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Prevention of Venous Thromboembolism Following Orthopaedic Surgery

Clinical Potential of Direct Thrombin Inhibitors

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Abstract

Patients undergoing total hip or total knee replacement are at high risk of venous thromboembolism (VTE), and are therefore considered to be populations well suited for the evaluation and dose optimisation of new anticoagulants. Deep vein thrombosis may lead to life-threatening pulmonary embolism, disabling morbidity in the form of the post-thrombotic syndrome, and risk of recurrent thrombotic events. There is increasing evidence that anticoagulant treatment for the prevention of VTE should be extended from 1 to at least 4 weeks after surgery. Anticoagulation with vitamin K antagonists (such as warfarin), low molecular weight heparin or unfractionated heparin effectively lowers the risk of VTE, but

these anticoagulants have limitations such as the need for coagulation monitoring and subsequent dose adjustment (vitamin K antagonists), difficulty of continuing prophylaxis out of hospital because of the requirement for parenteral administration, and risk of heparin-induced thrombocytopenia. The development of new anticoagulants has been pursued with the aim of finding more effective, safer and/or more convenient therapies.

Thrombin is a central regulator in the coagulation and inflammation process and several direct thrombin inhibitors (DTIs) with distinct pharmacological profiles, as well as pharmacological differences from the conventional anticoagulants, are currently in clinical use for certain indications or are under development. Clinical experience with parenterally administered DTIs has accumulated since the mid 1990s, although only desirudin (a recombinant hirudin) is currently approved for use in patients undergoing orthopaedic surgery. Two oral DTIs, ximelagatran and dabigatran etexilate, are in clinical development. Dabigatran etexilate has recently been evaluated in phase II clinical trials in patients undergoing total hip replacement. Several large phase III trials have now demonstrated the efficacy and safety of ximelagatran in the prevention of VTE following total hip or knee replacement. Ximelagatran can be used with an oral fixed dose without the need for coagulation monitoring or dose adjustment. Hence, it offers significant potential to facilitate the management of anticoagulation in or out of hospital.

Surgical trauma during major orthopaedic surgery markedly activates the coagulation system, which predisposes patients to venous thromboembolism (VTE).[1] The coagulation cascade, triggered by surgery and further enhanced by postoperative fibrinolytic shutdown, signs of decreased venous endothelial function and partial stagnation of the blood flow, results in an increased risk of developing thromboembolism for a long period after major hip and knee surgery.[2-4] Accumulated data have shown that, in the absence of thromboprophylaxis, approximately 40–84% of patients undergoing major lower limb orthopaedic surgery develop deep vein thrombosis (DVT) detectable by venography.[5]

National registries in countries including Finland, Denmark, Sweden and The Netherlands show an annual incidence of primary total hip replacement (THR) in the region of 93–113 per 100 000 inhabitants,[6-8] while figures for the US are 164–294 per 100 000.[9] An annual incidence of 63 per 100 000 inhabitants has been reported for total knee replacement (TKR) in Sweden.[10] As the proportion of elderly people in the population grows, the demand for orthopaedic surgery is also expected to grow and the predicted annual number of THR operations is expected to increase by at least 25–50% by 2020,[8] and TKR operations to increase by about one-third by 2030.[10] Hence, the number of patients at risk for vascular complications associated with these operations is expected to increase to the same extent.

Numerous clinical trials have established that provision of anticoagulant therapy – such as vitamin K antagonists (e.g. warfarin), unfractionated heparin (UFH) or low molecular weight heparin (LMWH) – substantially lowers the incidence of VTE. Nevertheless, these therapies have a number of limitations. For example, warfarin has a narrow therapeutic index and variable anticoagulant effect due to interactions with certain types of food and medications, and it therefore requires careful coagulation monitoring and dose adjustment to avoid serious adverse effects.[11,12] Heparin and other parenteral anticoagulants, such as specific factor IIa (thrombin) and Xa inhibitors, such as desirudin and fondaparinux sodium, are inconvenient for use after discharge from hospital.[13,14] For this reason, new drug development has been pursued to improve efficacy and safety, and overcome some of the inconveniences of

current therapy. Because of the central role of thrombin in coagulation and related processes, much effort has focused on the development of oral direct thrombin inhibitors (DTIs).

On the basis of their pharmacological profile, DTIs have potential advantages in relation to heparin and/or warfarin, such as: (i) the ability to inhibit clot-bound thrombin; (ii) resistance to neutralisation by platelet factor 4; (iii) lack of heparin-induced thrombocytopenia (HIT); and (iv) the possibility of avoiding the requirement for coagulation monitoring by providing a more predictable dose response. As with all anticoagulants, the balance between antithrombotic efficacy and risk of bleeding is critical. For this reason, consideration of various aspects of the pharmacology of new anticoagulants is important with respect to the potential for an improved benefit to risk ratio, as well as optimal clinical utility. A major advance lies in the development of an oral DTI that can be used without coagulation monitoring. Ximelagatran and dabigatran etexilate differ from the currently available DTIs, hirudin, bivalirudin and argatroban, in that they are suitable for oral administration.

This article describes the current development status of DTIs, provides a comparison of their pharmacological characteristics and evaluates the clinical potential of these new agents for thromboprophylaxis in patients undergoing THR and TKR. A search of the English-language literature for randomised clinical trials of DTIs for the prevention of VTE after THR or TKR was conducted using Medline records up to July 2003. This was supplemented by manual searches for conference abstracts published up to 1 December 2003.

Major orthopaedic surgery represents the preferred model for anticoagulant drug development.[15] Although anticoagulants are used for the prevention or treatment of thromboembolic disease in several settings; THR/TKR provides a well-defined patient group and specific endpoints for both efficacy and safety. These patients have a high risk of developing DVT detectable by venography, pulmonary embolism and bleeding from the surgical wound, therefore, outcomes can be evaluated using nonfatal endpoints that occur with relatively high frequency within a short timeframe. This explains the rationale for considering major orthopaedic surgery to be the proof of concept for new antithrombotic devices or drugs.

1. Development of Direct Thrombin Inhibitors (DTIs)

1.1 The Concept of Thrombin Inhibition

Thrombin is a key enzyme in haemostasis (figure 1), responsible for the cleavage of fibrinogen to fibrin monomers, which subsequently polymerise and cross-link to form a stable gel. This fibrin matrix, together with platelets, comprises the thrombus. Among various additional functions, thrombin activates coagulation factor XIII which promotes fibrin cross-linking, amplifies its own generation via positive feedback activation of other enzymes 'upstream' in the cascade of coagulation reactions and exerts regulation via the interaction of thrombin and thrombomodulin, which initiates the protein C pathway. Furthermore, thrombin inhibits fibrinolysis via activation of thrombin-activatable fibrinolysis inhibitor. It is a potent platelet activator, stimulating granule release, surface receptor expression and aggregation. Finally, thrombin plays a central role in regulation of inflammation and has hormone-like properties and modulates several cellular activities, such as proliferation of endothelial cells, revascu-

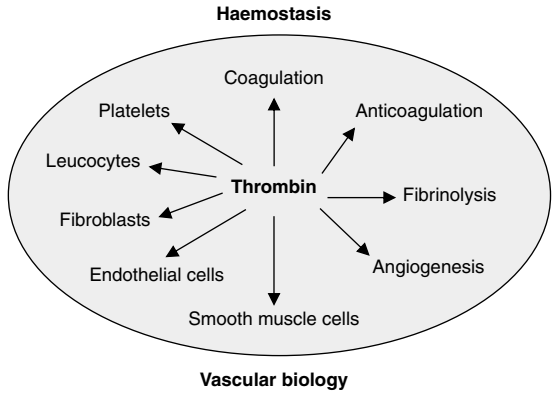

Fig. 1. Actions of thrombin that could be affected by direct thrombin inhibitors (reproduced from Kaplan,[18] with permission).

larisation, bone remodelling and nerve end stimulation.[16-18]

DTIs bind directly to the active catalytic site of thrombin that is responsible for biological activities, including activation of platelets and cleavage of fibrinogen to fibrin, and hirudin and bivalirudin also bind to a substrate (fibrinogen) recognition site on thrombin.[19,20]

1.2 Overview of Development of DTIs

The anticoagulant properties of saliva from the medicinal leech were documented in the 1880s, and the DTI hirudin, a 65 amino-acid polypeptide, was first isolated and purified in the 1950s. Insufficient amounts were available for therapeutic use until recombinant hirudins, lepirudin and desirudin, were produced in yeast cells. The results of clinical trials using DTIs have been published beginning in the mid 1990s.

Desirudin gained its first approval for use in the prevention of VTE in patients undergoing THR in 1997 after a series of studies beginning with a dose-finding trial published in 1994 (see section 3.1).[21] However, clinical trials conducted over the same period comparing r-hirudins (desirudin and lepirudin) with heparin in patients with acute coronary syndromes either failed to show a sustained efficacy advantage or showed excessive bleeding compared with heparin.[22-28] In two studies in patients with HIT and associated thromboembolic disease, lepirudin effectively prevented death, limb amputations and new thromboembolic complications in comparison with historical controls, which provided the basis for its current clinical use, first approved in 1997.[29,30]

Bivalirudin was investigated for VTE prevention in THR and TKR and for the treatment of DVT in phase II trials, the results of which were published in 1994 (see section 3.2).[31,32] Bivalirudin proved to be superior to heparin in the prevention of death, myocardial infarction or repeat revascularisation at 7 and 90 days in patients with unstable angina undergoing coronary angioplasty.[33,34] This led to the first approval of bivalirudin for this indication in 1999. These data have been confirmed in other cardiac studies in patients with acute coronary syndromes, which include the use of stenting and concomitant antiplatelet therapies.[35-37] Its efficacy and safety as an adjunct to thrombolytic therapy is less clear-cut.[38,39]

Argatroban, as an adjunct to thrombolytic therapy in patients with acute myocardial infarction, produced a similar reduction in the composite of death, recurrent myocardial infarction, cardiogenic shock or congestive heart failure, revascularisation and recurrent ischaemia at 30 days, and lower bleeding compared with heparin.[40] Argatroban was first approved in the year 2000 for use as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT, as it led to a more rapid rise in platelet count compared with historical controls.[41] Argatroban has subsequently been approved for use as an anticoagulant in patients at risk of HIT undergoing percutaneous coronary intervention.[42]

Development of an oral DTI with appropriate characteristics could greatly expand the utility of DTIs. The challenge has been to produce a molecule that can be absorbed via the gastrointestinal tract, yet be pharmacologically active and have predictable pharmacokinetics and pharmacodynamics. A prodrug approach has been adopted in ximelagatran and dabigatran etexilate. After oral administration these are rapidly absorbed and bioconverted to their active forms, melagatran and BIBR 953ZW, respectively. Of the two drugs, ximelagatran is at a later stage of clinical development. Ximelagatran has undergone phase III trials in prevention of VTE in elective hip or knee replacement surgery (see section 3.3)[43,44] and has shown promising phase III data in the treatment and long-term secondary prevention of VTE.[45-47] Recently a large study has demonstrated good efficacy and safety of fixed-dose ximelagatran in comparison with adjusted-dose warfarin in the prevention of stroke and other thromboembolic complications associated with atrial fibrillation.[48] Furthermore, in a dose-guiding study, ximelagatran plus acetylsalicylic acid (aspirin) was superior to acetylsalicylic acid alone in preventing major cardiovascular events during 6 months of

Table I. Characteristics of direct thrombin inhibitors

Direct thrombin inhibitor	Structure	Molecular weight (Da)	Thrombin binding sites	Type of binding
Recombinant hirudins	Recombinant protein; 65 amino acids	~7000	Active site/substrate recognition site	Slowly reversible (essentially irreversible)
Bivalirudin	Recombinant protein; 20 amino acids	2178	Active site/substrate recognition site	Reversible after slow cleavage by thrombin
Argatroban	Arginine derivative	527	Active site	Reversible
Melagatran (active form of ximelagatran)	Dipeptide	473	Active site	Reversible
BIBR 953ZW (active form of dabigatran etexilate)	Benzamidole derivative	–	Active site	Reversible

treatment in patients with a recent acute myocardial infarction.[49]

2. Pharmacological Properties

Several features of the chemistry and mode of action of DTIs have been postulated to contribute to a more favourable ratio of benefit (antithrombotic effect) to risk (bleeding) as compared with heparin and warfarin, and also to differences between DTIs. In addition, the individual pharmacokinetic and pharmacodynamic profiles of the inhibitors contribute to differences in their clinical utility in orthopaedic surgery or other indications. General characteristics and pharmacokinetic properties are summarised in table I and table II.

2.1 Theoretical Basis for Improved Benefit to Risk

It has been suggested that the limited capacity of heparin to prevent propagation of existing thrombi derives from its inability to inhibit clot-bound thrombin, which remains enzymatically active.[50] Heparin and LMWH are indirect thrombin inhibitors. By binding to endogenous antithrombin they convert it from a slow inhibitor to a rapid inhibitor of thrombin and, to varying degrees, factor Xa.[51] Thrombin bound to fibrin within a blood clot is protected from inhibition by the heparin or LMWH antithrombin complex, but susceptible to inhibition by direct inhibitors.[52] Nonetheless, hirudin is a less efficient inhibitor of clot-bound thrombin than the smaller DTIs. Whereas hirudin is approximately half as active against clot-bound thrombin as against soluble thrombin, the smaller DTIs inhibit both fluid-phase and clot-bound thrombin almost equally.[52-55] Hence, the higher concentrations of hirudin required to block clot-bound thrombin might be more likely to compromise haemostasis.

Another potential advantage of operating independently of antithrombin is that the activity of DTIs is not affected by antithrombin deficiency, a factor that can contribute to heparin resistance. In addition, heparin binds to platelet factor-4 released from activated platelets, which locally blocks heparin activity, whereas DTIs do not bind to platelet factor-4.[51]

The antigenic properties of the heparin-platelet factor-4 complex led to HIT with an estimated incidence of 1–3% for UFH and 1% for LMWH.[56] About 25–50% of these patients may develop thrombosis attributable to HIT.[56] This feature is not shared by DTIs.

Further differentiation between the DTIs arises from the essentially irreversible binding of hirudin to thrombin, as opposed to reversible binding of bivalirudin, argatroban and melagatran. Theoretically, inhibitors that dissociate from the active site may allow thrombin to participate in haemostasis, which would not be possible with a high-affinity, slowly reversible inhibitor such as hirudin.[57]

2.2 Balance of Efficacy and Bleeding in Animal Studies

Differences in the relationship between antithrombotic effect and bleeding have been observed in animal studies. For example, in a rat model of venous thrombosis, approximately equal doses of

argatroban and heparin reduced the thrombus weight to 50% compared with controls, whereas in a tail transection bleeding model the dose of argatroban required to double the bleeding time was 5-fold greater than that for heparin, suggesting a lower haemorrhagic potential.[58,59] Hirudin and ximelagatran achieved more thrombus regression than heparin in a rat thrombosis model when all three drugs were at clinically relevant concentrations in the plasma.[60]

Differences between melagatran and hirudin have also been observed. In models of arterial thrombosis prevention and bleeding in rabbits, both melagatran and hirudin produced dose-dependent increases in arterial patency. However, at doses that maintained 80–100% patency, melagatran produced 2- to 3-fold less bleeding than hirudin.[53]

There is also evidence that melagatran may have a wider therapeutic window than warfarin and heparin based on differences in the slopes of the dose-response curves for antithrombotic effect and bleeding for each agent. At doses required to achieve 80% antithrombotic effect of each drug, bleeding time and/or blood loss after tail transection were significantly increased over control values with warfarin and heparin, but there was no increase in bleeding with melagatran.[61]

Although these results need confirmation in head-to-head human studies, there is some evidence from clinical trials that the better benefit to risk profile may translate to clinical practice. For example, in patients with acute coronary syndromes, hirudin causes more bleeding than heparin, whereas bivalirudin causes less bleeding than heparin.[28,33-35]

2.3 Pharmacokinetics and Pharmacodynamics

Before comparing the pharmacological profiles of DTIs, key features of the conventional anticoagulants should be considered. The mode of action of warfarin (disruption of the vitamin K-dependent synthesis of coagulation factors II, VII, IX and X) leads to a lag in onset of anticoagulant effect of 3–5 days as well as a delayed offset of action. In addition, drug and food interactions, genetic polymorphisms and some disease states lead to fluctuations in the dose response of warfarin.[11,12] Because of the unpredictable anticoagulant effect, frequent coagulation monitoring and dose adjustment are required, and management of therapy can be difficult.[12]

UFH also provides an unpredictable anticoagulant response and has non-dose-proportional pharmacokinetics, largely because of its variable binding to plasma proteins, endothelial cells and macrophages, and its molecular constitution; its polysaccharide chains range from 3000 to 30 000Da (mean ~15 000Da), having heterogeneous anticoagulant activity and pharmacokinetics.[51] As a result, monitoring of anticoagulant effect and dose adjustment are required. In contrast, LMWHs have a molecular weight between 1000 and 10 000Da (mean ~5000Da), the smaller fragments having a relatively higher ratio of anti-factor Xa : antithrombin activity. LMWH has lower protein binding, more consistent pharmacokinetics and a more predictable dose response than UFH, and is generally used without coagulation monitoring.[51] After subcutaneous administration its time to reach peak concentration in the plasma (t_{max}) is 3–5 hours and the elimination half-life ($t_{1/2}$) of anti-factor Xa activity is approximately 3–4 hours. LMWH is principally renally eliminated and dose adjustment should be considered in severe, but not moderate, renal impairment.[51,62,63]

2.3.1 Parenteral DTIs

Recombinant Hirudins

Desirudin is administered subcutaneously in fixed, twice-daily doses for use in patients undergoing orthopaedic surgery. By this route it has a $t_{1/2}$ of 4–8 hours (table II).[64] Renal clearance and metabolism account for 80–90% of the systemic clearance of r-hirudins.[65,66] With desirudin, the activated partial thromboplastin time (aPTT) should be monitored in patients with hepatic dysfunction or moderate renal impairment. In severe renal failure (creatinine clearance <31 mL/min) mean area under the plasma drug concentration-time curve (AUC) was increased 7-fold compared with normal renal function.[67,68]

Table II. Pharmacokinetics of direct thrombin inhibitors in humans

Direct thrombin inhibitor	Indication, route and schedule of administration[a]	t_{max}	$t_{1/2}$	Elimination
Desirudin	TKR: SC 15mg bid for 9–12 days initiated 30min before surgery	1.3–2.5h	4–8h	Renal
Lepirudin	HIT: IV bolus 0.4 mg/kg followed by IV continuous infusion 0.15 mg/kg/h adjusted to target aPTT ratio of 1.5–2.5 for 2–10 days	Rapid	1.3h	Renal
Bivalirudin	UA/coronary angioplasty: IV bolus 1 mg/kg followed by IV continuous infusion 2.5 mg/kg/h for 4h	Rapid	36 min	Renal
Argatroban	HIT: IV continuous infusion 2 μg/kg/min adjusted to target aPTT 1.5- to 3-fold higher than the baseline HIT/PCI: IV continuous infusion 25 μg/kg/min and IV bolus 350 μg/kg, adjusted to target ACT of 300–450s	2–4h	40–50 min	Hepatic
Melagatran	SC	30 min	2h	Renal
Ximelagatran[b]	PO	2h	4–5h	Renal
Dabigatran etexilate[b]	PO	6h	15h	Renal

a For full details, refer to local prescribing information.

b Pharmacokinetics of melagatran and BIBR 953ZW following oral administration of ximelagatran and dabigatran etexilate, respectively.

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time; **bid** = twice daily; **h** = hours; **HIT** = heparin-induced thrombocytopenia; **IV** = intravenous; **min** = minutes; **PCI** = percutaneous coronary intervention; **PO** = oral; **s** = seconds; **SC** = subcutaneous; **$t_{1/2}$** = half-life; **TKR** = total knee replacement; **t_{max}** = time to peak plasma level; **UA** = unstable angina pectoris.

In clinical use in patients with HIT, lepirudin is given as a weight-adjusted intravenous bolus followed by infusion, and adjusted to a target aPTT ratio of 1.5–2.5. The $t_{1/2}$ after intravenous administration is 1.3 hours.[18] The dose of lepirudin must be decreased in patients with moderate renal insufficiency (creatinine clearance <60 mL/min or serum creatinine >1.5 mg/dL).

Clearance of r-hirudins may also be prolonged and anticoagulant activity increased by the development of antibodies. While this may not be clinically significant in orthopaedic surgery, anticoagulation monitoring has been recommended during prolonged treatment or during re-exposure of antibody-positive patients.[69-71]

Bivalirudin

Bivalirudin given by intravenous infusion provides a rapid onset of anticoagulant effect, has a short $t_{1/2}$ of 36 minutes[72] and is cleared renally as well as via degradation by endogenous peptidases.[73] The clearance rate was decreased by 45% in moderate renal impairment (creatinine clearance 30–59 mL/min) and 68% in severe renal impairment (creatinine clearance <30 mL/min).[55] Bivalirudin is given as a weight-adjusted intravenous bolus and infusion for patients with unstable angina undergoing coronary angioplasty. In patients with acute coronary syndromes, dose reduction based on monitoring of activated clotting time may be needed in patients with moderate or severe renal impairment. Drug interaction studies pertinent to the use of bivalirudin in acute coronary syndromes have shown no clinically relevant interactions with ticlopidine or glycoprotein IIb/IIIa inhibitors.[74] Bivalirudin does not bind to red blood cells or plasma proteins and its pharmacokinetics are linear in the dose ranges used therapeutically.[74,75]

Argatroban

Intravenous argatroban has a t_{max} of 2–4 hours and $t_{1/2}$ of 40–50 minutes.[76] Approximately 50% of argatroban circulates freely in the plasma and 50% is protein bound.[77] Administration to patients with HIT is by weight-adjusted dose infusion with dose amendment to a target aPTT of 1.5–3-fold greater than the baseline. For patients with HIT undergoing percutaneous coronary intervention, argatroban is administered as a bolus plus infusion with monitoring to ensure an activated clotting time >300 seconds before and during the procedure. Approximately 65% of argatroban is metabolised in the liver and elimination is predominantly via biliary excretion.[76,78] Dose reduction is needed in patients with hepatic dysfunction. The pharmacokinetics do not appear to be affected by renal dysfunction, age or

gender.[79] Although argatroban appears to be metabolised by cytochrome P450 (CYP) 3A4/5 enzymes, the CYP3A4/5 substrate erythromycin does not alter its pharmacokinetics.[78]

2.3.2 Oral DTIs

Ximelagatran

For orally administered drugs, issues such as the speed and consistency of absorption and bioavailability have to be addressed. Ximelagatran is rapidly absorbed and biotransformed to its active form, melagatran, resulting in plasma levels of melagatran (maximum concentration [C_{max}] and AUC) that increase linearly in relation to dose in healthy volunteers[80] and orthopaedic surgery patients.[81] When ximelagatran 20mg is taken orally twice daily, bioavailability is approximately 20%, t_{max} is 1.6–1.9 hours and $t_{1/2}$ is 2.5–3.5 hours in healthy individuals, with no relevant dependence on administration with or without food.[80] At therapeutic doses in patients, $t_{1/2}$ is approximately 4–5 hours.[81,82] Subcutaneous melagatran has a $t_{1/2}$ of 1.7–2.0 hours.[81,83] The pharmacokinetics of melagatran after oral administration of ximelagatran are not significantly affected by age,[84] obesity,[85] ethnic origin,[86] mild-to-moderate hepatic dysfunction or taking the drug with or without food.[87] Melagatran showed no clinically relevant drug interactions with drugs metabolised by CYP2C9, CYP2C19 or CYP3A4.[88] It shows a linear correlation between renal function and clearance after both oral (ximelagatran) or subcutaneous administration. The increase in AUC of melagatran in patients with severe renal dysfunction (creatinine clearance <12.5 mL/min) compared with healthy individuals was approximately 5- or 4-fold after oral or subcutaneous administration, respectively, suggesting that the dose should be reduced in patients with severe renal dysfunction.[89]

Dabigatran Etexilate

Dabigatran etexilate administered orally is rapidly converted to its active form BIBR 953ZW. When given to healthy individuals for 6 days, $t_{1/2}$ was 7.25 hours with a 50mg three times daily dose and 16–17 hours with 200 and 400mg three times daily doses. Moderate drug accumulation occurred suggesting that twice- or once-daily dose administration may be feasible.[90] C_{max} and AUC increased in proportion to dose in healthy volunteers[90] and orthopaedic surgery patients.[91]

In a dose-escalation study (Boehringer Ingelheim Study in ThROmbosis [BISTRO] I),[92] patients undergoing THR were administered dabigatran etexilate in doses of 12.5–300mg twice daily or 150 and 300mg once daily for 6–10 days. Steady-state concentration of BIBR 953ZW was attained in 2–3 days in accordance with a $t_{1/2}$ of 15 hours. Levels of BIBR 953ZW increased with decreasing creatinine clearance.[92] Prolongation of aPTT and ecarin clotting time correlated with plasma concentration of BIBR 953ZW, and prolongation was more pronounced early after surgery.[93] Following a single 150mg dose of an optimised formulation of dabigatran etexilate given 1–3 hours after surgery, onset of absorption was usually seen immediately after administration and t_{max} was approximately 6 hours.[92]

3. Basic Development Programmes in Orthopaedic Surgery

Efficacy and safety results of the key trials of DTIs for the prevention of VTE following THR or TKR are summarised, with reference to the optimisation of dose regimens for individual inhibitors. Preferences for the timing of first dose differ between Europe and North America. It is generally accepted that the risk of VTE and other coagulation-related complications begins during surgery[1,94,95] and, in Europe, commencement of LMWH 12 hours before surgery is preferred. However, there is controversy regarding the risk of bleeding with preoperative anticoagulation, particularly with the use of regional block anaesthesia, and prophylaxis started postoperatively is also known to be effective. Hence, in North America, LMWH is usually started 12–24 hours after surgery, or warfarin is used with a preoperative or early postoperative start.[5,96,97] Nevertheless, the timing and the dose of first administration can influence the efficacy and safety of VTE prophylaxis,[98] and the optimal timing will depend on the pharmacology of the individual anticoagulant.

Trials have followed the recommendations on endpoints given by regulatory authorities (European Medicines Evaluation Authority and the US FDA), although controversy exists concerning the clinical relevance of these endpoints. Clear definitions of bleeding endpoints are lacking, which makes head-to-head comparison of bleeding results between studies impossible.[99] All trials evaluated the presence of DVT by bilateral ascending venography and one used unilateral venography. Data from a meta-analysis have shown a clear association between a reduction in asymptomatic VTE and a reduced risk of fatal pulmonary embolism with the use of antithrombotic agents, and venography is accepted as the standard for comparison of efficacy of antithrombotic drugs in clinical trials.[5,100] In the larger studies, venographic results were adjudicated by independent experts blinded to treatment assignment. Clinically suspected pulmonary embolism had to be confirmed objectively, by ventilation/perfusion scintigraphy, for example.

3.1 Desirudin

Because desirudin reaches 90% of its peak plasma level within 30 minutes after subcutaneous injection and has a shorter $t_{1/2}$ than UFH or LMWH,[101] the first dose of desirudin in all studies was given within 30 minutes before surgery (and after regional block anaesthesia, if used). Desirudin has been investigated for the prevention of VTE following THR. The first study, with an open-label, ascending dose design, found no dose-dependent increase in bleeding or transfusion requirements with desirudin 10, 15 or 20mg twice daily subcutaneously.[21] The second was a double-blind comparison of desirudin 10, 15 and 20mg twice daily with UFH 5000IU three times daily started 2 hours before surgery. The results showed no difference in the incidence of bleeding complications and no significant differences in peri- or postoperative blood loss between the four groups, although total blood loss was higher with desirudin 20mg twice daily than with UFH. The frequencies of total and proximal DVT were significantly lower at each desirudin dose compared with UFH.[102]

On the basis of these findings and pharmacokinetic and pharmacodynamic results, coagulation monitoring was not considered necessary in subsequent phase III studies in which 15mg twice daily subcutaneously was the selected dose. In a double-blind comparison with subcutaneous UFH 5000IU three times daily, desirudin administered for 8–11 days was superior in the prevention of total VTE and proximal DVT/pulmonary embolism. VTE was found in 7 versus 23% of patients in the desirudin and heparin groups, respectively ($p < 0.0001$), and proximal DVT/pulmonary embolism in 3 versus 16% ($p < 0.0001$), with no significant differences between treatments in blood loss, transfusions or bleeding complications.[101]

A large study of 2079 patients conducted in ten European countries compared desirudin with subcutaneous enoxaparin sodium 40mg once daily started the evening before surgery; both treatments were continued for 8–12 days. This study found significantly lower rates of total VTE (18.4 versus 25.5%, $p = 0.001$) and proximal DVT/pulmonary embolism (4.5 versus 17.5%, $p = 0.01$) [figure 2] with similar safety to LMWH.[13] The rates of serious bleeding in the desirudin and enoxaparin sodium groups were 1.9 and 2.0%, respectively. It was suggested that, while the benefit of desirudin may arise from a more efficient mode of action of the DTI, the difference in

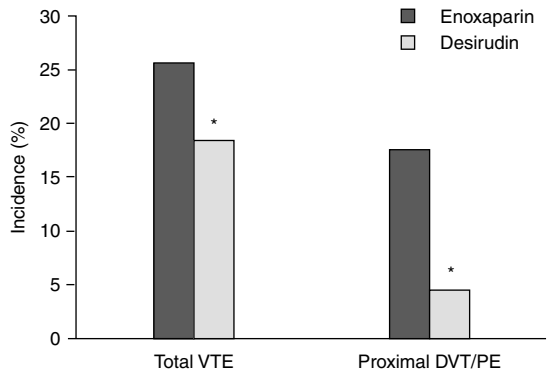

Fig. 2. Incidence of total venous thromboembolism (VTE) and proximal deep vein thrombosis (DVT)/pulmonary embolism (PE) during the treatment period in patients undergoing total hip replacement treated with desirudin 15mg SC bid started immediately before surgery versus enoxaparin sodium 40mg SC od started 12 hours before surgery.[13] **bid** = twice daily; **od** = once daily; **SC** = subcutaneous; * $p < 0.0001$ vs enoxaparin.

timing of initial drug administration might be partly contributory.[13] Overall, these findings confirmed that specific inhibition of thrombin with a fixed dose of subcutaneous desirudin 15mg twice daily, without coagulation monitoring, provided effective and well tolerated prevention of VTE in patients undergoing THR.

3.2 Bivalirudin

Bivalirudin was evaluated in patients undergoing THR or TKR, with dose administration initiated 12–24 hours postoperatively. This was a dose escalating design with five doses administered subcutaneously for up to 11 days: 0.3 mg/kg twice daily; 0.6 mg/kg twice daily; 1.0 mg/kg twice daily for 3 days then 0.6 mg/kg twice daily; 1.0 mg/kg twice daily; and 1.0 mg/kg three times daily. The incidence of major bleeding was 1.4% in the combined groups. The highest dosage regimen (1.0 mg/kg every 8 hours) provided rates of total and proximal DVT of 17 and 2%, respectively. These were significantly lower than the pooled rates for the other four regimens (43 and 20%, respectively) and were comparable with the pooled rates reported previously in studies using LMWH.[31] Bivalirudin has a short $t_{1/2}$,[72] and the results implied that dose administration four times daily might be necessary to maintain adequate anticoagulation; it has not been confirmed whether higher doses given twice or three times daily would be effective.[31]

3.3 Ximelagatran/Melagatran

Ximelagatran has undergone an extensive clinical development programme with separate study designs in Europe and the US based on clinical practice and recommendations from the health regulatory authorities in each region. In Europe, therapy was initiated with subcutaneous melagatran either preoperatively or 4–12 hours after surgery, followed by oral ximelagatran started within 1–2 days postoperatively (mostly on the day after surgery). The LMWH comparator was started 12 hours before surgery, and studies were conducted in both THR and TKR with separate and combined analyses. In North American studies, oral ximelagatran was started 12–24 hours after surgery without treatment initiation with subcutaneous melagatran, and most trials were in TKR patients and had warfarin as the comparator.

3.3.1 European Studies

MElagatran for THRombin inhibition in Orthopaedic surgery (METHRO) II was a double-blind, dose-response study in which the first dose of melagatran was given immediately before surgery (defined as 'knife-to-skin').[103] Melagatran dosages of 1, 1.5, 2.25 or 3mg twice daily subcutaneously were followed by ximelagatran 8, 12, 18 or 24mg twice daily, respectively. For the combined THR and TKR population, there was a significant dose response for efficacy across the doses. The highest dose group had a significantly lower incidence of total VTE and proximal DVT/pulmonary embolism in comparison with subcutaneous dalteparin 5000IU once daily (table III). The volume of blood transfused showed a dose response in patients undergoing THR and the frequency of severe bleeding was numerically higher in the highest ximelagatran dose group than with dalteparin (table III). Severe bleeding was defined as bleeding involving a critical site (intracranial, intraspinal, intraocular or retroperineal) or excessive bleeding as judged by the investigator; all episodes being adjudicated by an independent expert. None of the observed bleeding events involved a critical site.

In view of the high efficacy demonstrated when starting melagatran preoperatively with the highest dose (3mg/24mg twice daily), a further study (METHRO III) was undertaken to determine whether the good efficacy could be maintained without an increase in bleeding if melagatran was initiated postoperatively.[104] Melagatran was commenced 4–12 hours after surgery, followed by oral ximelagatran. The comparator, subcutaneous enoxaparin sodium 40mg once daily, was started 12 hours before surgery. There were no statistically significant differences in the incidence of total VTE, proximal DVT/pulmonary embolism or symptomatic DVT and pulmonary embolism between treatments (table III). Bleeding parameters were similar between treatments. Relative to LMWH in the METHRO II and

Table III. Efficacy and bleeding results in studies using the same dosage of melagatran/ximelagatran started immediately before or 4–12 hours after surgery versus low molecular weight heparin started 12 hours before surgery

Trial	THR + TKR		THR		TKR	
	total VTE (%)	severe bleeding (%)	total VTE (%)	severe bleeding (%)	total VTE (%)	severe bleeding (%)
METHRO II[103]						
Preoperative melagatran 3mg SC followed by ximelagatran	15.1	5.0	11.9	5.5	22.0	3.2
Dalteparin sodium	28.2	2.4	25.5	2.3	33.7	2.4
p-Value	<0.0001	NS	0.0005	NS	NS	NS
METHRO III[104]						
Postoperative melagatran 3mg SC followed by ximelagatran	31.0	1.4	25.4	1.7	44.1	0.9
Enoxaparin sodium	27.3	1.7	19.4	1.8	46.0	1.4
p-Value	NS	NS	0.004	NS	NS	NS

METHRO = MElagatran for THRombin inhibition in Orthopaedic surgery; **NS** = not significant; **SC** = subcutaneous; **THR** = total hip replacement; **TKR** = total knee replacement; **VTE** = venous thromboembolism.

III studies, the difference in timing of first dose had a greater impact on the efficacy of ximelagatran in patients undergoing THR than in those undergoing TKR, although this observation is based on two trials only.

A *post hoc* analysis of the combined THR and TKR population in METHRO III suggested that patients who received their first dose <8 hours after surgery in this study had a lower incidence of VTE (27.0%) compared with those patients whose first dose was >8 hours after surgery (35.4%).[104]

The METHRO studies showed that the dose *per se* and the timing of the first dose were crucial to the outcome. Therefore, the aim of the next study (EXpanded PRophylaxis Evaluation Surgery Study [EXPRESS][43]) was to evaluate the efficacy to bleeding profile using a modified dose administration regimen started preoperatively. Melagatran was started at a lower dose, 2mg subcutaneously, immediately before surgery, followed by 3mg on the evening of the day of surgery, then oral ximelagatran 24mg twice daily for a total treatment period of 8–11 days. The trial was designed with two sequentially assessed primary objectives as described in recent guidelines for drug development.[15] The first-stage primary objective was to demonstrate that ximelagatran was non-inferior to enoxaparin sodium in preventing major VTE. If non-inferiority was demonstrated, the analysis could proceed to the second stage, which was to demonstrate that ximelagatran was more effective than enoxaparin sodium in preventing total VTE. The rates of major and total VTE were significantly lower for both THR and TKR patients and the combined population in the ximelagatran group compared with enoxaparin sodium (figure 3). Bleeding events were more common with ximelagatran among patients undergoing THR but not TKR, but there were no differences between treatments in fatal bleeding, bleeding involving a

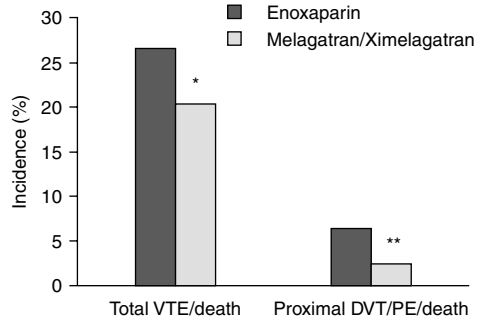

Fig. 3. Incidence of total venous thromboembolism (VTE) and/or death and proximal deep vein thrombosis (DVT)/pulmonary embolism (PE) and/or death (primary endpoint) during the treatment period in patients treated with melagatran 2mg SC immediately before surgery and 3mg SC on the evening of surgery, followed by ximelagatran 24mg PO bid versus enoxaparin sodium 40mg SC od started 12 hours before surgery (the EXPRESS study[43]). **bid** = twice daily; **EXPRESS** = EXpanded PRophylaxis Evaluation Surgery Study; **od** = once daily; **PO** = oral; **SC** = subcutaneous; * $p < 0.0004$, ** $p < 0.000002$ vs enoxaparin.

Table IV. Influence of timing and dose of melagatran administration on efficacy and bleeding[105]

Treatment/preoperative dose (trial)	Proximal DVT/PE [%] (95% CI)	Total DVT/PE [%] (95% CI)	Bleeding [%] (95% CI)	Blood loss during surgery [mL] (95% CI)
Melagatran/0mg (METHRO III)	5.7 (4.4, 7.2)	31.0 (28.3, 33.7)	1.4 (0.9, 2.2)	211.8 (190.3, 235.7)
Melagatran/2mg (EXPRESS)	2.3 (1.5, 3.3)	20.2 (17.9, 22.7)	3.3 (2.4, 4.4)	195.4 (175.5, 217.6)
Melagatran/3mg (METHRO II)	2.4 (1.0, 4.9)	15.1 (11.1, 19.8)	4.8 (2.8, 7.4)	215.0 (175.0, 264.2)
LMWH (pooled data)	6.3 (5.4, 7.3)	27.1 (25.4, 28.8)	1.5 (1.1, 2.0)	205.7 (191.6, 220.9)

DVT = deep vein thrombosis; **EXPRESS** = EXpanded PRophylaxis Evaluation Surgery Study; **LMWH** = low molecular weight heparin; **METHRO** = MElagatran for THRombin inhibition in Orthopaedic surgery; **PE** = pulmonary embolism.

critical organ or requiring re-operation, or in surgical site complications such as wound haematoma.

A combined analysis of results from METHRO II, METHRO III and EXPRESS illustrates the influence of timing and dose of melagatran on the relationship between efficacy and bleeding, and the balance achieved using the regimen of melagatran 2mg subcutaneously as an initial preoperative dose followed by 3mg subcutaneously and oral ximelagatran 24mg twice daily (table IV).[105] The lowest rates of bleeding were associated with the postoperative start of prophylaxis.

3.3.2 US Studies

In one US study in patients undergoing THR, oral ximelagatran 24mg twice daily was less effective than subcutaneous enoxaparin sodium 30mg twice daily when both were started 12–24 hours postoperatively. The difference was statistically significant, although the incidence of VTE was low in both groups (7.9 versus 4.6%).[106] However, in a dose-finding study in TKR patients (Study 203), the same ximelagatran regimen appeared to be at least as effective as enoxaparin sodium (table V).[107] Subsequently, a further phase III study (Study 236) in patients undergoing TKR compared oral ximelagatran 24mg twice daily with warfarin, the latter begun on the evening of the day of surgery with the dose adjusted to a target international normalised ratio of 2.5 (target range 1.8–3.0).[108] In this regimen, ximelagatran was at least as effective as warfarin, with VTE rates of 19.2 versus 25.7%, respectively ($p = 0.070$) [table V]. This study used unilateral venography in the operated leg for detection of asymptomatic DVT. There were no statistically significant differences in bleeding parameters.

A second major study, EXanta used to Lessen Thrombosis (EXULT) A, involving approximately 2300 patients undergoing TKR, was designed to determine whether a higher dose of oral ximelagatran would be safe and more effective than warfarin.[44] This proved to be the case; the composite endpoint of distal and/or proximal DVT and/or symptomatic DVT/pulmonary embolism (objectively confirmed) and/or death occurred with significantly lower frequency in the ximelagatran 36mg twice daily group compared with the warfarin group (20.3 versus 27.6%, respectively) [figure 4; table V]. There were no statistically significant differences between groups for proximal DVT, pulmonary embolism, death, major bleeding, blood loss or transfusion volumes, or wound drainage or appearance. Rates of VTE in the third group, assigned to ximelagatran 24mg twice daily, were similar to those seen with warfarin. Hence, when initiated 12–24 hours after surgery (a mean of 20.4 hours postoperatively), the higher dose of ximelagatran (36mg twice daily) achieved superior efficacy to adjusted-dose warfarin with no excessive bleeding or requirement for coagulation monitoring. These results have recently been confirmed in the EXULT B trial, which compared fixed-dose oral ximelagatran 36mg twice daily with adjusted-dose warfarin.[109]

3.4 Dabigatran Etexilate

Dabigatran etexilate has been tested in an open-label, dose-escalating study in THR with the first dose given 4–8 hours postoperatively. With oral doses of 12.5, 25, 50, 100, 150, 200 and 300mg twice daily, and 150 and 300mg once daily for 6–10 days, a dose response was observed for bleeding events. There were no major bleeding events, al-

Table V. Efficacy and bleeding results in studies using ximelagatran started 12–24 hours after total knee replacement surgery versus low molecular weight heparin started 12–24 hours after surgery or warfarin started on the evening of the day of surgery

Trial	Total VTE (%)	Proximal DVT/PE (%)	Major bleeding (%)
Study 203[107]			
Ximelagatran 24mg bid	15.8	3.2	0
Enoxaparin sodium	22.7	3.1	0.008
p-Value	NS	NS	NS
Study 236[108]			
Ximelagatran 24mg bid	19.2	3.3	1.7
Warfarin	25.7	5.0	0.9
p-Value	NS	NS	NS
EXULT A[44]a			
Ximelagatran 24mg bid	24.9	2.5	0.8
Ximelagatran 36mg bid	20.3	2.7	0.8
Warfarin	27.6	4.1	0.7
p-Value	0.003b	NS	NS

a In EXULT A, both efficacy endpoints also include death.

b Warfarin versus ximelagatran 36mg bid; difference between warfarin and ximelagatran 24mg bid was not statistically significant.

bid = twice daily; **DVT** = deep vein thrombosis; **EXULT** = EXanta Used to Lessen Thrombosis; **NS** = not significant; **PE** = pulmonary embolism; **VTE** = venous thromboembolism.

though at the highest dose two of 20 patients had multisite bleeding (urinary and intestinal). It was noted that about 20% of patients had low plasma concentrations of active drug after the first dose, suggesting that the experimental tablet formulation was not reliably absorbed. Hence, further exploration of the dose range was warranted.[91]

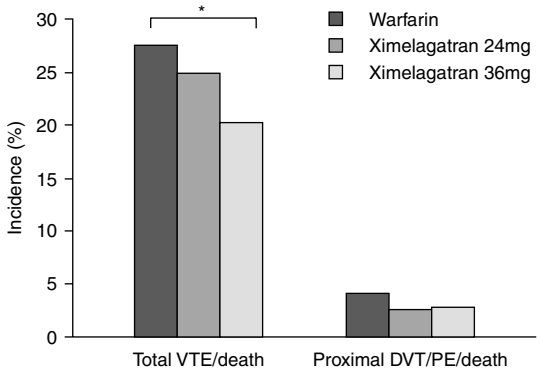

Fig. 4. Incidence of total venous thromboembolism (VTE) and/or death and proximal deep vein thrombosis (DVT)/pulmonary embolism (PE) or death during the treatment period in patients undergoing total knee replacement treated with ximelagatran 24mg bid versus 36mg bid initiated 12–24 hours after surgery versus warfarin (the EXULT A study[44]). **bid** = twice daily; **EXULT** = EXanta Used to Lessen Thrombosis; * p = 0.003 vs warfarin.

The BISTRO I trial evaluated doses of oral dabigatran etexilate from 12.5 to 300mg twice daily and 150 and 300mg once daily, commenced 4–8 hours after THR. A trend toward a decreased incidence of DVT and increased incidence of bleeding was seen with increasing drug AUCs.[92]

4. Clinical Potential of DTIs in Orthopaedic Surgery

The clinical potential of DTIs for the prevention of VTE following orthopaedic surgery depends on achieving demonstrable improvement in one or more components of efficacy, safety, convenience or cost.

Desirudin has shown superior efficacy to LMWH and warfarin with similar safety in the prevention of VTE. The factor Xa inhibitor fondaparinux sodium, started postoperatively, has also proved effective in comparison with enoxaparin sodium commenced the day before surgery in patients undergoing THR (Europe),[110] and in comparison with enoxaparin sodium started the day after surgery in patients undergoing TKR (North America).[111] However, this TKR study showed a statistically significant increase in major bleeding, and a North American THR study[112] showed no significant difference in

efficacy or safety parameters compared with enoxaparin sodium, illustrating how treatment regimens and surgical model can influence the outcomes of an anticoagulant drug being studied. Longer experience with the conventional anticoagulants and the relatively high cost of producing r-hirudins may preclude a major switch to these newer agents. The DTIs ximelagatran and dabigatran etexilate have the advantage of being administered orally. Recent large clinical trials indicate that ximelagatran also has an efficacy advantage over LMWH or warfarin. Dabigatran etexilate has undergone phase II clinical trials and further efficacy and safety data are awaited.

Unlike warfarin, ximelagatran is given in fixed doses with no requirement for coagulation monitoring. The combination of these features facilitates out-of-hospital prophylaxis, which may offer advantages in situations where earlier mobilisation and shorter hospital stay are encouraged, with the potential for improved patient acceptability compared with self-injection of LMWH. Ease of management, together with effective prevention of VTE and a low bleeding risk may contribute to cost-effectiveness advantages, although data are not yet available.

In the European regimen, subcutaneous melagatran is commenced near the time of surgery. Subcutaneous administration is appropriate for patients undergoing surgery, for whom oral administration may be unsuitable. Subsequently ximelagatran is given orally; in fact, 94% of surgeons in the EXPRESS study began oral therapy within the first postoperative day.[43] Alternatively, studies based on current North American practice have also shown that oral ximelagatran is effective when commenced 12–24 hours after surgery using a higher-dose regimen and radiological evidence of VTE as the efficacy outcome.

All of the DTIs, including orally administered ximelagatran, provide a rapid onset of anticoagulant action in contrast with warfarin. Thus, prophylaxis can be started, or restarted if an interruption is necessary, without a period of non-protection. A relatively rapid offset of action may offer safety and convenience advantages. Should severe bleeding complications occur or anticoagulation need to be interrupted for an elective surgical procedure, haemostasis will be restored within a few hours without the need for antidote or haemodialysis for DTIs with a short $t_{1/2}$ (e.g. 4–5 hours for ximelagatran versus 4–8 hours or longer for desirudin or 15 hours for dabigatran etexilate). No specific antidote to melagatran is available, although the effects of certain blood factors have been evaluated in a non-clinical setting.[113] In the event of serious bleeding with ximelagatran, cessation of treatment combined with diuresis may be all that is required to manage the event. In the case of an overdose, diuresis should be maintained and further measures, such as surgical haemostasis or transfusion of fresh frozen plasma, should be used if necessary.

Ximelagatran offers the potential for fixed doses in a wide range of patients without adjustment for bodyweight, age, renal impairment (except when severe), liver impairment or whether the patient has fasted or had food. A drug that is renally eliminated could be used despite impaired liver function associated with surgery or trauma, whereas argatroban would not be suitable. Although melagatran is mainly eliminated renally, studies have shown that the alteration in pharmacokinetics with mild or moderate renal impairment is not clinically significant and dose adjustment is not necessary.[81]

Furthermore, as increasing evidence now supports the benefit of extended prophylaxis in reducing the incidence of postoperative VTE,[114,115] an oral DTI without the requirement for coagulation monitoring may provide a convenient means of continuing prophylaxis beyond the conventional 8–11 days. Infrequent elevations of alanine aminotransferase (ALT) >3-fold higher than the upper limit of normal (ULN) have been seen during the 8- to 11-day conventional prophylaxis for orthopaedic procedures, and these were more common in the LMWH and warfarin groups than with ximelagatran.[44,103] Transient, asymptomatic elevations of ALT >3-fold higher than the ULN have been observed more often (in 6–13% of patients) during long-term therapy with ximelagatran.[47-49] Hence, as a precaution, if ALT is >2-fold higher than the

ULN prior to surgery, an alternative anticoagulant should be used. However, there is no requirement for ALT monitoring during the 11 days of treatment for which ximelagatran has been evaluated in the orthopaedic surgery setting.

5. Conclusions

LMWH and vitamin K antagonists are the mainstay of anticoagulation for patients undergoing THR or TKR. Recently, an injectable factor Xa inhibitor, fondaparinux sodium, has been approved for use in the orthopaedic surgery setting, offering potential efficacy advantages. The first DTI to be approved for the prevention of VTE in orthopaedic surgery was desirudin. However, a major advance in clinical practice may result from the availability of an oral DTI. Dabigatran etexilate is in phase II trials, while ximelagatran is in advanced clinical development. Ximelagatran shows great promise for the prevention of VTE following THR or TKR, providing similar or superior efficacy and safety compared with LMWH or well controlled warfarin therapy. Warfarin is the foremost cause of drug-related deaths (intracranial haemorrhage) in many countries, at least during long-term use.[116,117] Ximelagatran offers the potential for simpler management, its predictable dose response allowing fixed dose administration without coagulation monitoring, and its oral formulation facilitating out-of-hospital prophylaxis. The latter may be particularly important if extended prophylaxis after THR and TKR is practised widely in the future. Proof of concept studies for oral DTIs, and ximelagatran specifically, in orthopaedic surgery provide a stepping stone for much wider therapeutic applications such as prevention of stroke in patients with atrial fibrillation.

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