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Dabigatran Etexilate

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Contents

Abstract

▲ Dabigatran etexilate is an orally administered prodrug of dabigatran, which is a potent, concentration-dependent inhibitor of thrombus formation and thrombin-induced platelet aggregation.

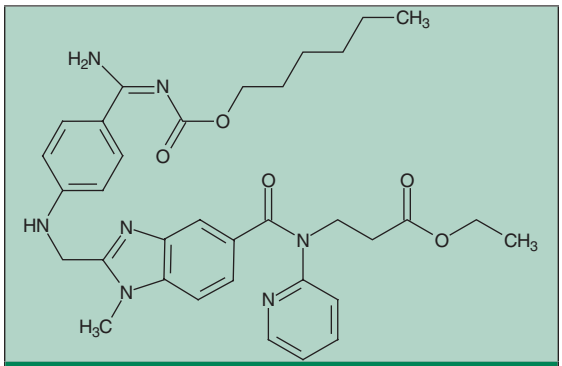
▲ Dabigatran etexilate pharmacokinetics were linear across a wide dosage range. There were no clinically important pharmacokinetic interactions with digoxin (a P-glycoprotein substrate), pantoprazole (a proton-pump inhibitor) or drugs that are substrates and/or inhibitors of hepatic cytochrome P450 enzymes.

▲ In two large, randomized, double-blind trials of the prevention of venous thromboembolism (VTE) in patients undergoing total hip or total knee replacement surgery, orally administered dabigatran etexilate 220 mg/day was noninferior to subcutaneous enoxaparin sodium 40 mg/day for the primary composite endpoint of total VTE events or all-cause mortality during the treatment period.

▲ There were no significant differences between dabigatran etexilate and enoxaparin sodium in major VTE events and VTE-related mortality. Across trials, ≤0.5% of patients experienced a symptomatic pulmonary embolus or died.

▲ Dabigatran etexilate was generally well tolerated. In patients undergoing total hip or total knee replacement surgery, there was no significant difference between dabigatran etexilate and enoxaparin sodium recipients in the incidence of major or minor bleeding.

Features and properties of dabigatran etexilate (Pradaxa®)	
Indication	
Prevention of venous thromboembolic events in adults undergoing elective total hip or total knee replacement surgery	
Mechanism of action	
Direct, selective, reversible inhibition of thrombin	
Dosage and administration	
Dosage and duration	220 mg/day for 28–35 days (total hip replacement surgery) or 10 days (total knee replacement surgery)
Route	Oral
Pharmacokinetic profile after a single 150 mg oral dose In patients undergoing total hip replacement surgery	
Mean peak plasma concentration (C_{max})	75.8 ng/mL
Median time to C_{max}	6.0 h
Mean area under the concentration-time curve from time 0 to 24 hours	962 ng • h/mL
Terminal elimination half-life in multiple dose studies in healthy men or healthy older adults (data unavailable for orthopaedic patients)	12–17 h
Most common adverse events (in clinical trials at various dosages)	
Bleeding, wound secretion, anaemia	



Dabigatran etexilate

Venous thromboembolism (VTE) is a common, life-threatening complication in hospitalized and recently discharged patients.[1] It occurs in >20% of patients after major surgery and >40% of patients undergoing orthopaedic surgery.[1] The risk of fatal pulmonary embolism (PE) after high-risk surgery is estimated to be as high as 5%.[1] Major orthopaedic surgery produces haemodynamic disturbances and provokes a coagulation cascade and fibrinolytic shutdown, leading to a prolonged, increased risk of VTE.[2] Therefore, anticoagulant drugs are considered essential in patients undergoing major orthopaedic surgery.[1] As deep vein thrombosis (DVT) event rates are particularly high in orthopaedic patients, new drugs are commonly investigated in this indication.[3]

The UK 2007 National Institute for Health and Clinical Excellence guideline for reducing the risk of VTE in surgical patients states that patients undergoing elective orthopaedic surgery should be offered mechanical prophylaxis and a low-molecular-weight heparin (LMWH) or fondaparinux sodium, and that in patients undergoing hip replacement surgery with one or more VTE risk factors, LMWH or fondaparinux sodium should be continued for 4 weeks after surgery.[1] Similarly, the guideline for the prevention of venous thrombosis from the American College of Chest Physicians recommends that patients undergoing hip or knee arthroplasty receive prophylactic treatment with an LMWH, fondaparinux sodium or an adjusted-dose vitamin K antagonist.[4]

Parenterally administered LMWH and fondaparinux sodium are replacing unfractionated heparin for this indication because they have similar efficacy, a better safety profile and are able to be administered once daily without regular blood coagulation monitoring.[5] Vitamin K antagonists, such as warfarin, are used less often because of frequent pharmacological interactions with drugs and foods, and because they require routine coagulation monitoring.[5] Considering these limitations, an oral anticoagulant drug that does not require routine coagulation monitoring would be useful because it would greatly simplify treatment over the extended VTE risk period associated with orthopaedic surgery.[5]

Direct thrombin inhibitors are a new class of anticoagulant that reversibly inhibit thrombin, interfering with the conversion of fibrinogen to fibrin.[5] In contrast, heparin and other indirect thrombin inhibitors block fibrin formation by catalyzing antithrombin and other naturally occurring thrombin inhibitors.[5] Dabigatran is a direct thrombin inhibitor that is not absorbed when administered orally.[2] Dabigatran etexilate (Pradaxa®)[1] was developed specifically as a prodrug of dabigatran for oral administration.[2] In the EU, it is approved for use in the primary prevention of VTE in adult patients who have undergone elective total hip or total knee replacement surgery.[6] This profile focuses on the pharmacological properties and clinical use of dabigatran etexilate within this indication.

1. Pharmacodynamic Profile

This section reviews the pharmacodynamic properties of dabigatran etexilate based on data from *in vitro* and *ex vivo* studies,[7-10] studies in healthy men,[11] and in older, healthy men and women,[12] supplemented by data from a review.[13] In the study in healthy men, subjects received either single doses (n = 40) or multiple doses (n = 40) of dabigatran etexilate.[11] The study in older adults (men and women aged ≥65 years [n = 36]) randomized sub-

1 The use of trade names is for identification purposes only and does not imply endorsement.

jects to 7 days of treatment with twice-daily doses of dabigatran etexilate 150 mg or dabigatran etexilate 150 mg plus a proton-pump inhibitor, pantoprazole 40 mg twice daily, commenced 2 days prior to dabigatran etexilate treatment.[12] All of the studies are fully published, apart from two *in vitro* studies of inhibition of thrombus formation[8] or platelet aggregation,[9] which are available as an abstract[8] or abstract with poster.[9]

- Dabigatran etexilate is a prodrug of dabigatran, a direct inhibitor of thrombin, the most potent physiological agonist of platelet aggregation.[13] Dabigatran has high affinity to thrombin and inactivates it by binding to it.[13] Binding is selective, rapid and reversible, which means that its anticoagulant effects should be more predictable than irreversible thrombin-binding drugs such as hirudin.[13]

- In *in vitro* and *ex vivo* studies, the dabigatran binding affinity for thrombin was 4.5 nmol/L and it was also highly selective, with a thrombin selectivity 700- to 10 000-fold higher than that of other key factors in the coagulation cascade.[7] Dabigatran did not inhibit arachidonic acid-, collagen- or adenosine diphosphate-induced platelet aggregation, but showed a potent inhibitory effect on thrombin-induced platelet aggregation; a concentration of 10 nmol/L achieved 50% maximal inhibition (IC_{50}).[7] The inhibitory effect of dabigatran on tissue factor-induced thrombin generation in human platelet-poor plasma was concentration dependent.[7]

- In platelet-rich plasma from healthy adults, dabigatran had a more potent inhibitory effect on tissue factor-induced platelet aggregation than two factor Xa inhibitors, rivaroxaban and apixaban (IC_{50} was 35 vs 312 and 817 nmol/L).[9] This suggests that dabigatran may be effective in preventing both venous thrombosis and arterial thrombosis, which is more dependent on platelet aggregation.[9] Furthermore, dabigatran treatment may be clinically useful when a thrombus has formed, and in catheterization procedures where surface-bound thrombin is activated because *in vitro*, it had a similar inhibitory effect on clot-bound and fluid-phase thrombin.[8]

- In healthy men, there was a rapid onset of the thrombin inhibitory effect of dabigatran etexilate.[11] Single, orally administered doses (10–400 mg) led to rapid, dose-dependent increases in mean activated partial thromboplastin time (aPTT), international normalized ratio, thrombin time and ecarin clotting time (ECT), with the maximum anticoagulant effect occurring at the same time as the maximum plasma dabigatran concentration (C_{max}).[11]

- Coagulation parameters closely followed drug concentrations when healthy men were given dabigatran etexilate 50–400 mg three times daily.[11] Maximum effects were achieved within 2 hours of administration of dabigatran etexilate and, for all but the lowest dosage, anticoagulant effects were still detectable at the end of the 8-hour dose administration interval.[11] Twelve hours after administration of dabigatran etexilate, blood coagulation prolongation was reduced to ≈50% of its maximum.[11]

- Similar pharmacodynamic effects were observed in healthy older subjects.[12] There were measurable anticoagulant effects according to aPTT and ECT values predose and throughout the day on days 4 and 7 of treatment with dabigatran etexilate, with 1.98- and 1.95-fold increases in pre-dose ECT values over baseline values.[12] Coadministration of pantoprazole decreased aPTT and ECT values, but not in all subjects.[12]

- The pharmacokinetic-pharmacodynamic relationship was further examined in a dose-ranging study[14] (section 3) by modelling the relationship between pharmacokinetic and coagulation parameters, specifically aPTT and ECT.[10] For aPTT, the concentration required to achieve 50% maximum effect was 94.7 ng/mL.[10] Dabigatran plasma concentrations were directly correlated to both aPTT and ECT prolongation, with the maximum response occurring immediately after surgery and then declining, indicating that dabigatran early in treatment had proportionally greater pharmacodynamic effects than later in treatment.[10]

2. Pharmacokinetic Profile

This section provides an overview of pharmacokinetic data for dabigatran etexilate in healthy and clinical populations, with a focus on data from a noncomparative, single-dose study of dabigatran

etexilate in patients undergoing total hip replacement surgery (n = 59).[15] Patients (median age 68 years) received dabigatran etexilate 150 mg/day.[15] This study used the marketed formulation, consisting of a multiparticulate pellet capsule containing tartaric acid to produce an acidic microenvironment conducive to drug dissolution and absorption.[13,15] Other data are from phase I studies in healthy men,[15] healthy older adults,[12] a study comparing healthy adults with patients with hepatic impairment,[16] a population pharmacokinetic analysis,[17] a recent comprehensive review[13] and the manufacturer's prescribing information.[6] All data are fully published, apart from the study in patients with hepatic impairment, which is available as an abstract.[16]

- Dabigatran is not orally available because it is a highly polar, zwitterionic molecule, while the prodrug dabigatran etexilate is absorbed after oral administration.[13]

- In patients undergoing total hip replacement, dabigatran etexilate administered as a single 150 mg dose 1–3 hours after surgery was rapidly absorbed by the majority of patients, with a mean C_{max} of 75.8 ng/mL reached within 1–24 hours.[15] The median time to dabigatran C_{max} (t_{max}) was 6.0 hours, with absorption delayed in 22% of patients (t_{max} >10 hours).[15]

- Median t_{max} was 2 hours in healthy men who received a single oral dose of dabigatran etexilate 150 mg,[15] and 2.5–3.0 hours in healthy elderly men and women who received oral dabigatran etexilate 150 mg twice daily for 4 days.[12]

- In patients undergoing total hip replacement surgery, after a single 150 mg dose of dabigatran etexilate, the mean area under the plasma concentration-time curve (AUC) during a 24-hour period (AUC_{24}) was 962 ng • h/mL.[15] There was considerable inter-individual variability, with C_{max} and AUC_{24} coefficients of variation of >65%.[15]

- Dabigatran etexilate was detectable in plasma for ≈2 hours after administration, with an AUC <0.4% that of dabigatran,[13,16] indicating that the prodrug is rapidly and almost fully converted to dabigatran. In the population pharmacokinetic analysis, during the first 24 hours after total hip surgery, the rate of absorption of dabigatran etexilate was reduced and inter-individual variability increased compared with subsequent days, presumably because of changes in gastric pH and gastrointestinal motility caused by surgery and coadministered drugs, such as opioids.[17] Although absorption was slowed, there was no negative impact on total exposure to dabigatran.[13]

- When dabigatran etexilate was administered in dosages of 10–1200 mg/day, dabigatran C_{max} and AUC increased in proportion to dose, indicating that it has predictable, linear pharmacokinetics over a wide dose range.[13]

- In single-dose, crossover trials in healthy men, administration of dabigatran etexilate with food slowed the rate of absorption, with a 2-hour increase in t_{max}.[13] The AUC and C_{max} were essentially unchanged, indicating that exposure to dabigatran was not negatively affected by administering dabigatran etexilate with food.[13,18]

- In healthy older adults (aged ≥65 years) who received dabigatran etexilate 150 mg twice daily, plasma dabigatran concentrations reached steady state in 2–3 days.[12] There was low intra-individual variability in the pharmacokinetics of dabigatran etexilate.[12] However, in comparison with historical data for healthy young adults, bioavailability increased 1.7- to 2-fold in elderly subjects, probably attributable to lower renal clearance.[12] When treating patients aged >75 years, a dabigatran etexilate dosage of 150 mg/day is recommended.[6]

- Dabigatran exposure is ≈40% higher in female than male patients, but dosage adjustments are not required for female patients.[6] Similarly, available data suggest that no dosage adjustment is necessary in patients with bodyweight <50 or >110 kg, although close surveillance is recommended in patients outside these weight limits.[6]

- Microsomal carboxylesterases catalyze the conversion of dabigatran etexilate to an intermediate, BIBR 1087, and then to dabigatran, ≈20% of which is conjugated to fully pharmacologically active glucuronide conjugates.[13] Dabigatran is only ≈35% bound to plasma proteins and its volume of distribu-

tion is 60–70 L, which exceeds total body water, suggesting a moderate tissue distribution of the drug.[6]

- The bioavailability of dabigatran after administration of dabigatran etexilate is reported to be 7%.[13] After oral administration of a single dose of radiolabelled dabigatran etexilate, 7.2% of the radioactivity was recovered in the urine, in comparison with 85% after intravenous infusion of radioactive dabigatran.[13] Dabigatran is chiefly eliminated via the kidneys. The constituents in urine were mainly unchanged dabigatran and small quantities of dabigatran glucuronides.[13]

- The half-life ($t_{1/2}$) is not available for orthopaedic patients, but the terminal elimination half-life ($t_{1/2}\gamma$) was 14–17 hours in healthy men who received dabigatran etexilate 50–400 mg three times daily,[11] while the steady-state $t_{1/2}\gamma$ was 12–14 hours in healthy elderly adults after receiving dabigatran etexilate 150 mg twice daily for 7 days.[12]

- Bioconversion of the prodrug to dabigatran was slightly slower in patients with hepatic impairment, while dabigatran exposure, glucuronidation and protein binding were relatively unaffected.[6,13,16] Compared with those without renal impairment, the exposure to dabigatran was 2.7-fold higher in patients with moderate renal impairment (creatinine clearance [CL_{CR}] 30–50 mL/min [1.8–3.0 L/h]) and 6-fold greater (with a doubling of $t_{1/2}$) in patients with severe renal impairment (CL_{CR} 10–30 mL/min [0.60–1.8 L/h]).[6] The use of dabigatran etexilate is contraindicated in patients with severe renal impairment (section 5).[6]

- Dabigatran is not an inducer or inhibitor of hepatic cytochrome P450 (CYP) enzymes, nor is it metabolized to any significant extent by CYP enzymes; therefore, interactions between dabigatran etexilate and drugs metabolized by these enzymes are unlikely to occur.[13] In clinical studies, there were no clinically relevant pharmacokinetic interactions when dabigatran etexilate was coadministered with pantoprazole (a proton pump inhibitor) or substrates and/or inhibitors of key metabolic enzymes, including atorvastatin (a CYP3A4 substrate and P-glycoprotein substrate/inhibitor), diclofenac (a CYP2C9 and uridine glucuronosyltransferase [UGT] 2B7 substrate and UGT1A substrate/inhibitor) or digoxin (a P-glycoprotein substrate).[13]

3. Therapeutic Efficacy

The efficacy of orally administered dabigatran etexilate in preventing VTE was evaluated in two phase III, randomized, double-blind, double-dummy international trials that compared it with the LMWH enoxaparin sodium, which is administered by subcutaneous injection.[19,20] The patients included were undergoing total hip[19] or total knee[20] replacement surgery.

A third phase III trial was conducted in the US, which compared the efficacy of dabigatran etexilate with that of enoxaparin sodium in patients undergoing total knee replacement surgery.[21] In this trial, dabigatran etexilate failed to meet the noninferiority criterion.[21] However, the comparator drug enoxaparin sodium was used at higher dosages than those that are approved in the EU (30 mg twice daily compared with 40 mg once daily), the administration of the first dose of dabigatran etexilate was delayed (6–12 hours after surgery vs 1–4 hours after surgery in the EU) and randomization was performed after surgery and included only patients who showed adequate haemostasis.[22] These drug administration, randomization and sampling differences prevent meaningful comparison with the pivotal trials conducted in the EU[19,20] and this trial is not considered further here. In a phase II, randomized, dose-ranging study in patients undergoing hip or knee surgery (n = 1949), dabigatran etexilate showed promise in reducing VTE events at dosages of 50–225 mg twice daily, with dose-dependent effects on DVT events.[23] As this trial was preliminary to the phase III trials, it is not discussed further here.

The phase III trials conducted in the EU recruited 3613 [19] and 2183[20] patients aged ≥18 years who were scheduled for elective unilateral total hip[19] or total knee[20] replacement surgery. The exclusion criteria were identical across the two trials and included any bleeding diathesis, acute intracranial disease or stroke, trauma, major surgery, uncontrolled

hypertension or myocardial infarction in the past 3 months.[19,20] Patients were also excluded if they had urogenital bleeding, gastrointestinal bleeding or ulcer in the past 6 months, hepatic enzymes raised >2-fold the upper limit of normal (ULN), severe liver disease, CL_{CR} <30 mL/min (<1.8 L/h), use of NSAIDs, or complicated spinal or epidural anaesthesia.[19,20]

The procedures and endpoints were almost identical across the two trials.[19,20] Patients were randomized on the day before surgery to one of three treatment groups; oral dabigatran etexilate 150 or 220 mg plus subcutaneous placebo injection once daily, or subcutaneous enoxaparin sodium 40 mg plus placebo pills once daily.[19,20] Generally, patients received the first subcutaneous injection the evening before surgery, although in some centres it was delayed until after surgery.[19,20] The initial dose of dabigatran etexilate was half the assigned dose administered 1–4 hours following surgery, after which full doses were administered.[19,20] In patients with inadequate haemostasis, the initial dose of dabigatran etexilate was a full dose given the day after surgery,[19,20] repeated in hip replacement patients within 12 hours.[19] Treatment was continued for 28–35 days in hip replacement patients[19] and for 6–10 days in knee replacement patients,[20] after which mandatory bilateral venography was performed (within 24 hours of the last dose).[19,20] Elastic compression stockings and concomitant low-dose aspirin and selective cyclo-oxygenase-2 inhibitors were permitted throughout.[19,20]

Patients were followed-up for 3 months after surgery, while the treatment period was from the initial dose to 3 days after the last dose of any study drug.[19,20] The primary efficacy outcome was a composite endpoint comprising total VTE events (defined as symptomatic or venographic DVT or symptomatic PE) and all-cause mortality during treatment.[19,20] Secondary efficacy outcomes included a composite of major VTE events (defined as proximal DVT or PE) or VTE-related mortality; proximal or distal asymptomatic DVT; symptomatic DVT; symptomatic PE; and all-cause mortality during the treatment period.[19,20]

Both trials were designed to assess noninferiority between treatments for the primary endpoint.[19,20] Noninferiority was established if the upper limit of the 95% confidence interval (CI) for the difference between dabigatran etexilate and enoxaparin sodium was <7.7% in the total hip replacement trial[19] and <9.2% in the total knee replacement trial.[20] In the knee replacement trial, if noninferiority was shown, then superiority of one treatment over the other was to be tested.[20] The populations for the primary efficacy analyses included all randomized patients who received at least one subcutaneous injection or oral dose of study medicine, had evaluable, adjudicated VTE event data based on venography or a symptomatic event or who died during treatment.[19,20]

In the total hip replacement trial, of 3613 enrolled patients, 3493 (96.7%) were randomized to dabigatran etexilate 150 mg/day (n = 1174) or 220 mg/day (n = 1157) or enoxaparin sodium 40 mg/day (n = 1162). Of these, 2651 (76%) were available for analysis of the primary endpoint.[19] Of those randomized, 784 patients (22.4%) did not have venography or it was judged to be inadequate. In the total knee replacement trial, of 2183 enrolled patients, 2101 (96.2%) were randomized to dabigatran etexilate 150 mg/day (n = 708) or 220 mg/day (n = 694), or enoxaparin sodium 40 mg/day (n = 699). Of these, 1541 (73%) were available for analysis of the primary endpoint.[20] Of those randomized, 515 patients (24.5%) did not have venography or it was judged to be inadequate. The mean ages in the total hip replacement trial were 63, 65 and 64 years in dabigatran etexilate 150 mg/day, dabigatran etexilate 220 mg/day and enoxaparin sodium 40 mg/day recipients, respectively;[19] corresponding mean ages in the total knee replacement trial were 68, 67 and 68 years.[20] In the total hip replacement trial, ≈56% of patients were female[19] and ≈66% were female in the total knee replacement trial.[20]

- Dabigatran etexilate was no less effective than enoxaparin sodium, according to the primary endpoint (figure 1).[19,20] In total hip replacement patients, the incidence rates of the composite of total

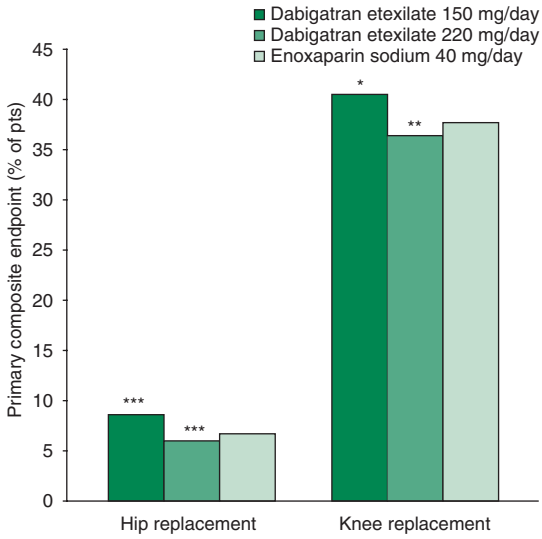


Fig. 1. Efficacy of dabigatran etexilate in patients (pts) undergoing total hip[19] or total knee[20] replacement surgery. Incidence of total venous thromboembolism (VTE) events or all-cause mortality (primary composite endpoint) in phase III, randomized, double-blind trials is shown for pts who received orally administered dabigatran etexilate 150 (n = 874) or 220 (n = 880) mg/day or subcutaneous enoxaparin sodium 40 mg/day (n = 897) for 28–35 days (total hip replacement)[19] and dabigatran etexilate 150 (n = 526) or 220 (n = 503) mg/day or enoxaparin sodium 40 mg/day (n = 512) for 6–10 days (total knee replacement).[20] Total VTE events include symptomatic pulmonary embolism and symptomatic or venographic deep vein thrombosis during the treatment period (pts could have events in more than one category). * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ for noninferiority vs enoxaparin sodium.

VTE and all-cause mortality were 8.6%, 6.0% and 6.7% in dabigatran etexilate 150 mg/day, 220 mg/day and enoxaparin sodium 40 mg/day groups, respectively.[19] In total knee replacement patients, the corresponding rates were 40.5%, 36.4% and 37.7%.[20]

- The upper limit of the 95% CI for the difference in rates of the primary composite endpoint between groups was less than the prespecified noninferiority margin in both trials for both dosage groups.[19,20] In the total hip replacement trial, differences versus enoxaparin sodium 40 mg/day were 1.9% (95% CI −0.6, 4.4) for dabigatran etexilate 150 mg/day and −0.7% (95% CI −2.9, 1.6) for dabigatran etexilate 220 mg/day;[19] corresponding differences in the total knee replacement trial were 2.8% (95% CI −3.1, 8.7) and −1.3% (95% CI −7.3, 4.6).[20] Subsequent superiority testing in the total knee replacement trial revealed that neither dosage of dabigatran etexilate was superior to enoxaparin sodium.[20]
- There were no significant between-group differences in the incidence of the secondary composite endpoint of major VTE events and VTE-related mortality (figures 2a and 2b). Distal asymptomatic DVTs accounted for the vast majority of VTE events in patients undergoing total knee replacement, with ≈33% of patients affected in each treatment group, compared with <5% for other endpoints (figure 2b).[20] This high DVT rate accounts for the large discrepancy in total VTE event rates between total hip and total knee replacement patients. Across treatment groups, few patients (≤0.5%) undergoing total hip or total knee replacement surgery experienced a symptomatic PE or died.[19,20]

4. Tolerability

This section summarizes data on the tolerability of dabigatran etexilate from the randomized, double-blind trials described in section 3, the dose-escalating study[14] and the manufacturer's prescribing information, which provides data for 10 084 patients included in VTE prevention trials.[6] The total hip[19] and total knee[20] replacement trials compared the tolerability of dabigatran etexilate with enoxaparin sodium, focusing on the occurrence of bleeding[19,20] and other adverse events[19] during the treatment period. The primary tolerability endpoint was the occurrence of bleeding events during treatment.[19,20] Haematological and blood chemistry tests were also performed before treatment, at discharge from hospital, on the last day that the study drug was administered,[19,20] at a 4- to 6-week[20] or 2-month[19] follow-up and at a 3-month follow-up.[19,20]

- In the total hip[19] and total knee[20] replacement trials, there were no significant differences in dabigatran etexilate 150 or 220 mg/day and enoxaparin sodium 40 mg/day recipients in the incidence of major, non-major (but clinically relevant) or minor bleeding events (primary endpoint) [figure 3].[19,20] In both trials, across groups, major bleeding events occurred in ≤2% of patients.[19,20]

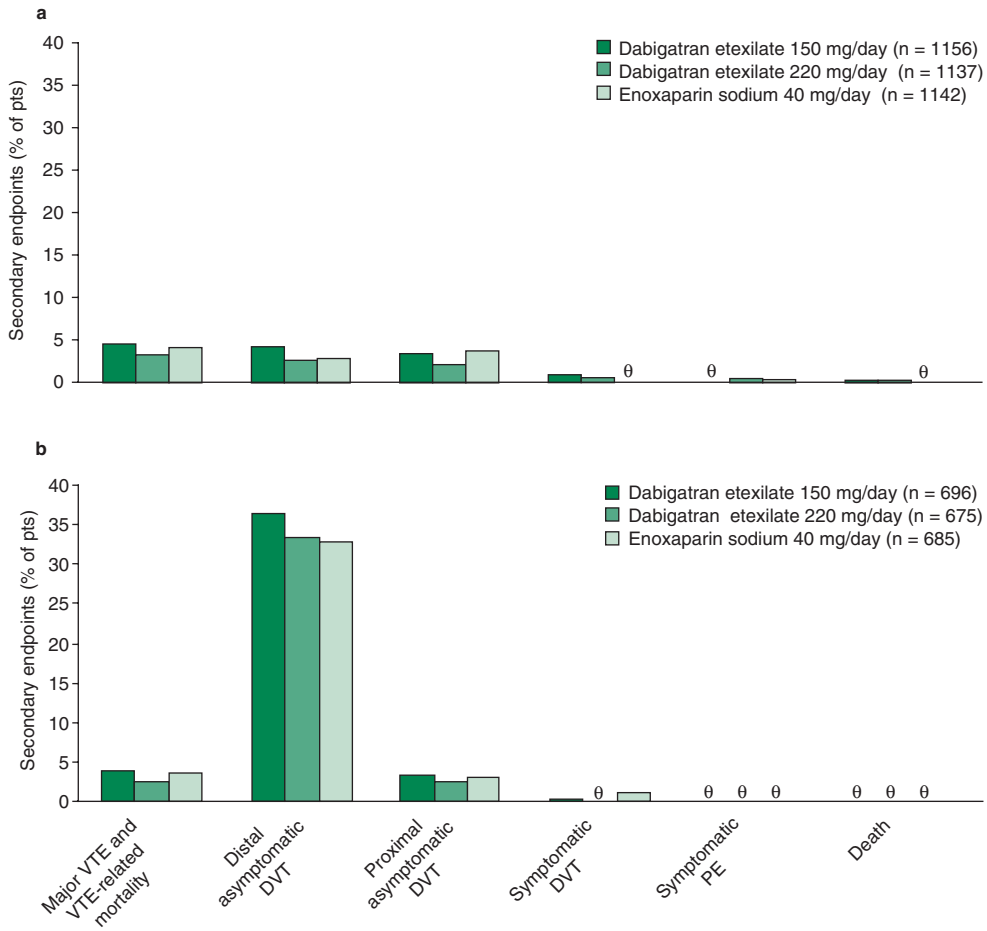


Fig. 2. Secondary efficacy endpoints in randomized, double-blind trials in patients (pts) undergoing (**a**) total hip[19] or (**b**) total knee[20] replacement surgery. Pts were treated with orally administered dabigatran etexilate 150 or 220 mg/day or subcutaneous enoxaparin sodium 40 mg/day for 28–35 days (total hip replacement)[19] or for 6–10 days (total knee replacement).[20] Percentage of pts experiencing venous thromboembolism (VTE) events or death during the treatment period (pt numbers varied across endpoints because of missing venography data). There were no significant differences in the incidence of the composite secondary endpoint of major VTE events and VTE-related mortality between dabigatran etexilate and enoxaparin sodium treatment groups (statistical analysis not provided for other variables). **DVT** = deep vein thrombosis; **major VTE** = proximal DVT plus PE; **PE** = pulmonary embolus; θ = event rate ≤0.1%.

- In the total hip replacement trial, 8%, 6% and 6% of patients experienced adverse events leading to treatment discontinuation in the dabigatran etexilate 150 mg/day, dabigatran etexilate 220 mg/day and enoxaparin sodium 40 mg/day groups, respectively;[19] corresponding rates were 3.7%, 3.7% and 4.6% in patients undergoing total knee replacement surgery (statistical analysis not reported).[20]

- Following total hip replacement surgery, transient elevations in serum ALT liver enzymes >3-fold the ULN were observed in 3%, 3% and 5% of dabigatran etexilate 150 mg/day, dabigatran etexilate 220 mg/day and enoxaparin sodium 40 mg/day recipients, respectively ($p < 0.01$ for both doses vs enoxaparin sodium);[19] corresponding rates in patients undergoing total knee replacement surgery were 3.7%, 2.8% and 4.0%.[20]

• Dabigatran etexilate was generally well tolerated when administered in VTE prevention trials.[6] In pooled analyses of patients receiving at least one dose of dabigatran etexilate 220 mg/day or enoxaparin sodium 40 mg/day, the most common adverse events were any bleeding events (13.8% and 13.4%), wound secretion (4.9% and 3.0%) and anaemia (4.4% and 4.5%).[6] In a dose-escalating study, there was a strong dose-response relationship between an increasing dose of dabigatran etexilate and minor bleeding events.[14]

• In the total hip replacement trial, 8%, 8% and 7% of dabigatran etexilate 150 mg/day, dabigtran etexilate 220 mg/day and enoxaparin sodium 40 mg/day recipients experienced serious adverse events;[19] in the corresponding treatment groups in the total knee replacement trial, 3.7%, 3.7% and 4.6% had adverse events leading to treatment discontinuation.[20]

• There was no obvious rebound increase in coagulation after dabigatran etexilate treatment ceased. In the total hip replacement trial, during the 2-month follow-up period, one patient in each treatment group developed symptomatic VTE.[19] Acute coronary events were reported in 0, 0 and 3 patients in the dabigatran etexilate 150 mg/day, 220 mg/day and enoxaparin sodium 40 mg/day groups, respectively.[19] For the corresponding groups in the total knee replacement trial, 2, 3 and 0 patients had symptomatic VTE events and 1, 0 and 2 had coronary-related events during the follow-up period.[20]

5. Dosage and Administration

The recommended dosage of dabigatran etexilate for the prevention of VTE in adult patients undergoing elective total hip or total knee replacement surgery is 220 mg administered orally once daily, initiated with a single 110 mg capsule within 1–4 hours of surgery and continued with full daily dosages thereafter.[6] If haemostasis is not secured at surgery, treatment should be delayed and initiated later at full dosages.[6] Treatment should be continued for 28–35 days in patients undergoing total hip replacement surgery and for 10 days in patients undergoing total knee replacement surgery.[6] These recommendations are based on the observed higher risk of VTE with total hip than total knee replacement surgery and the efficacy of extended thromboprophylaxis in total hip replacement.[24] Close clinical surveillance is recommended in patients whose clinical situation places them at increased risk of haemorrhage.[6] Dabigatran etexilate is contraindicated in patients with severe renal impairment

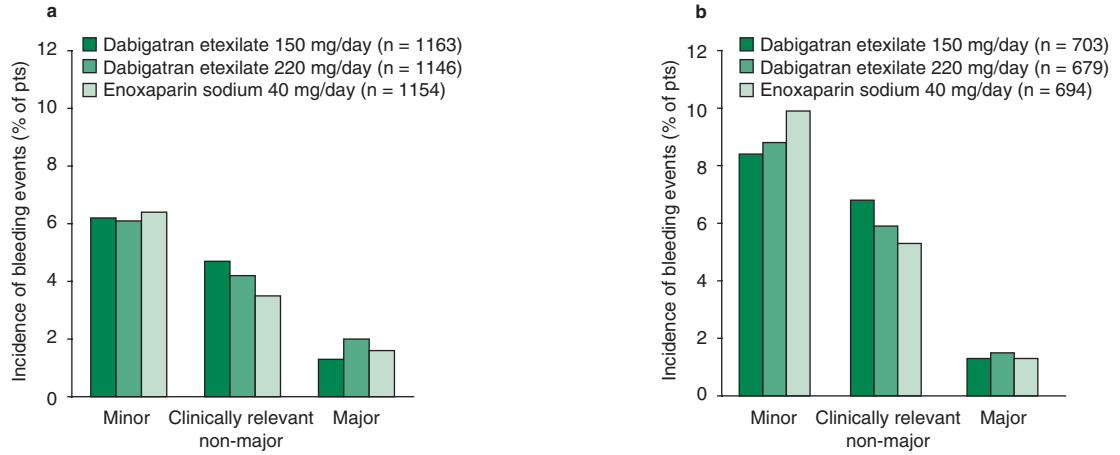


Fig. 3. Bleeding events in patients (pts) undergoing (**a**) total hip[19] or (**b**) total knee[20] replacement surgery. Incidence of minor, clinically relevant non-major and major bleeding episodes occurring during the treatment period in randomized, double-blind trials comparing orally administered dabigatran etexilate 150 or 220 mg/day with subcutaneous enoxaparin sodium 40 mg/day in pts undergoing total hip[19] or total knee[20] replacement surgery. Total hip replacement pts were treated for 28–35 days[19] and total knee replacement pts for 6–10 days.[20] There were no significant differences for all comparisons between dabigatran etexilate and enoxaparin sodium treatment groups.[19,20]

(CL_{CR} <30 mL/min [<1.8 L/h]) [see section 2] and it is not recommended in patients with liver enzymes >2-fold higher than the ULN, as these patients were excluded from the clinical trials.[6] Caution is recommended in patients with moderate renal impairment (CL_{CR} 30–50 mL/min [1.8–3.0 L/h]) and in patients aged >75 years;[6] in these patients, the recommended dosage of dabigatran etexilate is 150 mg/day (see section 2).[6]

Patients switched from dabigatran etexilate to a parenteral anticoagulant should wait for 24 hours after the last dose before commencing the parenteral anticoagulant.[6] However, there are no data to guide decisions about when to initiate treatment when switching from parenteral anticoagulants to dabigatran etexilate.[6]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Dabigatran Etexilate: Current Status

Dabigatran etexilate is approved in the EU for the prevention of VTE in adults undergoing elective total hip or total knee replacement surgery.[6] In two randomized, double-blind, international trials in total hip or knee replacement surgery patients, oral dabigatran etexilate was noninferior to subcutaneous enoxaparin sodium in preventing total VTE events or all-cause mortality (primary endpoint) and there were no significant differences on the composite secondary endpoint. The most common adverse events were bleeding events, but rates of major, clinically relevant non-major or minor bleeding events were not significantly different between dabigatran etexilate and enoxaparin sodium treatment groups.

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