Outcome Paper Option#3
Final Paper

Evaluation of Ximelagatran in Comparison to: Warfarin in Atrial Fibrillation, Placebo in Post DVT Patients, Either Warfarin or Enoxaparin in Joint Replacement.

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Introduction

Emergence of newer anticoagulants such as ximelagatran presents a need for evaluation and comparison to traditional agents such as warfarin and enoxaparin. There are many indications for anticoagulant therapy. The studies discussed in this paper where chosen based on their relevance to the practice specialties of a 400 bed hospital which is located within a retirement area.

Anticoagulant therapy has been proven effective for the prevention of thromboembolic events in a variety of conditions. Atrial fibrillation is one of the indications where warfarin has been proven to effectively reduce risk of stroke. One meta-analysis of pooled data found the annual rate of stroke to be 1.4% among patients with AF receiving dose-adjusted warfarin as compared with 4.5% among untreated patients (relative risk reduction 68%, 95% CI 50-79%); this finding was consistent across the various studies and patient subgroups.[1] Secondary prevention of venous thromboembolism is another area where anticoagulants are used. Previous studies have shown a risk of recurrence after six months of anticoagulant therapy of 5-7% per year.[2] [3] Low-molecular-weight heparins and warfarin are the drugs most frequently used for prophylaxis of venous thromboembolism in major orthopedic surgery.[4] The risk of proximal DVT is still 5-7% with prophylaxis in both total hip replacement and total knee replacement[4] which is a motivating factor to find a more effective agent.

Warfarin is a difficult drug to dose, posing the challenge of maintaining the INR within a narrow range complicated by numerous drug and food interactions. Warfarin is associated with an annual risk of major hemorrhage of 3-4%.[5] [6] [7] Major bleeding occurred more frequently in patients over the age of 75 years of age (5.1%/year) than in younger patients (1%/year).[8] Also, risk for intracranial hemorrhage may be increased among older patients, especially those >/= to 75 years old when the INR is above therapeutic levels.[9] These complications are of concern given the large volume of elderly patients we treat.

Ximelagatran is a new anticoagulant which is administered in a fixed dose eliminating the challenge of maintaining a narrow INR range. Long-term primary prevention of atrial fibrillation and secondary prevention of myocardial infarction and VTE with ximelagatran are associated with a low risk of bleeding.[8] Ximelagatran is rapidly absorbed and converted to its active form, melagatran, with bioavailability of approximately 20%. Melagatran has predictable and reproducible pharmacokinetic and pharmacodynamic properties, with a low binding affinity for plasma proteins and mainly renal clearance.[10] [11] [12] An FDA advisory committee ruled against ximelagatran for approval in September 2004. This was due to a theoretical concern of liver failure. Elevation of ALT in a significant number of patients has occurred in most if not all trials with this drug. The FDA would require this aberration to be fully investigated before ximelagatran would be approved for use in the US.

The purpose of this paper is to examine the effectiveness of ximelagatran in the areas of cardiology and joint replacement which constitute a large percentage of patients seen at our hospital. Studies within the area of cardiology include a comparison of ximelagatran versus warfarin for secondary prevention of DVT and for patients with non-valvular atrial fibrillation. In the joint replacement arena ximelagatran was compared with enoxaparin for post hip or knee prophylaxis and also compared with warfarin post knee surgery. A small pharmacokinetic study of ximelagatran in patients with renal impairment was included to help determine whether the drug should be restricted to patients with normal renal function should it become a formulary agent in the future. Evaluation of ximelagatran will help determine its role at our hospital should it attain FDA approval.

Evaluation of the Studies

Ximelagatran of Warfarin for Stroke Prevention in Patients with Atrial Fibrillation. SPORTIF III

SPORTIF III was an open labeled trial conducted in Europe and Australasia (Australia, New Zealand, and Asia). In this study ximelagatran 36mg bid was compared with warfarin adjusted to INR 2-3 in patients with non-valvular atrial fibrillation who had at least one additional risk factor for stroke and CrCl>30ml/min. The primary endpoint was defined as number of strokes or embolic events.[13] While it is possible to have bias introduced with an open label trial, the possibility would be minimized with objectively measured endpoints such as number of strokes or embolic events. Inclusion and exclusion data were specifically stated. The trial was sponsored by Astra Zeneca.

On-treatment analysis of stroke or embolic event revealed 2.2% per year in the warfarin group as compared with 1.3% per year in the ximelagatran group. The absolute risk reduction was 0.9% per year (0.2 to 1.7; p = 0.0180) with ximelagatran and the relative risk reduction was 43% (10 to 63). This suggested that ximelagatran was at least as effective as warfarin in preventing stroke and embolic events in patient with non-valvular atrial fibrillation. The occurrence of hemorrhage was slightly lower in the ximelagatran group, 25.8% per year as compared with 29.8% per year in the warfarin group. Warfarin was well controlled in this trial. Warfarin patients were within an expanded INR range of 1.8 - 3.2 81% of the time. Serum concentration of ALT rose above three times the upper limit of normal in 1% of warfarin patients and 6% of ximelagatran patients ($p<0.001$). Rises in ximelagatran-treated patients typically took place between 2 and 6 months after initiation of treatment and returned toward baseline without clinical sequelae either spontaneously or after cessation of treatment.

Ximelagatran of Warfarin for Stroke Prevention in Patients with Atrial Fibrillation SPORTIF V

SPORTIF V was a double blinded, American trial which compared ximelagatran 36mg bid with warfarin adjusted to INR 2-3 in patients with non-valvular atrial fibrillation who had at least one additional risk factor for stroke and CrCl>30ml/min. Inclusion and exclusion data were specifically stated. The trial was sponsored by Astra Zeneca.

The SPORTIF V results included 1.6% per year stroke or embolic event per year in the ximelagatran group vs. 1.2% per year in the warfarin group. The difference between the two groups was not significant (p=0.13). Rates of major bleeding incidence were similar between the two groups with 2.4% resulting from the ximelagatran group and 3.1% from the warfarin group. Warfarin was well controlled in this trial. Warfarin patients were within an expanded INR range of 1.8 - 3.2 83% of the time. ALT elevations reached three times the upper limit of normal in 6% of ximelagatran patients as compared with 0.8% of warfarin patients.

Thrombin Inhibitor in Venous Thromboembolism III
THRIVE III

The THRIVE III study was a double-blind trial which randomly assigned patients with venous thromboembolism who had undergone six months of anticoagulant therapy to extend secondary prevention with ximelagatran or placebo for an additional 18 months.[14] THRIVE III had fewer patients than either of the SPORTIF trials although it was still a large study which included 1233 patients. THRIVE III compared ximelagatran 24mg bid, a lower fixed dose than used in the SPORTIF trials, with placebo.

The average patient age was 57 years old and the two group demographics were evenly matched. Inclusion and exclusion criteria were less stringent in the THRIVE trial as compared with the SPORTIF trials. The THRIVE trial also differed in that up to 500mg per day of aspirin was allowed with doses in excess of 500mg/day on occasion. Seven percent of the ximelagatran group was taking aspirin and nine percent of the placebo group was taking aspirin but the doses were not specified. It is possible that aspirin may have biased the result in this small subset of patients due to the fact that the distribution of high dose aspirin was not specified.

The primary endpoint was recurrent thromboembolism which occurred in 12 of the ximelagatran patients and 71 of the patients randomized to receive placebo. Cumulative risk of an event during 18 months was 2.8% for ximelagatran group and 12.6% for placebo group. Major bleeding occurred in 6 of the ximelagatran group and 5 of the placebo group which was not a significant difference. The incidence of ALT elevation greater than or equal to three times the upper limit of normal was higher in the ximelagatran group (9.6%) as compared with the placebo group (1.2%).

The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement.
EXPRESS

The EXPRESS study randomized 2764 patients undergoing hip or knee arthroplasty to receive melagatran/ximelagatran or enoxaparin. Melagatran 2mg was administered subcutaneously prior to surgery followed by 3mg subcutaneously the evening after surgery. This group then received ximelagatran 24mg bid. The enoxaparin group received 40mg subcutaneously daily beginning the evening prior to surgery regardless of whether the patient was having knee surgery or hip surgery. This is the standard in Europe. The primary endpoint was proximal DVT and symptomatic pulmonary embolism which occurred in 2.3% of melagatran/ximelagatran patients and 6.3% of enoxaparin patients. In comparison with enoxaparin, this dosage regimen of melagatran/ximelagatran was associated with more surgery related bleeding in patients undergoing THR but not in patient's undergoing TKR. In the THR group 9.5% patients experienced bleeding with 4.0 % classified as severe bleeding as compared with 6.5% bleeding and 1.1% severe bleeding in the enoxaparin group. In the TKR group 8.4% of ximelagatran patients experienced bleeding with 1.9% severe. The enoxaparin TKR group reported 8.1% bleeding with 1.4% severe. This study made no mention of ALT elevations.

Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement.

Orthopedics is another arena where ximelagatran may be an option for DVT prevention. Francis, Berkowitz and Comp, et.al. compared warfarin, ximelagatran 24mg bid, and ximelagatran 36mg bid after total knee replacement. At 36mg ximelagatran proved superior to warfarin. Of the 1851 patients enrolled in the efficacy analysis, ximelagatran 36mg bid was superior to warfarin with respect to venous thromboembolism (20.3%) and death from all causes (27.6%). There were no significant differences between the groups with respect to major bleeding (incidence 0.8% ximelagatran and 0.7% warfarin).

This study did not address the overlap of low molecular weight heparins (or heparin) with warfarin. Patients in the warfarin group were apparently not given another anticoagulant to overlap until the INR was therapeutic. This may have made ximelagatran appear superior to warfarin.

This study reported ALT elevations at baseline, on the last day of treatment and at a 4-6 week follow-up visit. ALT elevations were broken down into three groups: greater than or equal to three times the upper limit of normal, greater than or equal to five times the upper limit of normal, and greater than or equal to seven times the upper limit of normal. In the ximelagatran 36mg bid group there were no ALT elevations at baseline. On the last day of treatment 0.8% of this group had an ALT elevation greater than or equal to three times the upper limit of normal which decreased to 0.6% at the 4-6 week follow-up visit. ALT elevations of greater than or equal to five times the upper limit of normal were 0.3% the last day of therapy decreasing to 0.1% on follow-up in the high dose group. In the ximelagatran 24mg bid group 0.1% of patients had an ALT elevation greater than three times the upper limit of normal and 0.1% had an ALT greater than or equal to five times the upper limit of normal at baseline. On the last day of therapy 0.6% of patients had an ALT greater than or equal to three times the upper limit of normal which decreased to 0.1% at the follow-up visit. The 0.1% of patients who had an ALT elevation of five times or greater at baseline remained consistent (still 0.1%) on the last day of therapy then declined to zero at the follow-up visit. On the last day of therapy the warfarin group showed 1.7% of patients with an ALT elevation of greater than or three times the upper limit of normal, 0.3% of patients with ALT greater than or equal to five times the upper limit of normal and 0.1% of patients with an ALT greater than or equal to seven times the upper limit of normal. The warfarin group did not have any patients with elevated ALT in these categories at baseline or at the follow-up visit.

Influence of Severe Renal Impairment of the Pharmacokinetics and Pharmacodynamics of Oral Ximelagatran and Subcutaneous Melagatran.

Patients with significant liver disease and CrCl<30ml/min were excluded from the major trials. Because these studies excluded renally compromised patients one small study sought to investigate the pharmacokinetic effects of single dose ximelagatran and melagatran in patients with CrCl<30ml/min. This non-blinded, randomized, two-period crossover study compared pharmacokinetics of a single 24mg ximelagatran tablet and a single 3mg subcutaneous injection of melagatran given on two separate study days with a 3 week washout period in between.[15] The study was limited by its small size and the fact that the groups were not matched for age, sex or bodyweight. The AUC of melagatran was five times higher on average after oral ximelagatran and four times higher after subcutaneous administration of melagatran in the severe renal dysfunction group. This implies the need for further study to determine dosing for renally impaired patients. ALT elevations were not mentioned in this study.

Summary of Findings

The SPORTIF III and V trials suggest that ximelagatran 36mg bid is at least as effective as warfarin in preventing stroke and embolic events in patient with non-valvular atrial fibrillation. There was no significant difference in major bleeding events between groups in either study. These studies indicate that unmonitored ximelagatran therapy is as effective and safe as dose-adjusted warfarin therapy. These results do not apply to renally impaired patients with CrCl<30ml/min.

In THRIVE III ximelagatran was shown to reduce the risk of thromboembolic recurrence without significantly increasing the risk of a bleeding event.

The EXPRESS study showed a 63% decrease in the occurrence of proximal DVT and symptomatic pulmonary embolism with melagatran/ximelagatran as compared with enoxaparin for patients undergoing hip and knee arthroplasty. The rates of bleeding were higher with the post THR melagatran/ximelagatran group.

Francis, Berkowitz and Comp, et.al. compared ximelagatran to warfarin after total knee replacement . Ximelagatran was found to be superior to warfarin with respect to venous thromboembolism and death from all causes when dosed at 36mg bid. There were no significant differences between the groups with respect to major bleeding.

An increase in ALT appeared in 6-9% of patients on ximelagatran in the SPORTIF and THRIVE studies. This was notably higher than the 0-1.2% ALT elevations in the comparative groups. In most cases this was transient and eventually decreased whether the drug was stopped or not. The mechanism for this rise in ALT is unknown and puzzling due to the fact that ximelagatran is extensively eliminated via the renal route. In the post total knee trial patients in both the ximelagatran group as well as the warfarin group experienced an increase in ALT. All of the patients in the warfarin group had an ALT within normal limits 4-6 weeks after the study. This was not the case with the high dose ximelagatran group. In the post study follow-up 4-6 weeks later 0.6% of ximelagatran patients still had an ALT greater than or equal to three times upper normal limit and 0.1% of patients had an ALT greater than or equal to five times the upper normal limit. The FDA has yet to approve this drug due to the concern of liver enzyme elevations.

The small study exploring pharmacokinetics of ximelagatran and melagatran in renally compromised patients (CrCl<30ml/min). The AUC of both oral and subcutaneous drugs were significantly higher in the renally impaired groups. While this study is not extensive enough to provide dosing guidelines in the renally impaired it suggests that patients with CrCl<30ml/min should not receive ximelagatran or melagatran until guidelines can be established.

Recommendations for Clinical Application

Based on the studies reviewed I would recommend ximelagatran over warfarin for patients with non-valvular atrial fibrillation and for patients requiring extended secondary DVT prevention. I would recommend ximelagatran over warfarin and enoxaparin for DVT prophylaxis after total knee replacement but not after total hip replacement due to the higher bleed rates reported in the EXPRESS trial. Elimination kinetics are significantly altered for patients with CrCl<30ml/min and ximelagatran should not be used for these patients until further studies are done and guidelines developed. Due to the consistent reports of ALT elevations this drug should not be used in patients with liver impairment or elevated ALT levels.

Outcomes Literature Evaluation
Study Comparison

Authors Date/ref#	Study Design	# of Subjects
SPORTIF III Ximelagatran of Warfarin for Stroke Prevention in Patients with Atrial Fibrillation Lancet 2003; 362: 1691-98	Randomized open label, parallel group, Blinded event assessment Dose of ximelagatran was 36mg bid.	3407 patients 259 sites in 23 countries (not US).
SPORTIF V Ximelagatran of Warfarin for Stroke Prevention in Patients with Atrial Fibrillation	Double blinded Dose of ximelagatran was 36mg bid.	3922 patients in 409 North America sites
THRIVE III Schulman S, Wahlander K, Lundstrom T, et.al. Thrombin Inhibitor in Venous Thromboembolism III NEngl J Med 349;18: 1713-1721	Multicentre, randomized, double blind, placebo-controlled, parallel-group study. Ximelagatran 24mg po bid x18months vs placebo.	1233 patients at 142 centers in 18 countries (not US).
Francis F, Berkowitz S, Comp P, et.al. Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement. N Engl J Med 2003;349:1703-12	Prospective, randomized, double blind trial comparing Ximelagatran 24mg bid, Ximelagatran 36mg bid with dose adjusted Warfarin.	2301 patients enrolled at 116 centers in various countries including US, Mexico, Canada, Israel, and Brazil. Patients included in safety study numbered 2285. Patients evaluated in efficacy study numbered1851.
EXPRESS Eriksson B, Agnelli G, Cohen A. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement. J Thromb Haemost 2003; 1: 2490-6.	Multicenter, randomized, double-blind, parallel group study conducted at 77 centers in Europe.	2835 patients enrolled at 77 sites in Europe. The ITT population consisted of 1856 THR and 908 TKR.
Erickson U, Johansson S, Attman P, et al. Influence of Severe Renal Impairment of the Pharmacokinetics and Pharmacodynamics of Oral Ximelagatran and Subcutaneous Melagatran. Clin Pharmacokinet 2003; 42(8): 743-753	Nonblinded, randomized, 2-period crossover with 2 treatments, each on a single study day, and separated by washout period of 1-3weeks. A single 24mg ximelagatran tablet and a single 3mg subcutaneous injection of melagatran were given on 2 separate study days.	12 volunteers with CrCl<30ml/min and control group of 12 volunteers with CrCl>/=50ml/min

Inclusion Criteria	Exclusion Criteria
SPORTIF III 1.Age>/=18y/o 2.persistent or paroxysmal non-valvular AF verified by at least 2 ECG readings, 1 of which was made within 2 weeks before randomization 3. >/=1 of the following stroke risk factors: HTN, age>/=75, previous strokes, TIA or systemic embolism, LVEF<40% or symptomatic CHF, age>/=65 & CAD, age>/=65 & DM	1. Stroke or systemic embolic event within 30days before, or TIA within 3 days before inclusion. 2. conditions associated with an increased risk of bleeding 3. Conditions predisposing to thrombosis that require conventional anticoagulant therapy. 4. AF secondary to reversible causes 5. HTN >180/100 despite antihypertensive medication 6. Active infective endocarditis 7. previous disabling stroke 8. Hospitalization for an acute coronary syndrome within 30days. 9. planned cardioversion 10. planned major surgery 11. Tx with platelet-inhibitor drugs, other than ASA</=100mg/day within 10 days, or fibrinolytic agents within 30days before randomization. 12. regular use of NSAIDs 123 CrCl <30ml/min 14. liver disease or LFT>/=2x norm 15. Childbearing potential, pregnancy or lactation. 16. Drug addiction and/or ETOH abuse. 17. Current atrial myxoma or left ventricular thrombus 18. anemia (hemoglobin<100g/L or platelet count,$100x10^9$/L)
SPORTIF V Same as above	Same as above 1-16
THRIVE III 1. 18y/o or older 2. Symptomatic, objectively confirmed deep venous thrombosis of the leg or pulmonary embolism which had been treated with anticoagulant therapy x6months without subsequent recurrence.	1. indication for continuous anticoagulant treatment 2. a condition associated with an increased risk of bleeding 3. Hgb <9.0g/dl 4. plt<90,000/mm^3 5. pregnancy, lactation 6. serious illness with expected survival <18months 7. CrCl <30ml/min 8. Significant liver disease or ALT >/=3x upper limit of normal.
Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement. 1. women (without childbearing potential) and men weighing 40-136kg. 2. patients undergoing primary knee replacement.	1. Pneumatic leg compression 2.immobilization >/= 3days 3.major surgery 4.stroke 5.myocardial infarction 6. receipt of any investigational drug within 30 days before surgery 7.intracranial, retroperitoneal, or intraocular bleeding or any other disorder associated with an increased risk of bleeding within 90 days before surgery, ulcer disease verified by endoscopic examination within 30 days before surgery, or both 8. uncontrolled HTN 9. cancer that required cystostatic treatment or was itself the reason for total knee replacement 10. an alanine or aspartate aminotransferase level greater than 2x the upper limit of the normal range 11.thrombocytopenia 12.drug or alcohol abuse within the previous 6 months 13.allergy to contrast medium or iodine 14.a contraindication to Warfarin therapy 15. CrCl<30ml/min 16. and traumatic epidural or lumbar puncture.
EXPRESS Consecutive patients undergoing total hip or total knee replacement	1. Recent (within 1 month) stroke 2. recent trauma or major surgical procedure 3. history of intracranial bleeding or of intraocular bleeding within the last year; history of gastrointestinal bleeding within 3 months prior to surgery; endoscopically verified ulcer disease; disorders associated with a risk of bleeding 4. ongoing malignancy 5. uncontrolled hypertension 6. severe renal impairment 7. known active liver disease, or liver insufficiency. 8. Women of childbearing age were excluded if they were pregnant, nursing or not using effective contraception.
Severe Renal Impairment of the Pharmacokinetics and Pharmacodynamics of Oral Ximelagatran and Subcutaneous Melagatran Men and women aged 20-80 years old.	1. Hx bleeding or thrombotic disorder 2. Hx hypersensitivity 3. cardiovascular, hepatic or significant gastrointestinal disease 4. hemoglobin<105g/L 5. HIV+ or hepatitis B or C 6. Hypersensitivity against radiographic contrast medium. 7. Hx drug or ETOH abuse 8. pregnancy, lactation 9. Severe illness other than renal 10. Clinically significant abnormal labs within 2 weeks of study.

Results	Limitations	other
SPORTIF III Primary endpoint was #strokes/embolic events. 2.3% per year of Warfarin patients had primary events and 1.6% per year of ximelagatran patients.	Open label (endpoint assessment was blinded).	Supported by Astra Zeneca 4% stopped Warfarin due to adverse events compared with 8% on ximelagatran (mainly related to elevation of serum transaminases in ximelagatran patients). Serum concentration of ALT rose above three times the upper limit of normal in 1% of warfarin patients and 6% of ximelagatran patients ($p<0.001$). Rises in ximelagatran-treated patients typically took place between 2 and 6 months after initiation of treatment and returned toward baseline without clinical sequelae either spontaneously or after cessation of treatment.
SPORTIF V Primary endpoint was #strokes/embolic events. Ximelagatran group had 51 strokes (1.6% per year). Warfarin group had 37 strokes (1.2% per year). Rates of major bleed 2.4% with ximelagatran, 3.1% with warfarin.	No limitations noted.	Supported by Astra Zeneca. ALT elevations reached 3x upper limit of normal in 6% of ximelagatran patients compared with 0.8% Warfarin patients.
THRIVE III Primary endpoint was symptomatic recurrent venous thromboembolism. 12 patients in ximelagatran group and 71 patients in the placebo group had a confirmed venous thromboembolism. Cumulative risk of an event during 18months was 2.8% for ximelagatran group and 12.6% for placebo group. No significant increase in bleeding complications with ximelagatran.	No limitations noted.	ASA up to 500mg/day or higher doses for occasional use were allowed. 7% of ximelagatran group took ASA, 9% placebo group took ASA. Doses not reported. NSAIDs allowed if T1/2<7hours. ALT >/=3x upper normal limit in 6.4% ximelagatran group vs. 1.2% placebo.
Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement. Of the 1851 patients enrolled in the efficacy analysis, Ximelagatran 36mg bid was superior to Warfarin with respect to venous Thromboembolism and death from all causes (20.3% vs. 27.6%). There were no significant differences between the groups with respect to major bleeding (incidence 0.8% and 0.7% respectively).	Low molecular weight heparins (or subcutaneous heparin) are often used after surgery with Warfarin until the INR is therapeutic. This study did not appear to explore this option. Use of heparin or low molecular weight heparins were not mentioned.	Groups were evenly matched for age, sex, weight, BMI and CrCl. A slightly higher portion of patients (4.4%) with a + Hx of venous Thromboembolism were assigned to the higher dose Ximelagatran group. Alanine Aminotransferase (ALT) became elevated to 3x upper normal limit in 0.8% Ximelagatran 36mg group and 1.7% of the Warfarin group. ALT was became elevated >/=5x the upper normal limit in 0.3% of the high dose Ximelagatran group and 0.3% of the Warfarin group. 0.1% of the Warfarin group developed an ALT >/=7x the upper limit of normal. The entire Warfarin group experienced a normal ALT 4-6 weeks post study. In the high dose Ximelagatran group 0.6% were still >/=3x upper normal limit and 0.1% were >/=5x the upper normal limit.
EXPRESS Rate of major VTE was 2.3% with ximelagatran and 6.3% with enoxaparin. Relative risk reduction 63% with ximelagatran. Relative risk of total VTE also reduced by 23.7%. THR ximelagatran bleed occurrence was 9.5% total, 4.0% severe. THR enoxaparin bleed occurrence was 6.5% with 1.1% severe. TKR ximelagatran bleed occurrence was 8.4% with 1.9% severe. TKR enoxaparin bleed occurrence was 8.1% with 1.4% severe.	No limitations noted	Sponsored by Astra Zeneca. Changes in LFT's were not mentioned in the article. European standard dose of enoxaparin is 40mg qd for TKA and THA while US standard dose of enoxaparin is 30mg bid for THA. European standard was used. ASA up to 500mg was allowed as well as short acting NSAID's and COX-2's
Severe Renal Impairment of the Pharmacokinetics and Pharmacodynamics of Oral Ximelagatran and Subcutaneous Melagatran AUC of melagatran was 5x higher on average after oral ximelagatran and 4x higher after subcutaneous administration of melagatran, in the severe renal dysfunction group.	Study groups were small (12 members) and groups were not matched for sex, age or bodyweight. Evaluation was of one dose only.	The use of anticoagulant, antiplatlet (including ASA), fibrinolytic or NSAID was not permitted from 1 week prior to study until completion. GFR was assessed with iohexol clearance and calculated CrCl.

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