 10}

ANTIPLATELET THERAPY: EVIDENCE FOR ASPIRIN

Aspirin does not have a similar thromboprophylactic efficacy in AF to warfarin, with the degree of reduction in risk of stroke being less pronounced. Table 1 summarises the six randomised trials of aspirin compared with placebo; meta-analysis of these trials shows an overall reduction of risk of all strokes of 22% (95%CI 2% to 38%).^{11–18} There was no significant increased risk of bleeding. Aspirin leads to an absolute stroke risk reduction of 1.5%/year for primary

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PROBLEMS ASSOCIATED WITH WARFARIN USE

Warfarin therapy is efficacious, but is beset with its own problems. Warfarin reduces the synthesis of vitamin K dependent procoagulant factors II, VII, IX, and X to exert its pharmacokinetic effects. Its dose response is influenced by various drugs as it is metabolised by the P450 enzyme complex. Other factors that can affect its dose response are liver dysfunction, genetic factors, changes in gut flora, patient compliance, and alcohol intake.³¹ A very narrow therapeutic window along with pronounced variability in its dose response necessitates frequent checks and hospital visits.³² Home monitoring has been touted as one possible solution; but adds to the initial cost and many patients may prefer first to choose this option. Clinical trial data have shown that ischaemic stroke is far more likely with an INR<2.0, whereas an INR>4.0 increases the risk of intracranial haemorrhage.^{33–35}

These concerns with warfarin use have led to the development of cautious prescription and under-treatment in an increasing litigious society.^{36–38} Patients are considered to be at an increased risk of major bleeding secondary to risk factors such as hypertension, history of falls, gastrointestinal haemorrhage, drug interaction worries, living alone with lack of assurance about compliance.^{39–43} Attempts to reduce the potential risk of bleeding by using a low and fixed dose of warfarin have proved unsuccessful, being associated with a fourfold increased risk of stroke.^{43–45}

XIMELAGATRAN

Ximelagatran is a novel oral direct thrombin inhibitor (fig 1) that is rapidly hydrolysed to melagatran, its active form, after absorption.⁴⁶ Melagatran has been shown to be a potent competitive inhibitor of human α thrombin that inhibits both thrombin activity and generation.⁴⁷ Melagatran has a wide therapeutic window—that is, unlike warfarin it can be given safely across a wide range of doses without a progressive increase in risk of bleeding. Although melagatran has all the requisite pharmacodynamic properties of a new antithrombotic agent, it has low oral bioavailability. This led to the development of its prodrug, ximelagatran, which is 170 times more lipophilic than melagatran and remains unchanged at intestinal pH. Ximelagatran has sufficient bioavailability (20%) for oral administration with low inter-subject variation.^{47 48}

The absorption and bioconversion of ximelagatran to melagatran is rapid and a peak plasma concentration of melagatran is achieved two to three hours after oral intake of ximelagatran. The mean elimination half life is three hours. Its pharmacokinetic profile is predictable and stable over time and is unaffected by patient bodyweight, age, sex, or ethnic origin.^{49–51} As it does not use the hepatic P450 system for its metabolism, there is lower potential for drug interactions, and no known food interactions.^{49 50 53 54} These factors would

seem to imply that coagulation monitoring and dose adjustments are unnecessary. However, this has to be tempered by the fact that recent data do suggest that a reduction in dose or an increase in the administration interval in patients with severe renal impairment, or both, would be required.⁵⁴ Furthermore, in the future drug interactions or a need for dose change may become evident. One important negative factor of ximelagatran is that at present there is no agent available to counteract drug related haemorrhage. Because of its short half life, there may be no clinical need for an antidote. In animal experiments, Feiba (factor eight inhibitor bypassing activity, a coagulation factor concentrate) reversed the prolonged bleeding time and melagatran induced inhibition of thrombin without being prothrombotic.⁵⁵

Additional potential advantages of ximelagatran include a targeted specificity for thrombin, the ability to inactivate clot bound thrombin, and an absence of plasma protein and platelet interactions thus avoiding potential problems such as thrombocytopenia associated with heparin use.

The role of ximelagatran in the prevention of stroke in AF patients has been studied in the stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) programme. The SPORTIF programme consists of a group of studies comparing the efficacy and safety of warfarin and ximelagatran in more than 7700 patients. The programme comprises two dose guiding and long term safety studies (SPORTIF II⁵⁶ and SPORTIF IV⁵⁷) and two randomised, phase III trials—SPORTIF III and V^{58 59}), assessing ximelagatran against warfarin. Bleeding was categorised as major when associated with functional deficit, haemoglobin decreased by 20 g/l, two units or more of transfusion was given, or critical anatomical sites (intracranial, intraspinal, intraocular, retro-peritoneal, pericardial, or intra-articular) were involved. All other overt bleeding was classified as minor.

SPORTIF II AND IV TRIALS: DOSE GUIDANCE AND LONG TERM SAFETY

SPORTIF II was a 12 week, randomised, double blind, parallel group, dose guiding study performed in 37 centres and 11 countries in Europe and North America.⁵⁶ Patients were enrolled with NVAf and at least one additional risk factor for stroke. The primary objective was to compare the tolerability and safety of three fixed doses of ximelagatran with warfarin in patients with NVAf. Three groups received fixed dose ximelagatran (n = 187) at 20, 40, and 60 mg twice daily given without coagulation monitoring, and a fourth group (n = 67) received adjusted dose warfarin with routine monitoring to achieve an INR of 2.0–3.0. The primary end point assessed the number of thromboembolic events and bleeding events.

A total of 254 patients received the study drug. One non-fatal ischaemic stroke and one transient ischaemic attack

Table 1 Non-valvular atrial fibrillation trial outcomes with aspirin

Trial	All strokes control events/1000 patient/year	Aspirin events/1000 patient/year	Relative risk reduction (%)	Absolute risk reduction events/1000 patient/year
AFASAK ¹¹	48	39	17	9
EAF ²⁹	122	103	11	19
ESPF II ¹⁴	207	138	29	69
SPAF ¹²	60	35	44	25
LASAF ¹⁶	22	27(125 mg/day)	–17	–5
LASAF ¹⁶	6	22(125 mg/2 days)	67	16
UK-TIA ¹⁷	67	58(300 mg/day)	17	9
UK-TIA ¹⁷	67	60(1200 mg/day)	14	7
Overview ¹⁸	80	63	22	17

Table 2 Non-valvular atrial fibrillation outcomes of randomised trials with warfarin

Trial	Control events/ 1000 patient/ year	Warfarin events/ 1000 patient/ year	Relative risk reduction %	Absolute risk reduction events/ 1000 patient/ year	Major bleed* absolute increase events/1000 patient/year
AFASAK ^{11, 24}	50	32	36	18	8
BAATAF ¹⁹	30	4	87	26	2
CAFA ²¹	38	26	32	12	15
SPAF ¹²	70	23	67	47	-1
SPINAF ²⁰	43	9	79	34	6
Overview ²²	45	14	68	31	3

*Major bleed defined as intracranial bleeding, a bleeding event requiring two units of blood, or an event requiring hospital admission.

(TIA) occurred in the ximelagatran group. Two TIAs occurred in the warfarin group.

No major bleeds were seen in the ximelagatran group but one major bleed occurred in a warfarin treated patient. Minor bleeding rates for all doses were similar to that in warfarin patients. Liver enzyme abnormalities were detected with increased serum alanine aminotransferase (ALAT) in eight patients (4.3%) taking ximelagatran, but normalised whether treatment was continued or withdrawn.

The authors concluded that fixed oral doses of ximelagatran up to 60 mg twice daily were well tolerated, without the need for dose adjustment or coagulation monitoring.

SPORTIF IV

This study is an ongoing, open label continuation of the dose guiding SPORTIF II study comparing the long term efficacy and safety of fixed dose ximelagatran compared with dose adjusted warfarin in patients with NVAF.³⁷ The primary objective is to compare ximelagatran and warfarin over a five year follow up for the prevention of stroke and systemic embolism in patients with chronic NVAF. Patients receive

either fixed dose ximelagatran 36 mg twice daily or dose adjusted warfarin (INR of 2.0–3.0). Patients were previously treated for between 21 and 26 months in SPORTIF II, and the follow up is continuing for a total of five years.

During SPORTIF IV a total of 187 patients have received ximelagatran and 67 patients have received warfarin. A two year interim analysis showed that two non-fatal ischaemic strokes occurred in the ximelagatran group and two fatal hemorrhagic strokes occurred in the warfarin group. One patient in the ximelagatran group and two patients in the warfarin group reported TIAs.

Major bleeds occurred in two patients from the ximelagatran group and two patients treated with warfarin. A total of five patients died, including the two warfarin treated patients who had strokes. In the ximelagatran group, three patients died, one died of cardiac arrhythmia, one patient died of brain tumour, and one elderly patient died of multiorgan failure associated with old age.

The authors concluded that fixed dose ximelagatran (36 mg twice daily) showed promise as an agent for prevention of stroke and systemic embolism and was well

Figure 1 Site of action on the clotting cascade of direct thrombin inhibitor ximelagatran.

Table 3 Trials comparing warfarin with aspirin for primary prevention of stroke in non-valvular atrial fibrillation

Trial	All strokes		Relative risk reduction (%)	Absolute risk reduction events/1000 patient/year
	Warfarin events/1000 patient/year	Aspirin events/1000 patient/year		
SPAF II ²³				
Age <75	17	19	10	2
Age >75	50	55	10	5
AFASAK ¹¹	22	39	45	17
AFASAK II ²⁴	31	25	-23	-6
EAF ²⁹	39	109	67	70
PATAF ²⁵	7	10	20	3
Overview ¹⁸	26	40	36	14

tolerated without the need for routine coagulation monitoring (similar bleeding rates to tightly controlled adjusted dose warfarin).

Large phase III clinical trials were subsequently conducted to assess the efficacy and safety of ximelagatran compared with warfarin for long term prevention of stroke and systemic embolic events in patients with AF (SPORTIF III and V^{58, 59}).

PHASE III STUDIES IN NVAF: SPORTIF III AND V

SPORTIF III was a randomised, open label trial involving 3407 patients from 23 countries in Europe, Asia, and Australia. This study had a non-inferiority design. However a rather "generous" prespecified absolute margin of 2% per year in primary events compared with warfarin was permitted considering, for example, that in the AFASAK trial of warfarin compared with placebo in NVAF an absolute difference in primary events of only 1.8% was found with warfarin use. The primary objective was to establish that fixed dose ximelagatran (36 mg twice daily) is at least as effective as dose adjusted warfarin (target INR 2.0–3.0) for the prevention of stroke and systemic embolic events in patients with atrial fibrillation. All patients enrolled had chronic NVAF and at least one other risk factor for stroke.⁵⁹ Liver function tests were done monthly for the first six months and every two months during year 1, and every three months thereafter. Study treatment was stopped if parameters of liver function rose above five times the upper limit of normal, if a rise between three and five times the upper limit of normal persisted for eight weeks, or if clinical signs of hepatotoxicity developed.

At the end of the study the mean per patient exposure was 17.4 months. Total exposure was 4941 patient years and 96 primary events occurred. By intention to treat analysis the primary event rate in the two groups was similar, 1.6% per year in ximelagatran patients and 2.3% per year in warfarin patients with a relative risk reduction of 29%. This established the non-inferiority of ximelagatran. Subset analysis showed that among the patients who remained on treatment throughout the study, there was a 43% reduction in the risk of stroke in the ximelagatran group, which was significant ($p = 0.018$).

The rate of major bleeds was low in both treatment groups but the combined rate of major and minor bleeds was significantly lower for ximelagatran compared with warfarin (25.8% per year compared with 29.8% per year, $p = 0.007$).

On the negative side however abnormal liver function tests as assessed by ALAT activities showed that ALAT increase of more than three times the upper limit of normal occurred in a much higher proportion of ximelagatran patients (107; 6.3%) compared with warfarin (14; 0.8%). Increases reached greater

than five times the upper limit of normal in 57 patients assigned to ximelagatran (3.4%). Of the 121 patients who had an increase in ALAT more than three times the upper limit of normal 52 stopped the study drug prematurely, 48 in the ximelagatran group and four in the warfarin group. Fifty nine patients in the ximelagatran group continued treatment with raised ALAT; 55 of these returned to normal, three returned to less than two times upper limit of normal, and one in whom ALAT was more than twice the upper limit of normal before the study remained at this value. Of the 48 patients in the ximelagatran group with raised ALAT who stopped treatment, 42 returned to normal, four returned to less than twice the upper limit of normal, and two died of unrelated diseases.

SPORTIF III therefore suggested that ximelagatran, given in a fixed dose without coagulation monitoring, provided protection against thromboembolic phenomenon in patients with atrial fibrillation against stroke as effectively as well controlled warfarin, and with less bleeding.

The SPORTIF V trial randomised 3922 NVAF patients (and more than one additional vascular risk factor) to receive ximelagatran 36 mg, twice daily or dose adjusted warfarin.⁵⁸ Unlike SPORTIF III this study was not open label but a double blind double dummy trial.

At the end of the study the mean per patient exposure was 20 months. Total exposure was 6405 patient years and 88 primary events occurred. Primary event rates (all strokes and systemic emboli events) were 1.2%/year in the well controlled warfarin group (INR within target range 68% of the time) and 1.6%/year in the ximelagatran group ($p = 0.13$).

Rates of major bleeding did not differ significantly between groups (2.4% compared with 3.1%), but combined minor and major bleeding was lower in the ximelagatran group (37% compared with 47%, $p < 0.0001$).

Serum ALAT increases to more than three times the upper limit of normal occurred in 6.0% of patients receiving ximelagatran compared with 0.8% of patients receiving warfarin—($p < 0.001$) within the first six months of treatment—but generally returned toward baseline activities whether the treatment was continued or discontinued.

Thus in this large, double blind trial, fixed dose oral ximelagatran was at least as effective as well controlled warfarin for prevention of stroke and systemic embolic events and resulted in less overall bleeding, supporting the results of the SPORTIF III trial.⁶⁰

A pre-specified pooled analysis of 7329 patients from the SPORTIF programme (SPORTIF III and V), was presented as an oral presentation at American Heart Association meeting in November 2003, and confirmed the efficacy (event rate of 1.6%/year compared with 1.6%/year) in a large pooled patient population with NVAF and at high risk of stroke.

Liver function abnormalities

The optimism of the efficacy data from SPORTIF III and V has to be severely tempered however by the safety data. Both the SPORTIF studies and other clinical studies using ximelagatran (for example, ESTEEM study⁶¹ in patients with recent myocardial infarction) consistently show liver abnormalities in 6%–9.6% of patients and the increases seem to be hepatocellular in origin. Typically, these abnormalities occur between six weeks and six months of treatment. In the SPORTIF studies there has been one case of a biopsy confirmed drug induced liver failure leading to death. There was a second probable case of drug induced liver failure leading to coagulopathy and subsequently death. These data have led the Cardiovascular and Renal Drugs Advisory Committee to the US FDA recently in September 2004 to advise that more data were needed to support the approval of ximelagatran. They felt that on present data ximelagatran should not be recommended for the indications sought (prevention of strokes in patients with AF, prevention of blood clots in patients undergoing knee replacement surgery, and for the long term secondary prevention of blood clots after standard treatment of a clot). The committee also felt that intense protocol mandated liver enzyme monitoring did not prevent serious liver toxicity in the two cases who died and thus liver enzyme monitoring as a risk management strategy may not be entirely fool proof.

SUMMARY

Ongoing and completed safety and efficacy trials of ximelagatran in the treatment and prevention of venous thromboembolic,^{62–67} and in post-myocardial infarction situations⁶¹ should ensure this drug a wide clinical platform. The current efficacy data on AF are encouraging but liver toxicity problems are an important issue that will require further ongoing attention before clinical use can even be considered. Oral antithrombin agents such as ximelagatran, which do not require dose monitoring, or titration are likely to encourage an increased uptake of antithrombotic therapy in appropriate AF patients.^{68–69} Ximelagatran, however, because of its potential liver toxicity problems may not be the agent to replace warfarin.

Finally, other alternatives to warfarin may be around the corner. There is an ongoing study (ACTIVE) comparing combination antiplatelet therapy of aspirin and clopidogrel with warfarin. Intravenous factor Xa inhibitors are already being assessed in clinical settings and an oral factor Xa inhibitor may become available for use in AF patients in the near future.⁷⁰

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