Introduction

Atrial fibrillation (AF) is the most common cardiac disorder, affecting one in 20 people older than age 60.1 The prevalence of AF is on the rise, owing largely to increased life expectancy and increased longevity among patients with chronic cardiac disease, which predisposes to AF.2,3 The incidence of stroke is increased five-fold to ~5% per year for primary events and 12% per year for recurrent events in patients with AF, despite a large number of these events being preventable by oral anticoagulant treatment of the highest-risk patients.4,5 The vitamin K antagonist (VKA) warfarin provides highly effective prophylaxis. Meta-analysis of key trials demonstrates that anticoagulation with adjusted-dose warfarin reduced stroke by 62% [95% confidence interval (CI), 48–72%], with absolute risk reductions of 2.7% per year [number needed to treat for 1 year to prevent one stroke (NNT), 37] for primary prevention and 8.4% per year (NNT, 12) for secondary prevention.6 Unfortunately, the long list of limitations associated with warfarin7 and the need for regular coagulation monitoring means that physicians and patients are reluctant to start using this effective prophylactic treatment,8 which has led to wide variations in management strategies for AF. This has spurred renewed efforts in the development of novel oral agents which may provide, after more than 60 years, a viable alternative to VKAs.

Direct thrombin inhibition

Thrombin has a central role in the coagulation cascade, and inhibition of its activity is pivotal in the prevention of thromboembolic events. Thrombin is the enzyme responsible for the conversion of fibrinogen to fibrin, a process required for the initiation and propagation of thrombus development. Consequently, thrombin was identified as a promising target for drug development. In contrast to other anticoagulants that inhibit thrombin activity indirectly, the direct thrombin inhibitors are small molecules that bind directly to the active catalytic site, allowing them to inhibit clot-bound as well as free thrombin.9,10 In addition, these inhibitors bind specifically to thrombin and do not form interactions with plasma proteins, producing a more consistent anticoagulant response. A number of direct thrombin inhibitors have been developed including hirudin, bivalirudin, argatroban, lepirudin, and desirudin, but these require parenteral administration,11 which has limited their use and development in the outpatient setting.
Ximelagatran

Ximelagatran is the first oral direct thrombin inhibitor. It is a lipophilic molecule that readily penetrates intestinal epithelial cells and is rapidly bioconverted to its active form, melagatran.12,13 Melagatran potently and reversibly inhibits thrombin with a half-life of 4–5 h. Ximelagatran has twice-daily fixed dosing, a fast onset and offset of action, no food or alcohol interactions,14,15 a low potential for drug interactions,16 and low inter- and intra-individual variability in dose–response relationship.11 Crucially, the predictable and consistent effect of ximelagatran means that it can be used the need for monitoring coagulation.13 Therefore, ximelagatran fulfils many of the criteria expected to increase confidence in anticoagulation use mentioned earlier. The efficacy and safety of ximelagatran have also been addressed by large, randomized clinical trials.

Ximelagatran clinical trial programme

The programme of clinical trials for ximelagatran development has involved more than 30 000 participants to date. The Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) clinical trial programme has evaluated the efficacy and safety of ximelagatran in high-risk patients with non-valvular AF.17 These trials represent the largest clinical studies to date involving antithrombotic therapy in patients with AF. SPORTIF III was carried out at 259 centres in Europe, Asia, and Australasia; and SPORTIF V at 409 centres in North America.17,18 The protocols for the two studies differed only in regard to treatment blinding, which accommodates differences in regulatory requirements in the different regions. SPORTIF III used open-label ximelagatran or warfarin, whereas anticoagulation treatment in SPORTIF V was double-blinded. Though the trials were run independently, their similar designs allowed a pre-specified analysis of the pooled results.

Given the proven efficacy of warfarin in patients with AF, the SPORTIF studies had an active-control design testing for non-inferiority within a margin of 2% per year of ximelagatran 36 mg twice daily, relative to dose-adjusted warfarin [target international normalized ratio (INR), 2.0–3.0] with blinded endpoint assessment.17,18 Each study accrued at least 4000 patient-years with a minimum per-patient exposure of 12 months. The mean duration of the trials was 17 months in SPORTIF III (n = 3407) and 20 months in SPORTIF V (n = 3922), with follow-up for up to 36 months. Primary analysis was based on intention to treat.

Publication of the final detailed analysis of the pooled SPORTIF III and V data is pending. Here we report published results from the individual SPORTIF III and SPORTIF V trials.18,19

Patient characteristics

The principal inclusion criteria for both studies were age of at least 18 years, persistent or paroxysmal AF (verified
by an electrocardiogram no more than 2 weeks before randomization), and at least one of the following risk factors for stroke: hypertension, age of at least 75 years, previous stroke, transient ischaemic attack (TIA) or systemic embolism, left ventricular dysfunction, or age of at least 65 years with coronary artery disease or diabetes mellitus.\textsuperscript{17}

The randomized population was predominantly white men and, as may be expected from a typical AF patient population, the majority of individuals were older than 65 years, with 35–40% older than 75. AF was persistent in 89% of patients, with a minority of patients having paroxysmal AF. The majority of patients (72%) had more than one risk factor for thromboembolism; hypertension was found in 77% of the cohort, a history of stroke or TIA in 21%, and left ventricular dysfunction in 37%.\textsuperscript{17}

Quality of warfarin control

For patients randomized to warfarin, the dose was adjusted to maintain the INR between 2.0 and 3.0, based on coagulation monitoring at maximum intervals of 4 weeks. In patients assigned to the warfarin groups of SPORTIF III and V, INR values were within the therapeutic range (INR, 2.0–3.0) for 66 and 68% of the time, respectively, and >80% of values were within the extended INR range of 1.8–3.2.\textsuperscript{18,19} This quality of warfarin management is considerably better than that generally achieved in clinical practice,\textsuperscript{20} and might account for the lower stroke rates in warfarin-treated patients in the SPORTIF studies when compared with other trials involving patients at comparable risk.\textsuperscript{21}

Efficacy and safety endpoints

The primary efficacy endpoint was to compare the efficacy of ximelagatran with that of warfarin for the prevention of all stroke (ischaemic or haemorrhagic) and systemic embolic events (SEE).\textsuperscript{17} Secondary endpoints included major and minor bleeding, treatment discontinuation, death, acute myocardial infarction, and TIA. Bleeding was defined as major when it was associated with functional deficit, when haemoglobin fell by 20 g/L, when transfusion was administered, or when it involved critical anatomical sites—including intracranial, intraspinal, intraocular, retroperitoneal, and pericardial—or atraumatic intra-articular haemorrhage. All other bleeding was classified as minor.\textsuperscript{17}

SPORTIF III and V: efficacy results

Intention-to-treat analysis of SPORTIF III and V demonstrated that the efficacy of ximelagatran was non-inferior to that of warfarin within the pre-specified margin of 2% per year. In the intention-to-treat analysis of SPORTIF III there was a non-significant absolute reduction in the cumulative events rates for the primary endpoints of stroke and SEE at 21 months in the ximelagatran group compared with the warfarin group. The primary event rate was 1.6% per year with ximelagatran and 2.3% per year with warfarin (absolute risk reduction, 0.7%; 95% CI, −0.1 to 1.4; \( P = 0.10 \)).\textsuperscript{18} In SPORTIF V, primary event rates were 1.6% per year and 1.2% per year in the ximelagatran and warfarin groups, respectively (Figure 2),\textsuperscript{19} giving an absolute difference of 0.45% per year (95% CI, −0.13 to 1.03; \( P = 0.13 \)) with upper limits of 95% confidence well below the predefined non-inferiority margin.

Safety

Rates of disabling stroke, haemorrhagic stroke, and major bleeding (Figure 3) showed no significant difference between warfarin and ximelagatran in both the SPORTIF studies.\textsuperscript{18,19} Ximelagatran, however, produced a statistically significant reduction in the annual incidence of the composite endpoint of major and minor bleeds compared with warfarin in both SPORTIF III (25.8 vs. 29.8%; \( P < 0.0065 \)) and SPORTIF V (37 vs. 47%; \( P < 0.0001 \)).\textsuperscript{18,19}

Liver safety was assessed through the testing of hepatic enzyme levels. In SPORTIF III and V, alanine aminotransferase (ALAT) elevation, defined as more than three times the upper limit of normal, occurred in 6% of patients taking ximelagatran compared with 1% of those taking warfarin.\textsuperscript{18} Similarly, in SPORTIF V, ALAT elevations occurred in 6 and 0.8% of patients treated with ximelagatran and warfarin, respectively.\textsuperscript{19}
time course reveals that, consistent with previous observations, these elevated ALAT levels typically occurred during the first 6 months of treatment and were mostly transient and resolved spontaneously without clinical sequelae, whether treatment was continued or not (Figure 4). On the basis of these findings, regular testing of hepatic enzymes followed by a period of surveillance will be appropriate. This precautionary testing, however, remains substantially less burdensome than the frequent coagulation monitoring and dose adjustments required for patients on warfarin therapy.

SPORTIF III and V: net clinical benefit

To summarize what the SPORTIF trial data mean to our patients, we can determine the net clinical benefit in terms of a composite of primary event rate (stroke and SEE), major bleeding rate, and mortality. SPORTIF III data reveal a significantly reduced composite event rate of 4.6% for ximelagatran compared with 6.2% for warfarin \( (P = 0.019) \), which equates to a relative risk reduction of 26%. SPORTIF V data also showed a reduced event rate with ximelagatran (5.8%) compared with warfarin (6.3%), suggesting a net clinical benefit in favour of ximelagatran (Figure 5).

Conclusions

Oral anticoagulation with warfarin is highly effective for stroke prevention in AF, but is associated with numerous limitations in terms of safety and convenience. The phase III SPORTIF clinical trials have demonstrated the potential of ximelagatran as an alternative treatment option to warfarin for stroke prophylaxis in high-risk patients with non-valvular AF. Ximelagatran (36 mg twice daily) was at least as effective as well-controlled warfarin (INR, 2.0–3.0) for the prevention of stroke and SEE, without increasing the rate of major bleeding. Ximelagatran caused liver enzyme elevations in ~6% of patients.
patients, and further evaluation of these effects is ongoing.

Ximelagatran has the potential to overcome many of the challenges associated with oral anticoagulation that currently face physicians and patients. The predictable pharmacokinetic profile, lack of interactions with food/ alcohol, and low potential for drug interactions associated with ximelagatran results in a consistent anticoagulant response that allows ximelagatran to be used safely without coagulation monitoring or dose adjustments.

Anticoagulation for stroke prevention is a critical component of AF management that is currently underprescribed. The oral direct thrombin inhibitor ximelagatran has the potential to favourably influence the management of patients with AF by maximizing the potential of anticoagulation for stroke prevention.

References


