# Dabigatran etexilate: an oral direct thrombin inhibitor

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Dabigatran etexilate is a direct thrombin inhibitor that offers potential advantages over existing anticoagulants for the prevention and treatment of venous and arterial thrombosis. It is administered orally, has a rapid onset of action, a predictable anticoagulant effect and does not require laboratory monitoring. Trial results indicate that dabigatran etexilate has similar efficacy, risk of bleeding and tolerability compared with currently used anticoagulants. Dabigatran etexilate is approved in Europe and Canada for the prophylaxis of venous thromboembolism in patients undergoing hip- and knee-replacement surgery. Trials involving more than 40,000 patients are evaluating the safety and efficacy of dabigatran etexilate for the treatment of deep-vein thrombosis and pulmonary embolism, primary and secondary prevention of venous thromboembolism, prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and prevention of cardiac events in patients with acute coronary syndromes. The drug may have its greatest impact in providing a much-needed and attractive alternative to vitamin K antagonists.

Thrombotic disorders are a major cause of mortality and morbidity. Recent data from North America indicates that in 2005, over 1.4 million cases of acute coronary syndrome (ACS), 250,000 cases of venous thromboembolism (VTE) and 780,000 cases of stroke were encountered [1]. Effective antithrombotic therapy may treat or prevent these disorders, but all of the presently available agents have limitations. For over 60 years, vitamin K antagonists (VKAs) such as warfarin have been the only orally available compounds for long-term anticoagulation. Although effective, these compounds are challenging to use because of their slow onset and offset of action, narrow therapeutic window, multiple dietary and drug interactions and unpredictable anticoagulant effect [2]. Several new oral anticoagulants that target either thrombin or activated factor X (factor Xa) and have the potential to replace VKAs are presently in advanced stages of clinical development [3,4]. Designed to be administered in fixed doses with little or no coagulation monitoring, these drugs are certainly likely to be more convenient than VKAs.

## Unmet needs in the prevention of venous thromboembolism after hip & knee replacement

The need for thromboprophylaxis after major orthopedic surgery is well documented. It is also recognized that the risk of VTE in orthopedic surgery patients extends beyond the usual period of hospitalization (currently 3–4 days), and current guidelines therefore recommend that patients undergoing knee or hip replacement surgery receive thromboprophylaxis, such as low-molecular-weight heparins, VKAs or pentasaccharide, for at least 10 days after surgery, extending to 28–35 days for hip-replacement surgery [5,6,101]. Epidemiological data also show that the risk of developing VTE extends for at least 3 months after joint-replacement surgery [7–9]. While this risk is greatest in the first days after surgery, a second peak occurs several weeks after surgery, after most patients have been discharged from hospital. Despite these data and the availability of effective thromboprophylaxis options, therapy is often discontinued following hospital discharge due to complexities and inconvenience in administration [9]. As a result, VTE is one of the most common causes of hospital readmission following orthopedic surgery [10–12]. Oral agents that are effective without the need for monitoring could play an important role in increasing the uptake of prophylaxis beyond hospital discharge.

## Oral direct thrombin inhibitors as a therapeutic approach for the prevention of venous thromboembolism

Thrombin plays a central role in blood coagulation and thrombus (clot) formation, by converting fibrinogen to fibrin. Thus, effective anticoagulation can be achieved via thrombin inhibition [13]. Direct thrombin inhibitors

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(DTIs) directly neutralize thrombin by occupying its catalytic binding sites, its fibrinogen binding sites or both [13]. DTIs have a predictable mechanism of anticoagulation. They inhibit thrombin in both its inactive fluid phase and its stabilized fibrin-bound state, as well as any thrombin already bound to surfaces, and neutralize further progression of thrombus growth [14]. Two oral DTIs have been tested: ximelagatran and dabigatran etexilate.

Numerous trials, involving approximately 30,000 patients, evaluated the use of ximelagatran in deep-vein thrombosis (DVT) prophylaxis and treatment, stroke prevention in patients with atrial fibrillation (AF) and secondary prevention of recurrent ischemia after acute myocardial infarction. Phase III trial results indicated that ximelagatran had similar efficacy and risk of bleeding compared with currently used anticoagulants [15]. Ximelagatran was approved in Europe in 2004 for prophylaxis of VTE in patients undergoing hip or knee surgery. However, an adverse effect of ximelagatran is liver enzyme elevation, which was observed in approximately 8% of patients who were treated for at least 35 days. Although initially felt to be transient in nature, subsequent data suggested a small but real risk of significant hepatotoxicity. Following a further report of serious liver injury in early 2006 during longer-term treatment [16], ximelagatran was withdrawn in countries where it had been approved, and further development elsewhere ceased [17,102]. In several studies, a higher number of cardiovascular events was also observed after ceasing ximelagatran treatment, raising the possibility of a ximelagatran-induced rebound effect on the coagulation system after drug discontinuation [18]. Ximelagatran did, however, have many desirable properties, validating thrombin as an appropriate therapeutic target and demonstrating that an oral anticoagulant specifically targeting thrombin without routine monitoring could be highly effective, with bleeding rates comparable with those seen with low-molecular-weight heparins and VKAs. Recently, dabigatran etexilate, another synthetic small-molecule oral DTI, seemingly devoid of the limitations of ximelagatran, was approved in the EU for the primary prevention of VTE in patients having undergone elective total hip- and knee-replacement surgery [103]. The properties of this new agent and its clinical trial results are reviewed here.

## Dabigatran etexilate chemistry

Dabigatran is a benzamidine-based thrombin inhibitor that binds reversibly to the active site of the thrombin molecule and inhibits this protease with an inhibition constant of 4.5 nM [19,20]. Addition of a hydrophobic side chain led to the orally absorbed prodrug dabigatran etexilate. The molecular weight of dabigatran etexilate is 628, whereas dabigatran has a molecular weight of 471 [20].

## Pharmacokinetics & metabolism of dabigatran etexilate

Dabigatran etexilate was developed to overcome the limited oral bioavailability of dabigatran; it is a prodrug of dabigatran with absolute bioavailability of 6.5% in the fed and fasting state (**Table 1**) [21–23]. To further facilitate gastrointestinal absorption, dabigatran etexilate is presented in capsules containing multiple pellets with a tartaric acid core [24].

Following rapid absorption, dabigatran etexilate is converted into its active metabolite, dabigatran, with a maximum plasma concentration ($C_{max}$) of dabigatran being reached 1.5–3 h after administration [21,25]. Food prolongs the time to peak plasma levels by approximately 2 h without any effect on $C_{max}$ or overall exposure, measured as the area under the plasma concentration curve (AUC) [23]. For patients undergoing hip-replacement surgery, absorption of dabigatran etexilate is reduced for 24 h after surgery ($C_{max}$ at ~4 h), but this has no impact on the overall exposure [26]. This pharmacokinetic profile immediately after surgery, with slow and prolonged absorption, the absence of a high $C_{max}$ yet an unchanged total exposure, may help to reduce the risk of bleeding, even when the drug is administered very early after surgery (**Figure 1**). With subsequent doses after the day of surgery, dabigatran absorption is prompt, with $C_{max}$ occurring at approximately 2.5 h. Overall drug exposure ($C_{max}$ and AUC) is reduced by 20–25% if dabigatran-treated patients are administered proton pump inhibitors; however, this is not considered to be clinically relevant [23,25].

The conversion of dabigatran etexilate to dabigatran occurs in various sites in the body by rapid esterase-catalyzed hydrolysis, and is neither dependent on the cytochrome P450 (CYP) enzyme system nor localized to the liver [22]. Dabigatran is not metabolized [22] and does not inhibit CYP isoenzymes *in vitro* [22]; therefore, it has a low potential for interactions with other drugs [23,25,27,28]. The mean plasma terminal half-life of dabigatran is 12–14 h in healthy young

**Table 1. Pharmacokinetic and pharmacodynamic features of dabigatran etexilate.**

| Characteristic | Value | Ref. |
|---|---|---|
| Absolute bioavailability | 6.5% | [21–23] |
| Relative bioavailability | ~85% | [43] |
| Time to peak drug level* | 1.5–3 h in healthy volunteers, 3.7–4.5 h on day of surgery, 2.3–2.9 h at steady state after surgery | [21,25,26] |
| Food effect | No clinically relevant interactions | [23] |
| Apparent volume of distribution | 60–70 l | [103] |
| Half-life‡ | 12–14 h | [21,24,25] |
| Apparent total oral clearance | 71–144 l/h | [21,29] |
| Biliary excretion | ~20% | [21] |
| Renal excretion | 80% | [21] |
| Plasma protein binding | 35% | [22] |
| Cytochrome P450 metabolism | No | [22] |
| Maximum increase in pharmacodynamic parameters§ | aPTT: 2.3-times baseline, ECT: 5.2-times baseline, INR: 1.8-times baseline, TT: 27-times baseline | [21] |

*Median*

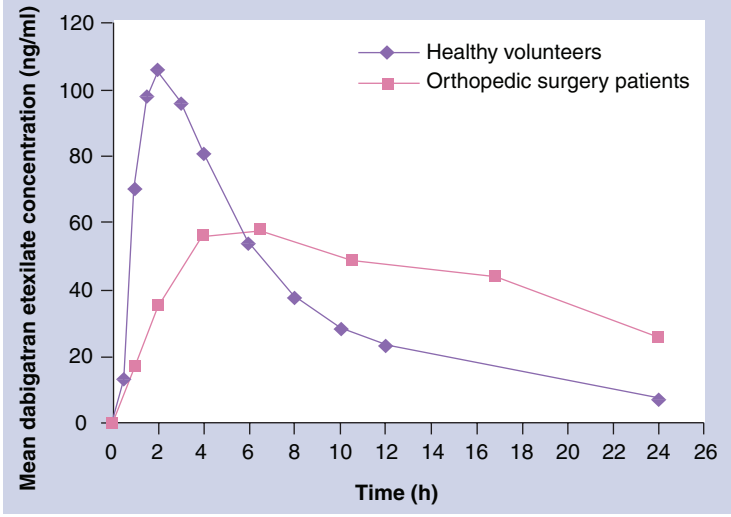
‡*Mean*

§*At steady-state with dose of 200 mg three-times daily for 7 days.*

*aPTT: Activated partial thromboplastin time; ECT: Ecarin clotting time; INR: International Normalized Ratio; TT: Thrombin clotting time.*

and elderly subjects [21,24,25]. Dabigatran etexilate is largely excreted unchanged in the urine (80%); the remaining 20% is conjugated with glucuronic acid to form acylglucuronides, which are predominantly excreted via the bile [21].

**Figure 1. Plasma concentration curve of the first postoperative dose (150 mg) of dabigatran etexilate compared with that observed in healthy volunteers.**




Based on data from the Boehringer Ingelheim Study in Thrombosis (BISTRO Ib) study [23], a slow and steady absorption profile on the day of surgery was noted, with reduced and delayed peak plasma concentrations occurring approximately 6 h following drug administration (8 h following surgery). On subsequent postoperative days, absorption was more rapid, with peak plasma concentrations occurring 2 h after drug administration.

Exposure to dabigatran in healthy subjects is not substantially affected by age, weight and gender [23,25,29], or by moderate impairment in hepatic function (Child–Pugh B) [30], and appears to depend only on renal function [29]. Subjects with moderate renal impairment (creatinine clearance [$CL_{CR}$] 30–50 ml/min) have slower excretion rates and elevated plasma concentrations of dabigatran [103], indicating that dose reduction may be necessary in patients with renal insufficiency. For patients undergoing hip- or knee-replacement surgery, the licensed dose of dabigatran etexilate is 220 mg once-daily, with a half dose on the day of surgery [103]. For those with moderate renal impairment, a lower 150 mg daily dose is recommended, with a half dose on the day of surgery. Dabigatran etexilate is contraindicated in patients with severe renal impairment ($CL_{CR}$ <30 ml/min) [103]. In healthy volunteers, variations in plasma concentrations and pharmacokinetic parameters were low to moderate (overall interindividual coefficient of variation [CV] 30–40%) after administration of dabigatran etexilate [21,23,25], with low intraindividual variability (CV <30%) [25].

Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (P-gp). When coadministered with amiodarone, a potent P-gp inhibitor, the overall exposure ($C_{max}$ and AUC) of dabigatran is increased by approximately 50 and 60%, respectively [103]. The mechanism responsible for this interaction has not been

completely elucidated, and a reduced dose of dabigatran etexilate is recommended when it is administered in conjunction with this drug. Quinidine, a strong P-gp inhibitor, is contraindicated for use in conjunction with dabigatran etexilate [103]. *In vivo* studies with healthy volunteers show no interaction between dabigatran and the P-gp inhibitors/substrate transporters atorvastatin [27], digoxin [31] and the NSAID diclofenac [28]. Further investigations are ongoing to clarify the significance of a P-gp interaction. In addition, dabigatran etexilate has no additive effects on platelet aggregation when coadministered with aspirin or diclofenac [28].

## Pharmacodynamics of dabigatran etexilate

The antithrombotic properties of dabigatran have been demonstrated in several venous and arterial thrombosis models in animals [32–35]. In a rabbit venous thrombosis model [33], oral dabigatran etexilate reduced thrombus formation in a dose-dependent fashion; maximum inhibition was achieved within 1 h of administration of a 10-mg/kg dose, suggesting a rapid onset of action. Dabigatran etexilate prolongs conventional coagulation assays, including prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin clotting time (TT) [21,25,36]. In Phase I studies, a linear relationship was observed between the plasma concentration of dabigatran and TT, indicating that this global test may be useful if information on the anticoagulant effect is needed. A curvilinear relationship exists between dabigatran plasma concentrations and aPTT, reaching a plateau with high doses (see **Table 1**) [21,25,36]. While the measurement of aPTT may provide a qualitative indication of anticoagulant activity, it is not suitable for the precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran.

Dabigatran has little effect on PT at clinically relevant plasma concentrations [21]. The ecarin clotting time (ECT) and TT, which are particularly sensitive to the effects of DTIs, display a linear dose–response relationship with concentration of dabigatran within the therapeutic range. TT exhibits a 50-fold or greater increase and is probably too sensitive for emergency monitoring. By contrast, the ECT is less sensitive, with the ECT ratios increased fivefold after a single 200-mg dose of dabigatran etexilate [21]. The variability in these parameters is low, with CV generally less than 10% after single or multiple doses.

## Clinical studies with dabigatran etexilate

Owing to the significant clinical and economic burden imposed by VTE in wide groups of patients, and the rising incidence of AF and ACS in the elderly population, there are several potential patient populations and indications for novel, safe and effective oral anticoagulants, such as dabigatran etexilate. Therefore, a broad range of clinical trials has been designed to evaluate the safety and efficacy of dabigatran etexilate in patients at risk for arterial and venous thrombosis. In the following sections, the completed, ongoing and planned clinical trials of dabigatran etexilate, according to the corresponding clinical indications, are discussed.

### *Prophylaxis of venous thromboembolism after hip- or knee-replacement surgery*

Proof of principle for the use of dabigatran etexilate in the prevention of VTE was first demonstrated in a Phase IIa study (Boehringer Ingelheim Study in ThROmbosis [BISTRO I]) of 314 patients undergoing total hip replacement (THR) [37]. In this open-label, dose-escalation study, patients received one of nine oral doses of dabigatran etexilate (12.5, 25, 50, 100, 150, 200 and 300 mg twice-daily or 150 and 300 mg once-daily) administered 4–8 h after surgery, for 6–10 days until mandatory bilateral venography was performed. This was primarily a safety study, with dose escalation based on clinical and pharmacokinetic data. The primary safety end point was major bleeding; the primary efficacy end point included venographic DVT and symptomatic VTE during the treatment period. No major bleeding events were observed, while a dose response was demonstrated for minor bleeding. The DVT rates were relatively low, confirming the antithrombotic potential of the drug. No dose–response relationship was apparent, but the study was not powered for such an analysis. Two patients receiving the highest dose experienced bleeding from multiple sites, suggesting a wide therapeutic window between the lowest and highest doses (12.5 and 300 mg twice-daily). While successful, this study was limited by the open-label design and inadequate power to compare efficacy between enoxaparin and individual dabigatran etexilate doses.

BISTRO Ib was a small, single-dose (150 mg) study evaluating a new capsule formulation of dabigatran etexilate with improved pharmacokinetic properties compared with the tablet used in BISTRO I [23]. The capsule was administered 1–3 h following surgery and proved to be effective, with prompt absorption and peak plasma

**Table 2. Safety and efficacy of dabigatran etexilate in a Phase IIb study of venous thromboembolism prophylaxis following total hip- or knee-replacement surgery (BISTRO II) [26].**

| | Dabigatran etexilate groups | | | | Enoxaparin 40 mg o.d. |
|---|---|---|---|---|---|
| | *50 mg b.i.d* | *150 mg b.i.d* | *300 mg o.d.* | *225 mg b.i.d* | |
| Total VTE* (%) (95% CI)‡ | 28.5 (23.5–33.9) | 17.4 (13.1–22.3) | 16.6 (12.5–21.5) | 13.1 (9.5–17.5) | 24.0 (19.3–29.2) |
| p-value vs enoxaparin | 0.25 | 0.04 | 0.02 | 0.0007 | |
| Major VTE§ (%) | 5.0 | 4.0 | 2.1 | 1.7 | 5.6 |
| Major bleeding¶ (%) (95% CI) | 0.3 (0.0–1.4) | 4.1 (2.4–6.6) | 4.7 (2.8–7.3) | 3.8 (2.2–6.2) | 2.0 (0.9–4.0) |

**Total VTE = composite of any DVT (symptomatic or asymptomatic detected by venography) and PE during treatment.*

*‡p-value for dabigatran etexilate dose response < 0.0001.*

*§Major VTE = composite of proximal DVT, nonfatal PE and VTE-related death.*

*¶Major bleeding events (including those at the wound site) were defined as clinically overt bleeding associated with >20 g/l fall in hemoglobin; clinically overt leading to transfusion of >2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation.*

*b.i.d.: Twice-daily; DVT: Deep-vein thrombosis; o.d.: Once-daily; PE: Pulmonary embolism; VTE: Venous thromboembolism. Data from [26].*

concentrations of dabigatran occurring 6 h after administration. Peak plasma concentrations and systemic exposure of dabigatran using this new capsule formulation were approximately 85% of those seen at steady-state using the tablet formulation. These characteristics confirmed its suitability for use in future clinical trials.

BISTRO II was a large, multicenter, parallel-group, Phase IIb double-blind study that enrolled 1973 patients undergoing either THR or total knee replacement (TKR) [26]. Patients received one of four dabigatran etexilate doses (50 or 150 mg twice-daily; 300 mg once-daily; or 225 mg twice-daily), starting 1–4 h after surgery, or enoxaparin (40 mg once-daily) initiated the evening before surgery, for 6–10 days. There was a significant dose-dependent decrease in total VTE with higher doses of dabigatran etexilate (13.1–28.5 vs 24% for enoxaparin). Major bleeding (including wound-site bleeding) was significantly lower with the lowest (50 mg twice-daily) dose of dabigatran etexilate (0.3 vs 2.0%; p = 0.047) compared with enoxaparin, with an increase at the higher, more effective doses (3.8–4.7%) (**Table 2**). Based on the same total daily dose, once-daily dosing of dabigatran etexilate was equally as effective compared with twice-daily dosing, with comparable rates of bleeding. Using a logistic regression model, plasma concentration data were combined with clinical outcomes of clinically relevant bleeding (major plus clinically significant) and VTE events to determine the optimal efficacy–safety balance for dabigatran etexilate doses to be evaluated in subsequent Phase III trials. Using this model, the optimal efficacy–safety involved administration of a half dose of dabigatran etexilate immediately after surgery, with full doses commenced thereafter.

Three large, noninferiority Phase III studies have been completed and reported (**Table 3**) [38–40]. All three studies compared two doses of dabigatran etexilate (150 and 220 mg once-daily) with the approved enoxaparin regimen for that region; in all three studies the first dose of dabigatran etexilate was given as a half dose on the day of surgery. Two studies, conducted in Europe (RE-MODEL and RE-NOVATE) showed dabigatran etexilate 150 and 220 mg once daily to be noninferior to enoxaparin (40 mg once-daily, presurgery) for the prevention of the composite of total VTE and all-cause mortality after TKR or THR [38,39]. In both studies, the efficacy results in the 220-mg dose group were numerically slightly better than in the 150-mg group (**Table 4**). The rates of major bleeding (which included surgical-site bleeding) were low (1.3–2.0%) and similar between the treatment groups in both studies. However, in a third study of 2615 patients conducted in North America (RE-MOBILIZE), which compared 12–15 days of dabigatran etexilate commenced 6–12 h after surgery or enoxaparin 30 mg twice-daily started 12–24 h post TKR surgery, both doses of dabigatran etexilate missed the prospectively defined criteria for noninferior efficacy compared with enoxaparin for the prevention of the composite of total VTE and all-cause mortality [40]. Differences in the efficacy outcome between the treatments were predominantly due to asymptomatic distal DVTs, since clinically relevant major VTE events (composite of proximal DVT, nonfatal PE and VTE-related

**Table 3. Study design of Phase III trials of dabigatran etexilate for the prevention of VTE after hip- and knee-replacement surgery.**

| | RE-MOBILIZE | RE-MODEL | RE-NOVATE |
|---|---|---|---|
| Target population | Total knee replacement | Total knee replacement | Total hip replacement |
| Study location | North America, UK | Europe, South Africa, Australia | Europe, South Africa, Australia |
| Time of randomization | Postoperative | Preoperative | Preoperative |
| Time to first dose of dabigatran etexilate | 6–12 h postoperative | 1–4 h postoperative | 1–4 h postoperative |
| Enoxaparin dose regimen | 30 mg b.i.d., initiated 12–24 h postsurgery | 40 mg o.d., initiated evening before surgery | 40 mg o.d., initiated evening before surgery |
| Treatment duration | 12–15 days | 6–10 days | 28–35 days |
| Primary end point | Total VTE plus all-cause mortality | Total VTE plus all-cause mortality | Total VTE plus all-cause mortality |
| No. patients randomized | 2615 | 2076 | 3494 |

*b.i.d.: Twice-daily; o.d.: Once-daily; VTE: Venous thromboembolism.*

death) occurred at similar rates in all treatment groups. Major bleeding events occurred in 0.6% of patients treated with either dose of dabigatran etexilate, and in 1.4% of those administered enoxaparin. Although not statistically significant, major bleeding was more than 50% lower with either dose of dabigatran etexilate ($p = 0.14$ for 220 mg and $p = 0.09$ for 150 mg).

Although the study designs of these three trials were very similar, significant differences in practice patterns between Europe and North America (shown in Table 3), including differences in the registered doses of comparator drugs (enoxaparin 40 vs 60 mg total daily dose) and differing recommendations for the initiation of dabigatran etexilate (1–4 h in RE-MODEL and RE-NOVATE vs 6–12 h in RE-MOBILIZE) probably contributed to the divergent findings observed.

**Table 4. Safety and efficacy of dabigatran etexilate in Phase III studies of venous thromboembolism prophylaxis following total hip- or knee-replacement surgery.**

| | Dabigatran etexilate | | Enoxaparin |
|---|---|---|---|
| | *220 mg* | *150 mg* | |
| ***Total VTE, all-cause mortality (%)*** | | | |
| RE-MODEL | 36.4 | 40.5 | 37.7 |
| RE-NOVATE | 6.0 | 8.6 | 6.7 |
| RE-MOBILIZE | 31.1 | 33.7 | 25.3 |
| ***Major VTE (%)*** | | | |
| RE-MODEL | 2.6 | 3.8 | 3.5 |
| RE-NOVATE | 3.1 | 4.3 | 3.9 |
| RE-MOBILIZE | 3.4 | 3.0 | 2.2 |
| ***Major bleeding* (%)*** | | | |
| RE-MODEL | 1.5 | 1.3 | 1.3 |
| RE-NOVATE | 2·0 | 1·3 | 1·6 |
| RE-MOBILIZE | 0.6 | 0.6 | 1.4 |

**Major bleeding included wound-site bleedings.*
*VTE: Venous thromboembolism.*

Based on the results described above, a new study (RE-NOVATE II) has therefore been initiated in North America, comparing 220 mg of dabigatran etexilate (commenced 1–4 h after surgery) with enoxaparin (40 mg o.d., approved for long-term use in North America) for an extended treatment period of 28–35 days in patients undergoing THR ([104]; identifier: NCT00657150).

### *Treatment & secondary prevention of venous thromboembolism*

No Phase II trials have been performed with dabigatran etexilate for the treatment of VTE. Nonetheless, the drug is being studied for initial treatment of VTE (RE-COVER trial) and secondary prevention (RE-MEDY and RE-SONATE) of VTE at a dose of 150 mg twice-daily, a dose that has been evaluated in a Phase II trial for stroke prevention in AF (Prevention of Embolic and ThROmbotic events in patients with persistent AF [PETRO]) [41] and has been carried forward into a large Phase III trial (Randomized Evaluation of Long-term anticoagulant therapy [RE-LY]) for this indication.

### *Stroke prophylaxis in nonvalvular atrial fibrillation*

Results from the dose-finding PETRO study [41] in patients with AF suggested that dabigatran

etexilate (150 mg twice-daily) had similar efficacy and safety to warfarin. Twice-daily dosing rather than once-daily dosing was selected for the Phase III AF trial based on the premise that maintained trough levels and low peak:trough ratios with twice-daily dosing are important for efficacy to reduce the stroke rate in AF, and for safety to reduce the bleeding rate. Blinded doses of dabigatran etexilate 110 and 150 mg twice-daily were chosen for the Phase III trial (RE-LY) evaluating its efficacy and safety for the prevention of stroke in patients with AF, versus warfarin. This study has completed enrolment of more than 18,000 patients and results are expected in early 2009.

### *Secondary prevention of recurrent coronary events after acute coronary syndrome*

The RandomizEd Dabigatran Etexilate dose finding study in patients with acute coronary syndromes post index Event With additional risk factors for cardiovascular complications also receiving aspirin and clopidogrel (RE-DEEM) trial is a Phase II placebo-controlled, randomized study designed to evaluate the safety of dabigatran etexilate in more than 2200 patients with recent ACS ([104]; identifier: NCT00621855). The trial will enrol patients who have symptoms suggestive of ACS, a diagnosis of ST-segment elevation or non ST-segment elevation myocardial infarction within the past 7 days and at least one additional high-risk feature. Patients are being randomized to placebo, or one of four twice-daily doses of dabigatran etexilate in addition to standard dual antiplatelet treatment. The primary end point is a composite of major and clinically relevant minor bleeding events during 6 months of treatment. Indicators of efficacy include changes in markers of coagulation activity and cardiovascular mortality/morbidity clinical end points.

## Safety & tolerability

Over 10,000 patients have completed Phase II and III trials to date, with dabigatran etexilate exhibiting a good safety profile. Given the hepatotoxicity observed with ximelagatran, particular attention has been focused on surveillance of liver function in patients receiving dabigatran etexilate. In all completed Phase III trials, patients were frequently monitored and assessed for liver enzyme elevations by an independent data safety monitoring committee. In the RE-NOVATE trial [39], patients randomized to 4 weeks' treatment of dabigatran etexilate had a lower incidence of liver enzyme aminotransferase (ALT) levels greater than three-times the upper limit of normal (3 vs 5%; $p < 0.01$) compared with those receiving enoxaparin. Similar observations were noted in the RE-MODEL and RE-MOBILIZE trials. In 360 patients with AF at high risk for stroke or systemic embolism, treatment with dabigatran etexilate for approximately 1 year demonstrated transaminase elevations in 1.5% of patients [42]. While there is no evidence of increased hepatotoxicity with dabigatran etexilate in multiple Phase II studies, or in Phase III studies of VTE prophylaxis, intensive safety surveillance is ongoing in the longer treatment duration trials. To date, the RE-LY study has not been associated with any specific safety concerns, and the planned reduction in frequency of hepatic monitoring was endorsed by the independent study safety committee. Enrolment in this study of over 18,000 patients was completed at the end of December 2007; patients randomized to dabigatran etexilate have received at least 6 months of treatment (involving more than 9000 patient-years), supporting the long-term safety profile for this compound.

In Phase III VTE prophylaxis trials [38–40], the incidence of acute coronary events was low, particularly in the 3-month follow-up period. In RE-MODEL and RE-NOVATE, adjudicated acute coronary events (confirmed unstable angina, myocardial infarction and cardiac death) during follow-up were observed in none, one and five patients in the 220 mg, 150 mg and enoxaparin groups, respectively. This suggests no rebound activation of coagulation after drug discontinuation. A favorable tolerability profile, comparable with enoxaparin, was also reported, with a low number of adverse events leading to treatment discontinuation.

## Regulatory affairs

In Europe and Canada, dabigatran etexilate (marketed as Pradaxa®) is approved for use in the prevention of VTE in patients undergoing hip- and knee-replacement surgery [103,105]. The licensed dose of dabigatran etexilate is 220 mg once-daily, with a half dose on the day of surgery [103]. For those patients with moderate renal impairment, over 75 years of age, or receiving amiodarone, a lower 150-mg daily dose is recommended, with a half dose on the day of surgery [106].

## Executive summary

***Mechanism of action***

- Dabigatran etexilate is an oral direct thrombin inhibitor that specifically and selectively inhibits both free and clot-bound thrombin to prevent thrombus formation.

***Pharmacokinetic properties***

- Dabigatran etexilate offers once-daily fixed oral dosing regardless of age, weight, gender and ethnicity, and provides a predictable and consistent anticoagulant effect with no requirements for coagulation monitoring.
- Following oral administration, the prodrug dabigatran etexilate is rapidly converted by rapid esterase-catalyzed hydrolysis to its active form, dabigatran.
- Dabigatran has a predictable and consistent pharmacokinetic profile that is not significantly affected by interactions with food.
- Dabigatran etexilate has a rapid onset of action, with peak plasma concentration achieved within 2 h of administration in healthy volunteers.
- The half-life of dabigatran etexilate is 12–14 h in healthy young or elderly subjects, independent of dose.
- Dabigatran etexilate is eliminated mainly via the kidneys (up to 80%).

***Clinical efficacy***

- In Phase III trials reported to date, dabigatran etexilate has been proven to be effective in preventing venous thromboembolic events after hip- and knee-replacement surgery.

***Safety & tolerability***

- In completed Phase III trials, dabigatran etexilate demonstrated a low incidence of major bleeding events (including those occurring at the surgical site), similar to enoxaparin.
- Rates of liver enzyme alanine aminotransferase elevations greater than three-times the upper limit of normal with dabigatran etexilate in completed Phase III trials were low and comparable with enoxaparin at any time post baseline, supporting hepatic safety.
- Dabigatran etexilate displayed a favorable cardiac safety profile; a low number of cases of adjudicated acute coronary events were reported during 3 months' follow-up in completed Phase III trials, suggesting no rebound activation of coagulation once treatment ends. A favorable tolerability profile, comparable with enoxaparin, was also reported following a low number of adverse events, leading to treatment discontinuation.

***Drug interactions***

- Dabigatran etexilate is not metabolized by cytochrome P450 and does not affect the metabolism of other drugs that utilize this system, leading to a low potential for drug interactions.

***Dosage & administration***

- For thromboprophylaxis after hip- or knee-replacement surgery, dabigatran etexilate is available as a fixed oral dose of 220 mg once-daily. A single capsule of 110 mg (half dose) is administered 1–4 h following surgery, continuing with two capsules once-daily thereafter for a total of 10 days in total knee-replacement patients and 28–35 days in total hip-replacement patients.
- A dosage of 150 mg administered as two 75-mg capsules is recommended for specific patient populations, including patients aged over 75 years and those with moderate renal impairment, which enables patient-specific dosing to obtain the best efficacy–safety balance.

## Conclusion & future perspective

In summary, the clinical need for new oral anticoagulants is well recognized. While efficacy is paramount, so too is safety, given the morbidity and mortality associated with bleeding, especially in the predominantly elderly population in whom oral anticoagulants are prescribed. In addition, close observations of potential hepatic dysfunction and cardiovascular events are essential areas of interest in assessment of the benefit:risk ratio of new anticoagulant therapies.

Dabigatran etexilate is a new novel oral anticoagulant recently approved in Europe for the prevention of VTE after elective hip- and knee-replacement surgery. Dabigatran etexilate prevents thrombus formation by specifically and selectively inhibiting thrombin, the central and essential enzyme that enables the conversion of fibrinogen into fibrin during the coagulation cascade, and therefore prevents the development of a thrombus. Dabigatran also acts on clot-bound thrombin and may be effective in the treatment of acute venous thrombi. Dabigatran etexilate has a rapid onset and offset of action and predictable anticoagulation effect, avoiding the need for coagulation monitoring. It exhibits no drug–food interactions and has a low potential for drug–drug interactions. Following clinical investigation in thousands of patients, dabigatran etexilate appears to have no significant hepatotoxicity and a bleeding risk comparable with other conventional anticoagulants.

An extensive clinical trial program (known as RE-VOLUTION) is evaluating the efficacy and

safety of dabigatran etexilate in five major therapeutic areas: primary prevention of VTE (trials complete in the EU and ongoing in North America), treatment of acute VTE (recruitment ongoing), secondary prevention of VTE (recruitment ongoing), prevention of stroke in AF (recruitment complete) and prevention of cardiac events in patients with ACS (recruitment ongoing). By the time all the currently enrolling trials have concluded, more than 40,000 patients will have been evaluated in all randomized, controlled trials of dabigatran etexilate.

In addition to dabigatran etexilate, enormous clinical development programs are ongoing with different compounds targeting other specific coagulation pathways. The majority of these compounds are targeted against factor Xa, with rivaroxaban and apixaban being agents at the most advanced stage of clinical development. Whether thrombin generation is attenuated (by factor Xa inhibitors) or thrombin activity is suppressed (by DTIs), these new oral compounds are promising alternatives to traditional anticoagulants for the prevention and treatment of VTE and for stroke prevention in AF. Since head-to-head trials comparing factor Xa inhibitors with DTIs are unlikely to be conducted in the next 5–10 years, we will see parallel development of these two therapeutic strategies. Dabigatran etexilate is the only one of these novel oral anticoagulants that is currently approved for clinical use, and is at an advanced stage in clinical development for various indications targeting the replacement of VKAs.

### Financial & competing interests disclosure

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