REVIEW

Ximelagatran, the Oral Anticoagulant of the Future
An Evidence Based Review

***Salam A.,**Al Homsi U.,*Gehani A.A.**
**Cardiology and Cardiovascular Surgery Department*
***Hematology/Oncology Section, Department of Medicine*
Hamad Medical Corporation, Doha, Qatar

Abstract:

This article presents the available data on Ximelagatran, a novel oral direct thrombin inhibitor and explores its therapeutic potential. Recent large clinical trials have evaluated the efficacy and safety of this anticoagulant compared to the standard anticoagulation therapy with warfarin and heparins in several thrombotic disorders. These trials provide strong evidence for the efficacy and safety of ximelagatran in the following clinical indications; the prevention of venous thromboembolism after knee or hip replacement, the treatment of deep venous thrombosis, and prevention of stroke in patients with atrial fibrillation. Further evaluation of this promising oral anticoagulant is warranted in other thrombotic cardiovascular disorders requiring chronic oral anticoagulation therapy such as in patients with prosthetic heart valves, intracardiac thrombi, dilated cardiomyopathy, after myocardial infarction and post percutaneous coronary interventions.

Key words: *Anticoagulation, Atrial Fibrillation, Cerebrovascular Disease, Coronary Artery Disease, Direct Thrombin Inhibitors, Heparin, Melagatran, Stroke Prevention, Clinical Trials, Thrombosis, Venous Thromboembolism, Warfarin, And Ximelagatran.*

1. Introduction:

It is well know that thrombosis plays a pivotal role in the aetiology of several cardiovascular diseases. Heparins and the vitamin K antagonist warfarin have been the standard anticoagulants in clinical use for more than 50 years. However, both are associated with several well-documented disadvantages that limit their use.

The disadvantages of Warfarin and vitamin K antagonist are many and include that they have a relatively long onset of action (peak anticoagulant effect 72-96 hours), a narrow therapeutic window; large inter-individual dosing differences; interactions with dietary vitamin K; the need for frequent monitoring using the international normalized ratio (INR); many interactions with a number of other medications due to their dependence on the cytochrome P-450 system; the potential for serious and even fatal bleeding in patients treated with therapeutic doses; recurrences of thromboembolism in spite of therapeutic INRs; and the need for thorough patient education and compliance.

Unfractionated heparin also has several important limitations. It should be administered parenterally, has an inconsistent anticoagulant effect, needs frequent monitoring, and is inactivated by plasma proteins and platelet factor-4. Additional limitations include a rebound increase in thrombogenicity after cessation of infusion, activation of platelets, and the risk of heparin-induced thrombocytopenia (HIT) and osteoporosis.

Low molecular weight heparins (LMWH) have significantly improved heparin management since monitoring is not needed in most patients and the dose response is predictable. They also cause less osteoporosis than unfractionated heparins and have a decreased risk of inducing HIT. Nonetheless LMWH still have to be administered parenterally and they cannot be administered to patients with HIT as the antibodies in HIT frequently cross react with LMWHs.

These limitations created a need for safer, more convenient alternative anticoagulants.

The proposed model of the ideal anticoagulant is that which has the following characteristics; maximal efficacy (preferably at the site of pathologic thrombus formation); safety and lack of serious toxicities; oral bioavailability (for long-term use); mechanism of action independent of the vitamin K metabolic pathway (i.e. metabolism independent of the cytochrome P-450 system); lack of significant binding to plasma proteins; a wide therapeutic window; no need for monitoring; easy reversibility (an available antidote); Rapid establishment of anticoagulation and rapid offset of action; safety during pregnancy and cost effectiveness.

Ximelagatran, a novel oral direct thrombin inhibitor, has

Address for correspondence:
***Amar M. Salam**, MB, BS, MRCP(UK)*
Cardiology and Cardiovascular Surgery Department
Hamad Medical Corporation, P. O. Box 3050, Doha, Qatar
Tel.: (+974) 4392642; Fax: (+974) 4392454
E-mail: ***amaramin@yahoo.com***

many of these features[1]. Ximelagatran inhibits the final step in the coagulation process-namely, the conversion of fibrinogen to insoluble fibrin by thrombin. It is converted to its active form, melagatran, after oral administration. Melagatran inactivates both circulating and clot-bound thrombin by binding to the thrombin active site, thus, inhibiting platelet activation and/or aggregation and reducing fibrinolysis time. Ximelagatran has stable pharmacokinetics independent of the hepatic P450 enzyme system, and no known clinically significant food or drug interactions. It can be administered in a fixed dosage, which obviates the need for anticoagulation monitoring, thus simplifying treatment and improving compliance. After oral administration ximelagatran is rapidly absorbed from the gut and converted to its active form, melagatran. The maximum concentration of melagatran is attained 1.6 to 1.9 hours after administration. Melagatran is not metabolised or bound to plasma proteins, and its clearance is predominantly via the kidneys, with a half-life of 4 to 5 hours.

Ximelagatran has therefore undergone extensive research and study to evaluate its potential in the treatment and prevention of thrombotic disorders[2], either alone or in combination with melagatran, compared to the standard available anticoagulants.

2. Venous Thromboembolism:

Venous thromboembolism (VTE) is a significant public health problem worldwide. The disease manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE), and is a major consequence of various surgical procedures and medical conditions. The manifestations of PE are often clinically silent and death can occur suddenly before effective treatment can be initiated and even with treatment mortality due to PE remains extremely high. In addition, DVT is associated with long-term morbidity, with 20%-30% of patients developing post-thrombotic syndrome within 7-13 years after an acute episode of DVT. Due to the risk of morbidity and fatal PE associated with VTE, prophylaxis has become the standard of care for patients at high risk of thrombosis.

Various anticoagulants are currently used in the prophylaxis and treatment of VTE including unfractionated heparin, LMWH and the vitamin K antagonist warfarin. In view of the favourable profile of ximelagatran and its active form, melagatran, several clinical trials have been conducted to compare the efficacy and tolerability of ximelagatran with standard therapies, for the prophylaxis and treatment of VTE.

2.1 Clinical Trials Of Melagatran/Ximelagatran for VTE Prophylaxis After Surgery

Melagatran and/or ximelagatran have been compared with either LMWH or warfarin prophylaxis in a series of clinical trials. In an initial phase II dose-finding study[3]Heit and colleagues randomly assigned 443 adults undergoing total knee replacement to receive oral ximelagatran twice daily in blinded doses of 8 mg, 12 mg, 18 mg, or 24 mg, or open-label enoxaparin sodium at 30 mg subcutaneously (SC) bid. Both were started 12 to 24 h after surgery and continued for 6 to 12 days. The rates of overall VTE and proximal DVT or PE for ximelagatran, 24 mg, vs. enoxaparin did not differ significantly. There was no major bleeding with ximelagatran at 24 mg bid. In a follow-on phase III double-blind clinical trial[4], 838 patients undergoing elective total hip replacement were randomly assigned to prophylaxis with oral ximelagatran at 24 mg bid or enoxaparin sodium at 30 mg SC bid. Both drugs were started on the morning after surgery. Both the overall VTE and proximal DVT or PE rates were higher for ximelagatran at 24 mg vs. enoxaparin, while the major bleeding rates were low and did not differ significantly.

The Melegatran for Thrombin Inhibition in Orthopedic Surgery (METHRO) trials were then undertaken to further define the role of subcutaneous melagatran followed by oral ximelagatran compared to LMWH as prophylaxis after total hip or knee replacement. In a small initial dose-finding pilot study the METHRO-I[5], 135 total hip or knee replacement patients were randomly allocated to melagatran (1 mg, 2 mg, or 4 mg SC bid, started immediately before surgery) for 2 days, followed by oral ximelagatran (6 mg, 12 mg, or 24 mg bid) for 6 to 9 days, or to dalteparin sodium at 5,000 IU SC od (started the night before surgery). Including all melagatran/ximelagatran prophylaxis study arms, the overall VTE rate was 18.5% compared to 20.5% for the dalteparin study arm. The METHRO-I study established melagatran/ximelagatran to have safety and efficacy comparable to dalteparin in patients undergoing total knee or hip replacement. In a much larger phase II dose-finding study; METHRO II[6], 1,900 patients were randomly assigned to one of four melagatran/ximelagatran doses: 1.00 mg/8 mg, 1.50 mg/12 mg, 2.25 mg/18 mg, or 3.00 mg/24 mg or to the LMWH dalteparin 5000 IU once daily SC. The first melagatran dose was injected SC immediately before surgery but after administration of neuraxial (spinal or epidural) anaesthesia. A second melagatran injection was administered 7 to 11 h after surgery, followed by twice-daily injections until oral ximelagatran could be started (usually 1 to 3 days after surgery). In contrast dalteparin was given SC from the evening before surgery. Treatment was given for 7-10 days after surgery, after which all patients mandatory bilateral venography. A highly significant dose-dependent decrease in VTE (both overall and for proximal DVT) was seen with increasing doses of melagatran/ximelagatran. The highest dose (3 mg subcutaneous melagatran twice daily the day before surgery followed by 24 mg ximelagatran orally twice daily started on the day after surgery) was significantly more effective than dalteparin (5000 IU once a day) with VTE rates

of 15.1% vs. 28.2% (p<0.0001). The rates of excessive bleeding ranged from 1.1% to 5.0% in the ximelagatran groups compared with 2.4% in the dalteparin group, but the difference between the highest dose of ximelagatran and the dalteparin group was not significant. The METHRO II study demonstrated a dose-dependent effect in both VTE prevention and the development of bleeding complications in orthopaedic surgery patients receiving melagatran/ximelagatran started preoperatively. These benefits (and detriments) tended to be similar or greater than those seen with dalteparin (also started preoperatively).

A subsequent phase III double-blind study, METHRO III study[7], evaluated a postoperative regimen with melagatran followed by oral ximelagatran in a, 2788 patients undergoing total hip or knee replacement, randomly assigned to receive for 8 to 11 days either 3 mg of subcutaneous melagatran started 4-12 h postoperatively, followed by 24 mg of oral ximelagatran twice-daily or 40 mg of subcutaneous enoxaparin once-daily, started 12 h preoperatively. Ximelagatran was to be initiated within the first two postoperative days. The primary efficacy endpoint was VTE (deep-vein thrombosis detected by mandatory venography, pulmonary embolism or unexplained death). The main safety endpoint was bleeding. VTE occurred in 355/1146 (31.0%) and 306/1122 (27.3%) patients in the ximelagatran and enoxaparin group, respectively, a difference in risk of 3.7% in favour of enoxaparin (p = 0.053). Bleeding was comparable between the two groups. METHRO III results suggested that melagatran/ximelagatran started postoperatively might be less efficacious than enoxaparin started preoperatively.

Another phase III study, the Expanded Prophylaxis Evaluation Surgery Study (EXPRESS)[8] then reverted back to starting melagatran preoperatively in 2800 patients undergoing total hip or knee replacement surgery, randomised to receive either standard prophylaxis with subcutaneous enoxaparin (40 mg once daily), begun the evening before surgery, or melagatran, given subcutaneously in a dose of 2 mg immediately before surgery, followed by 3 mg in the evening after surgery, then switched the following morning to 24 mg bid of oral ximelagatran. Treatment was continued for 8-11 days, at which time patients underwent venography. The melagatran/ximelagatran group's rate of major VTE was 2.3% compared to 6.3% in the enoxaparin group (p < 0.000002), a 63 % relative risk reduction. Additionally, the total rate of VTE was significantly lower in the ximelagatran group at 20.3% compared to 26.6% in the enoxaparin group (p < 0.0003).

While bleeding events (3.3% vs. 1.2%) and transfusion rates (66.8% vs. 61.7%) were more common in the melagatran/ximelagatran group compared to the enoxaparin group, there were no significant differences between the two groups in fatal bleeding, critical organ bleeding, or bleeding requiring re-operation. The EXPRESS study, which reverted back to starting melagatran preoperatively (continuing with ximelagatran postoperatively), demonstrated a statistically significant reduction in thrombotic events compared with enoxaparin (also begun preoperatively).

2.2 Clinical Trials Of Ximelagatran alone as VTE Prophylaxis After Surgery

Three clinical trials have also investigated the safety and efficacy of ximelagatran alone (without prior melagatran treatment) for VTE prevention compared to adjusted-dose warfarin sodium prophylaxis. In a double blind clinical trial[9] Francis and colleagues randomly assigned 680 patients undergoing elective total knee replacement, to oral ximelagatran (24 mg bid, started on the morning after surgery) or adjusted-dose warfarin INR, 2.5; range, 1.8 to 3.0; started on the evening after surgery). The overall VTE rates did not differ significantly between the ximelagatran and warfarin groups (19.2% vs. 25.7%, p = 0.07). Similarly, the proximal VTE rates also did not differ significantly (3.3% vs. 5.0%, p > 0.2). The rates of major and minor bleeding were low and not significantly different. In the EXanta Used to Lessen Thrombosis (EXULT A) Study[10], 2301 patients undergoing total knee replacement were randomly assigned to prophylaxis with oral ximelagatran (24 mg or 36 mg bid, started the morning after surgery) or adjusted-dose warfarin (target INR, 2.5; range, 1.8 to 3.0; started the evening after surgery). The rates of overall VTE or death were significantly less among the ximelagatran, 36 mg, group compared to the warfarin group (20.3 percent vs. 27.6 percent; P=0.003). The rates for proximal DVT or death were not significantly different. The rates of major and minor bleeding were low and did not differ significantly between the three groups. EXULT A showed that the 36-mg twice-daily dose of ximelagatran was associated with a 26.4% relative risk reduction compared with warfarin.

This was followed by the EXULT B trial [11]. EXULT B was a double -blind, double-placebo phase III trial compared fixed-dose ximelagatran 36 mg twice daily with warfarin, adjusted to achieve a target International Normalized Ratio of 2.5 (range: 1.8 to 3.0) in 2303 patients undergoing total knee replacement. Each treatment was administered for 7 to 12 days; warfarin was initiated the evening of the day of surgery, and the first dose of ximelagatran was given the morning after surgery. Symptomatic VTE was confirmed by objective means and mandatory bilateral venography determined VTE rates. The primary endpoint of the EXULT B trial was the composite of confirmed VTE plus all-cause mortality. Ximelagatran showed efficacy statistically significant over warfarin in this endpoint (22.5%, ximelagatran vs. 31.9%, warfarin ($P < 0.001$), corresponding to an adjusted relative risk reduction of 29.3% ($P < 0.001$) with ximelagatran. Proximal VTE occurred in 3.5% of patients assigned to ximelagatran in EXULT B, compared with 4.0% of

those assigned to warfarin, a difference that was not statistically significant. Major bleeding events were not statistically significant between the two treatments (1.0%, ximelagatran vs. .4%, warfarin). The combination of major and minor bleeding also occurred with similar frequency between the warfarin- and ximelagatran treated patients (3.8% vs. 5.0% [$P = 0.158$]). About 33% of patients in each study arm received transfusions. The rates of unplanned transfusions (i.e., serious bleeding or complications from surgery) were 7.6% with ximelagatran and 6.8% with warfarin.

The results of the EXULT A and B trials clearly show that ximelagatran is clinically effective and superior to well-controlled warfarin in preventing total VTE and/or all-cause mortality in patients undergoing total knee replacement.

2.3 Clinical Trials Of Ximelagatran in patients with established VTE

A series of clinical trials have tested ximelagatran for the treatment and secondary prevention of established VTE in the THRIVE (THRombin Inhibitor in Venous thromboEmbolism) program. Similar to the prophylaxis trials, ximelagatran was administered as a fixed oral dose and without laboratory monitoring of the anticoagulant effect or dose adjustment. Two initial studies used thrombus regression/progression or new embolism as study endpoints. In an initial dose-finding study, THRIVE I[12], 350 patients with acute proximal or extensive isolated distal (length > 7 cm) DVT confirmed by venography were randomly assigned to one of four oral ximelagatran doses (24 mg, 36 mg, 48 mg, or 60 mg bid), or to dalteparin sodium (200 IU/kg SC od) followed by adjusted-dose warfarin (INR range, 2.0 to 3.0). Venography was repeated after 14 days of therapy, and the extent of each thrombus was quantified according to progression or regression of thrombus size and the Marder score. Regression of thrombus size was noted in 69% of both treatment groups, while thrombus progression was noted in 8% of ximelagatran and 3% of dalteparin/warfarin patients. Changes in Marder score also were similar in both groups. Therapy was discontinued due to bleeding in two patients in each group. In summary, the THRIVE I study demonstrated ximelagatran to have similar efficacy in preventing thrombus progression compared with a dalteparin/warfarin regimen with comparable rates of bleeding in patients with an acute proximal DVT. In another open-label cohort study; the THRIVE IV pilot study [13], 12 patients with PE verified by ventilation/perfusion lung scan (with or without DVT) were treated with oral ximelagatran, 48 mg bid, for 6 to 9 days, followed by conventional heparin and warfarin therapy. All patients improved clinically. Repeat lung scans after completing ximelagatran showed regression or no change in all but one patient with malignancy; five patients had essentially normal perfusion scan findings. There were no major bleeding episodes or deaths. The THRIVE IV pilot study suggested that ximelagatran might also be effective in the treatment of hemodynamically stable PE.

In the THRIVE III trial[14], 1,233 patients with confirmed DVT or PE who had completed 6 months of standard anticoagulation therapy were subsequently randomised to continued secondary prophylaxis with oral ximelagatran, 24 mg bid, or placebo for an additional 18 months. Among the 612 patients receiving ximelagatran, 12 acquired recurrent VTE. In contrast, 71 of the 611 patients receiving placebo acquired recurrent VTE (2.8% vs.12.6%, $p<0.001$). The all-cause mortality and major and minor bleeding rates did not differ significantly between the two groups. Ximelagatran patients were more likely to have transient and generally asymptomatic increases (more than threefold the upper normal limit) in serum alanine aminotransferase (ALT) compared to placebo (6.4% vs. 1.2%, $p<0.001$). This study proved that ximelagatran, given for 18 months to patients who had already received 6 months of warfarin therapy for VTE, provided additional protection against recurrent VTE with a low risk of bleeding.

The THRIVE Treatment study[15] included 2491 patients with acute DVT, of whom 37% had confirmed PE. They were randomised to receive either ximelagatran in a dose of 36 mg bid for six months or subcutaneous enoxaparin (1 mg/kg bid) for a minimum of five days, followed by warfarin administered to a target INR of 2.0 to 3.0 for six months.

At baseline, bilateral compression ultrasonography of the legs and perfusion-ventilation lung scanning were performed. An independent committee adjudicated all recurrences of VTE, the primary endpoint, as well as bleeding events and mortality. The study aimed to determine whether ximelagatran is non-inferior to enoxaparin/warfarin in the prevention of recurrent VTE, by comparing Kaplan-Meier estimates of the cumulative risk of an event at 6 months. The rates of recurrence of VTE were almost identical, 2.1% with ximelagatran and 2.0% with enoxaparin/warfarin in the ITT (Intention To Treat) analysis. Safety and mortality outcomes also showed a favourable trend for ximelagatran over enoxaparin/warfarin with respect to the risk of major bleeding: (estimated cumulative risk 1.3% vs. 2.2%, On Treatment analysis) and all-cause mortality: (estimated cumulative risk 2.3% vs. 3.4%, ITT analysis). Laboratory evaluation showed a cumulative risk of ALAT elevations (> 3 times the upper limit of normal) of 9.8% for patients receiving ximelagatran vs. 2.0% for patients receiving enoxaparin/warfarin. The THRIVE Treatment study demonstrated ximelagatran to be as effective as (non-inferior to) enoxaparin plus warfarin in preventing recurrent VTE in patients being treated for DVT without a higher risk of bleeding.

3. Stroke Prevention in Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice that affects cardiovascular

morbidity and mortality and generates significant health care costs. It is also the strongest independent risk factor for stroke and systemic embolic events. The incidence of stroke is increased 5-fold in patients with AF to approximately 5% per year for primary events and 12% per year for recurrent events, compared with patients without AF. Management of AF has therefore been subjected to extensive research to determine the optimal therapies for this important and common arrhythmia.

It has been well established from recent studies in AF [16] that anticoagulation constitutes an important therapy in patients with AF for the prevention of thromboembolic stroke. For decades warfarin has been the gold standard anticoagulant that is recommended for such indication. The limitations of warfarin result in under-treatment of a considerable proportion of the AF population at risk and create a need for safer, more convenient alternatives to warfarin for stroke prevention. The Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) program has been investigating the safety and efficacy of ximelagatran for the prevention of stroke in patients with AF.

A phase 2 study, SPORTIF II[17], was a 12-week, randomised, parallel-group, dose-guiding study of patients with non-valvular AF with at least one high-risk marker for stroke and systemic embolism. Seventy-five percent had two or more risk markers, most common of which was hypertension. The primary endpoint was the number of thromboembolic events and bleedings. Three groups received ximelagatran (n = 187) at 20 (n = 59), 40 (n = 62), or 60 (n = 66) mg twice a day, given in double-blind fashion without coagulation test monitoring. The fourth group, given warfarin (n = 67), was managed and monitored to achieve and maintain INRs in the 2.0 to 3.0 range. A total of 254 patients received study drug. One nonfatal ischemic stroke and one transient ischemic attack occurred in the ximelagatran patients. One major bleed occurred in the warfarin patients. The number of total bleeds (major plus minor) was low in both groups but rose slightly with an increase in ximelagatran dose. The 60-mg twice-daily group had the same bleeding event rate as warfarin. SPORTIF IV[18] was a long-term (5-year) continuation of SPORTIF II for patients who elected to remain on study drug, at 36 mg twice daily of ximelagatran (n = 125) versus INR-adjusted warfarin (n = 42). To date, the rate of significant bleeding has been less with ximelagatran than with warfarin. The only issue of concern in SPORTIF II has been the observation that ximelagatran was occasionally associated with elevations of hepatic chemistries. ALT was increased to more than three times the upper limit of normal in eight patients taking ximelagatran in SPORTIF II, but it resolved in both those who did and who did not discontinue the drug.

SPORTIF III[19] and SPORTIF V[20] were phase III clinical trials conducted independently but their designs were similar in order to facilitate pooling of their results when completed. The main difference between the two trials is that the North American trial (SPORTIF V) was double blind and the predominantly European study (SPORTIF III) was an open-label trial. Their primary objective was to determine whether the efficacy of ximelagatran 36 mg twice daily, was ***noninferior*** to adjusted-dose warfarin (INR 2.0 to 3.0) for the prevention of all strokes and systemic embolism among patients with nonvalvular AF (persistent or paroxysmal) who had at least 1 additional risk factor for stroke and a calculated creatinine clearance $\geq$ 30 mL/min.

In SPORTIF III, treatment with ximelagatran or warfarin was randomly allocated ***open-label*** to 3407 patients in 23 countries of Europe and Australasia. In contrast, in SPORTIF V treatment with ximelagatran or warfarin was randomly allocated double-blind to 3922 patients in the United States and Canada. The mean duration of treatment was 17 months in SPORTIF III and 20 months in SPORTIF V. Among the patients assigned to warfarin, the INR was maintained between 2.0 and 3.0 for 66% of the entire follow-up period in SPORTIF III and 68% in SPORTIF V, and between 1.8 and 3.2 for 81% of the entire follow-up period in SPORTIF III and 83% in SPORTIF V.

The primary outcome measure was all stroke and systemic embolic events. Patient outcome was evaluated by a blinded local study-affiliated neurologist and a blinded central events adjudication committee. The primary analysis was based on intention-to-treat. The pre-specified threshold for non-inferiority was an absolute margin of 2% per year for the difference in the rates of the primary outcome measure between ximelagatran and warfarin.

In the 7329 patients randomised in the SPORTIF III and V trials, there were a combined total 91 primary outcome events (stroke or systemic embolism) among patients allocated ximelagatran (2.5%) and 93 events among those allocated warfarin (2.5%) (annualised rates were 1.6% versus 2.3% in SPORTIF III and 1.6% versus 1.2% in SPORTIF V). Both trials fulfilled the criteria for non-inferiority of ximelagatran compared with warfarin. The pooled rate of major bleeding was 2.5% among patients allocated ximelagatran and 3.4% among patients allocated warfarin (annualised rates 1.3% versus 1.8% in SPORTIF III and 2.4% versus 3.1% in SPORTIF V). There was no statistical evidence of heterogeneity between the trials for major bleeding (P=0.63). It is of note that ximelagatran was associated with significantly less major bleeding than warfarin despite the fact that anticoagulation was carefully monitored and adjusted among patients receiving warfarin, and anticoagulation intensity was not monitored or regulated in patients receiving ximelagatran. The absolute rates of bleeding in both treatment groups may be, however, underestimates of those en-

countered in general practice. This is because most patients enrolled in both studies had preserved renal function and had already been receiving anticoagulant medication for chronic AF. Individuals who were not considered suitable for anticoagulation or who had not tolerated anticoagulation previously were not enrolled.

As in prior studies with ximelagatran there was a significant excess of elevated liver enzymes (ALT) compared with warfarin (pooled data: 6.1% versus 0.8%; $P< 0.0001$). It typically occurred 2 to 6 months after initiation of ximelagatran, and was asymptomatic, transient (returning to baseline spontaneously or after cessation of treatment), and without sequel.

SPORTIF III and V therefore showed that a fixed oral dose of ximelagatran, without coagulation monitoring, is ***not inferior*** to well-controlled, adjusted-dose warfarin in preventing stroke and systemic embolic events among high-risk patients with AF who do not have impaired renal function.

4. Coronary Artery Disease

Platelet activation and thrombin generation are key mechanisms in the pathophysiology of acute MI. Reperfusion strategies and the use of antithrombotic and anticoagulant therapy significantly improved the prognosis of acute MI. During the subsequent months, however, morbidity and mortality remain high because of recurrent thrombotic events. Long-term acetylsalicylic acid is the mainstay of antiplatelet therapy, reducing the relative risk of MI, stroke, or vascular death by about 25%[21]. Long-term anticoagulation with warfarin further reduces cardiovascular events in these patients[22] However, use of warfarin in these patients is restricted because of the many interactions with other drugs, the need for frequent monitoring and the risk of bleeding, especially when combined with acetylsalicylic acid and other antithrombotics. Such limitations have prompted development and evaluation of new oral anticoagulants in this setting.

The potential of ximelagatran to reduce arterial thrombotic events in patients with coronary artery disease was investigated in the Efficacy and Safety of the oral Thrombin inhibitor ximelagatran in combination with aspirin, in patiEnts with rEcent Myocardial damage (ESTEEM)[23] trial. It was a multicenter, placebo-controlled, double-blind dose-finding study that compared the safety and efficacy of 4 doses of the direct oral thrombin inhibitor ximelagatran in combination with aspirin against placebo in the long-term treatment of patients who had recently been admitted for ST-segment elevation or non-ST-segment myocardial infarction (MI). 1883 Patients within two weeks of acute MI were randomised in a double-blind manner to placebo (n=638) or one of four doses of ximelagatran (24, 36, 48, or 60 mg twice daily; n=1,245) for six months. Patients also had one high-risk feature, including older age, diabetes, or hypertension. All patients also received aspirin 160 mg/day. The primary efficacy outcome was the relation between the dose response of ximelagatran compared with placebo for the composite of death, MI, or severe recurrent ischemia. The primary endpoint was lower for pooled ximelagatran compared with placebo (12.7% vs. 16.3%, p=0.036), but there was no dose response relationship associated with the use of ximelagatran. The composite of death/MI/stroke also occurred more frequently in the placebo arm compared with the combined ximelagatran doses (11% vs. 7%, p = 0.01), although this was a post-hoc analysis. Any bleeding increased in a dose-response manner (13% placebo vs. 19%, 20%, 25%, and 24% for 24 mg, 36 mg, 48 mg, and 60 mg, respectively), but there was no difference in major bleeding (1% placebo vs. 2%, 1%, 3%, and 2% for 24 mg, 36 mg, 48 mg, and 60 mg, respectively). Liver function tests were increased in the ximelagatran arm after 2–6 months of treatment, usually returning to normal within 60-90 days with treatment continuation or discontinuation.

The ESTEEM trial supports the notion that long-term treatment with ximelagatran reduces arterial thrombotic events. Ximelagatran in combination with acetylsalicylic acid was more effective than acetylsalicylic acid alone in reducing the frequency of major cardiovascular events during 6 months of treatment in patients with a recent MI. The lowest dose of 24 mg ximelagatran twice daily achieved maximum efficacy at an acceptable safety profile under the conditions studied in ESTEEM. Confirmatory large-scale future studies of ximelagatran will require studies with active comparator arms, including comparisons with warfarin and clopidogre. Additionally, this study suggests that the combination of ximelagatran and aspirin may be more effective than current antiplatelet regimens in preventing serious vascular events among patients with atherothromboembolic transient ischemic attack and ischemic stroke. This concept remains to be tested by further studies.

5. Conclusions

These trials provide strong evidence for the efficacy and safety of ximelagatran in the following clinical indications; the prevention of venous thromboembolism after knee or hip replacement, the treatment of deep venous thrombosis, and prevention of stroke in patients with atrial fibrillation. The main area of safety concerns is that ximelagatran appears to require monitoring of hepatic function during the early months of therapy. Other disadvantages of ximelagatran are the need for twice-daily administration, and the need to estimate creatinine clearance (because ximelagatran is primarily eliminated by the kidneys). Nonetheless, the advantages of ximelagatran are that it has a rapid onset and offset of action, a predictable pharmacokinetic profile and therefore it is not necessary to adjust the dose or monitor anticoagulation activity. Furthermore, ximelagatran has a wider therapeutic margin than warfarin and a low poten-

tial for food and drug interactions. Moreover, while the exact acquisition cost of ximelagatran is unclear, it will likely cost more than warfarin. However, the potential increases in drug costs may be offset by a reduction in monitoring costs including blood tests for coagulation monitoring and doctor visits. Further evaluation of this promising oral anticoagulant is warranted in other thrombotic cardiovascular disorders requiring chronic oral anticoagulation therapy such as in patients with prosthetic heart valves, intracardiac thrombi, dilated cardiomyopathy, after myocardial infarction and post percutaneous coronary interventions.

References:

1. *Gustafsson D, Elg M: The pharmacodynamics and pharmacokinetics of the oral direct thrombin inhibitor ximelagatran and its active metabolite melagatran: A mini-review. Thromb Res. (2003) 109 (Suppl 1): S9-15.*
2. *Salam AM Al Mousa EN: The therapeutic potential of ximelagatran to become the anticoagulant of choice in medicine: A review of recently completed clinical trials. Expert Opin Pharmacother. (2004) 5(6): 1423-30.*
3. *Heit JA, Colwell CW, Francis CW: Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement. Arch Intern Med. (2001) 161: 2215-2221.*
4. *Colwell CW, Berkowitz SD, Davidson BL: Randomized, double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and enoxaparin to prevent venous thromboembolism after total hip replacement (abstract). Blood (2001) 98: 706a.*
5. *Ericksson BI, Arfwidsson AC, Frison L: A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: Metrhro I. Melagatran for Thrombin inhibition in Orthopedic surgery. Thromb Haemost (2002) 87: 231-237.*
6. *Ericksson BI, Bergqvist D, Kalebo P: Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the Methro II randomised trial. Lancet (2002) 360: 1441-1447.*
7. *Ericksson BI, Agnelli G, Cohen AT: Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. The Methro III study. Thromb Hemost. (2003) 89: 288-296.*
8. *Ericksson BI, Agnelli G, Cohen AT: The oral direct thrombin inhibitor ximelagatran, and its subcutaneous form melagatran, compared with enoxaparin for prophylaxis of venous thromboembolism in total hip and total knee replacement: The Express Study (abstract). Presented at the 17th International Congress on Thrombosis; Italy, October (2002).*
9. *Francis CW, Davidson BL, Berkowitz SD: Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind trial. Ann Intern Med (2002) 137: 648-655.*
10. *Francis CW, Berkowitz SD, Comp PC: Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. N Engl J Med. (2003) 349: 1703-1712.*
11. *The Exult B Trial; The Second Phase III Trial to Compare Ximelagatran to Warfarin in Patients Undergoing Total Knee Replacement Surgery. Presented at The 45th Annual Meeting of the American Society of Hematology on December 6-9, (2003).*
12. *Ericksson H, Wahlander K, Gustafsson D: A randomized controlled dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: Thrive I. J Thromb Hemost (2003) 1: 41-47.*
13. *Wahlander K, Lapidus L, Olsson CG: Thrive IV: an open-label, pilot study of the treatment of pulmonary embolism with the oral direct thrombin inhibitor ximelagatran (abstract). Blood (2001) 98: 268a.*
14. *Shulman S, Wahlander K, Lundstorm T: Secondary prevention of venous thromboembolism with the oral direct thrombic inhibitor ximelagatran N Engl J Med. (2003) 349: 1713-1721.*
15. *Huisman MV, for the Thrive Treatment Study Investigators: Efficacy and safety of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for acute symptomatic deep vein thrombosis, with or without pulmonary embolism: a randomized, double-blind, multinational study. J Thromb Hemost (2003) 1 (Suppl 1): Abstract OC003.*
16. *Salam AM. Rate control versus rhythm control for the management of atrial fibrillation: the verdict of the AFFIRM trial. Expert Opin Investig Drugs. (2003) 12: 1231-7.*
17. *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: 1445-1451.*
18. *Peterson P, on behalf of the Sportif II and IV Investigators. A long-term follow-up of ximelagatran as an oral anticoagulant for the prevention of stroke and systemic embolism in patients with atrial fibrillation [abstract]. Presented at the 43rd Annual Meeting of the American Society of Hematology, Orlando, Florida, December 10, (2001).*
19. *Executive Steering Committee. on behalf of the Sportif III Investigators: Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): Randomized controlled trial. Lancet. (2003) 362: 1691–1698.*
20. *Halperin J, on behalf of the Sportif V Investigators: Efficacy and safety study of oral direct thrombin Inhibitor ximelagatran compared with dose-adjusted warfarin in the prevention of stroke and systemic embolic events in patients with atrial fibrillation (Sportif V) (abstract). Presented at the American Heart Association Annual Scientific Meeting, Orlando, Florida, November 9–12, 2003.*
21. *Antithhrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ (2002) 324: 71–86.*
22. *Hurlem M, Abdelnoor M, Smith P: Warfarin, aspirin, or both after myocardial infarction. N Engl J Med (2002) 347: 969–74.*
23. *Wallentin L, Wilcox RL, Weaver WD: Oral ximelagatran for secondary prophylaxis after myocardial infarction: The Esteemrandomized controlled trial. Lancet. (2003) 362: 789-797.*