Dabigatran etexilate: a new thrombin inhibitor

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ABSTRACT

- Dabigatran etexilate was recently approved by the Therapeutic Goods Administration for thromboprophylactic use in adults undergoing elective total hip or knee replacement.
- Dabigatran etexilate is the prodrug of the active moiety dabigatran, an orally active agent that could replace enoxaparin in some clinical indications.
- Dabigatran is a direct thrombin inhibitor; it has stable, predictable pharmacokinetics and does not require routine monitoring.
- Pooled efficacy data from large-scale phase III clinical trials of dabigatran use in orthopaedic thromboprophylaxis have shown non-inferiority to enoxaparin, with total venous thromboembolism results of 3.8% for dabigatran etexilate 150 mg and 3.0% for dabigatran etexilate 220 mg, compared with 3.3% for enoxaparin.
- Pooled safety results for dabigatran are similar to those for enoxaparin, with major bleeding rates of 1.1% for dabigatran etexilate 150 mg and 1.4% for dabigatran etexilate 220 mg, compared with 1.4% for enoxaparin.
- Dabigatran failed to demonstrate non-inferiority compared with enoxaparin 30 mg twice daily for orthopaedic thromboprophylaxis.
- Issues relating to the use of dabigatran include its lack of antidote, limited application in renal disease, and interaction with drugs such as amiodarone and verapamil.
- Several trials investigating the use of dabigatran for other indications, such as stroke prevention in atrial fibrillation and acute coronary syndromes, are underway.
- Given its safety profile, efficacy, oral bioavailability and stable pharmacokinetic properties, dabigatran may be a viable alternative to enoxaparin for thromboprophylaxis in orthopaedic surgery.

MJA 2010; 192: 407–412

Patients undergoing major orthopaedic surgery such as lower limb joint arthroplasty have traditionally been regarded as being at high risk of venous thromboembolic disease. Indeed, of patients who undergo major orthopaedic surgery without appropriate thromboprophylaxis, up to 60% will develop venous thromboembolism (VTE).[1] For the most part, parenteral heparins, including the low-molecular-weight enoxaparin, have been used for thromboprophylaxis in these situations, occasionally substituted by warfarin if deemed more appropriate.[2] Although heparins and warfarin both have a documented history of utility as anticoagulants in several indications, they are also associated with several clinical shortcomings. Heparins, whose use is associated with haemorrhage, require parenteral administration, which limits their application in an outpatient setting. Similarly, the use of warfarin is associated with myriad difficulties, including its delayed onset of action, its need for complex individualised dosing, its numerous interactions with food and medications, and the inherent risk of bleeding it entails.[3]

In light of the limitations of current anticoagulation therapies, a significant amount of research in recent years has investigated potential alternatives to warfarin and heparins. Several novel agents have undergone large-scale clinical trials to evaluate their safety and efficacy for thromboprophylaxis in the orthopaedic setting. These agents have the desirable properties of being orally active, demonstrating predictable dose–response pharmacokinetics, having a sound safety profile and yielding few drug–drug interactions. The most recent research has focused on agents that operate via the targeted inhibition of specific factors within the coagulation cascade, in particular, the inhibition of proteases such as thrombin or activated factor X (Xa). One agent that has recently emerged is rivaroxaban, an oral direct factor Xa inhibitor that has demonstrated superiority over enoxaparin in large clinical trials[4] and is now approved for use in Australia. Other oral factor Xa inhibitors, such as apixaban, are currently undergoing phase III clinical trials.[5]

The thrombin inhibitors

Targeted inhibition of thrombin within the coagulation cascade has been another focus of research in the investigation of novel anticoagulants. One of the early orally active thrombin inhibitors, ximelagatran, demonstrated promising safety and efficacy compared with enoxaparin for thromboprophylaxis in major orthopaedic surgery but was subsequently abandoned after it was found to cause liver dysfunction in some patients.[6] More recently, clinical trials have been performed on a new oral thrombin inhibitor, dabigatran etexilate. Dabigatran etexilate has undergone large-scale international trials for orthopaedic thromboprophylaxis, demonstrating sound safety and efficacy, and is now approved for use in the United Kingdom, Europe and Canada. In November 2008, dabigatran etexilate was approved by the Therapeutic Goods Administration (TGA) for use in Australia for prevention of VTE in adults after major limb orthopaedic surgery (elective total hip or knee replacement). Here, I discuss the evidence available to support the use of dabigatran etexilate and highlight some of the potential advantages and disadvantages associated with use of this agent. Levels of evidence are provided according to the taxonomy of the National Health and Medical Research Council (NHMRC) (Box 1).[7]

Properties of dabigatran etexilate

Dabigatran etexilate is a low-molecular-weight prodrug that itself exhibits no pharmacological activity. However, after oral administration, dabigatran etexilate is rapidly absorbed and converted to its active moiety, dabigatran, by catalysed hydrolysis in plasma and in the liver.[8] Dabigatran is a potent, competitive and reversible direct inhibitor of the thrombin enzyme, with an oral bioavailability of 6.5%. Dabigatran has a terminal half-life of 14–17 hours, thereby facilitating once-daily dosing. The agent is eliminated primarily by renal excretion (about 80%), with the remainder conjugated and excreted via the bile. The onset of action of

1 Classification of levels of evidence endorsed by the National Health and Medical Research Council (NHMRC)[7]

E1: evidence obtained from a systematic review of all relevant randomised controlled trials.

E2: evidence obtained from at least one properly designed randomised controlled trial.

E3: evidence obtained from well designed pseudo-randomised controlled trials, comparative controlled studies, cohort studies or controlled interrupted time series studies (including historical control groups).

E4: evidence obtained from case series, opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. ◆

dabigatran is within 1 hour of dosing and the anticoagulant effects parallel plasma concentration.[9] Dabigatran inhibits thrombus formation by preventing the conversion of fibrinogen into fibrin in the coagulation cascade (see Box 2). Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.[8,9] As dabigatran is orally active, has stable, predictable pharmacokinetics and can be administered without laboratory monitoring or dose titration, it affords several potential advantages in comparison with the current generation of anticoagulation therapies (Box 3).

Clinical studies of dabigatran

Dabigatran has undergone several large-scale clinical trials to evaluate its safety and efficacy, and the results of these trials eventuated in the drug being approved for use in Australia. All the phase III studies of dabigatran were prospective, double-blind, double-dummy, randomised, multicentre trials in adults aged at least 18 years who underwent primary elective total lower limb joint replacement.

Use of dabigatran for orthopaedic thromboprophylaxis

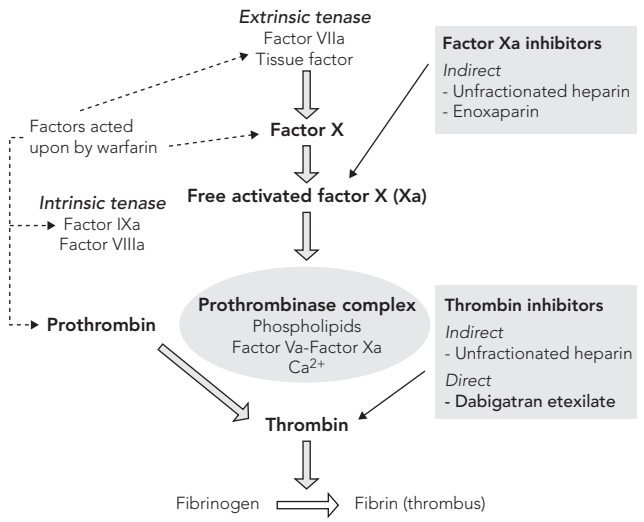
Three large phase III clinical trials have evaluated the use of dabigatran in patients undergoing total hip or knee arthroplasty. These were powered for non-inferiority — that is, they aimed to establish whether dabigatran was no worse than enoxaparin for thromboprophylactic use in orthopaedic surgery. In two of the three trials, the primary efficacy end point was met. The primary end points for the efficacy analysis were total VTE (the composite of deep vein thrombosis [DVT], non-fatal pulmonary embolism and all-cause mortality) and the composite of major VTE (venographic or symptomatic proximal DVT and pulmonary embolism) and VTE-related mortality. The main safety end point was the frequency of major bleeding events occurring between the first dose of study medication and 3 days after the last dose. Box 4 provides a synopsis of the efficacy and safety results from these three trials.

The RE-NOVATE study randomly assigned 3494 patients undergoing total hip replacement to receive 28–35 days' treatment with dabigatran etexilate 150 mg daily, dabigatran etexilate 220 mg daily or subcutaneous enoxaparin 40 mg daily. The dosing regimen for RE-NOVATE was such that dabigatran therapy was started with a half dose 1–4 hours after surgery — 75 mg or 110 mg for patients assigned to receive 150 mg and 220 mg, respectively — and enoxaparin therapy was started the day before surgery. For this trial, a third of the lower boundary of the 95% confidence interval, 7.7%, was chosen as a conservative estimate of the non-inferiority margin. In RE-NOVATE, both doses of dabigatran were found to be non-inferior to enoxaparin (E2).[12] The primary efficacy outcome occurred in 6.7% of individuals ($n = 60$) in the enoxaparin group, compared with 6.0% of patients in the dabigatran 220 mg group (absolute difference −0.7%; 95% CI, −2.9% to 1.6%) and 8.6% of patients in the 150 mg group (absolute difference 1.9%; 95% CI, −0.6 to 4.4%). There was also no statistically significant difference in major bleeding rate with either dose of dabigatran compared with enoxaparin ($P = 0.60$ for dabigatran 150 mg; $P = 0.44$ for dabigatran 220 mg).

The RE-MODEL trial, a phase III study comparing two doses of dabigatran etexilate (150 mg daily and 220 mg daily) with subcutaneous enoxaparin 40 mg daily, was performed in the context of knee arthroplasty.[13] In this trial, dabigatran therapy was started with a half dose 1–4 hours after surgery — 75 mg or 110 mg for patients assigned to receive 150 mg and 220 mg, respectively — and enoxaparin therapy was started the day before surgery. In this study, one-third of the lower boundary of the 95% confidence interval, 9.2%, was selected as an estimate of the non-inferiority margin. The results of RE-MODEL with respect to the primary end point (total VTE including asymptomatic VTE plus all-cause mortality) showed that dabigatran's antithrombotic effect for both doses tested was statistically non-inferior to the effect of enoxaparin (E2). The primary efficacy outcome in RE-MODEL occurred in 40.5%, 36.4% and 37.7% of patients assigned to dabigatran etexilate 150 mg or 220 mg or enoxaparin, respectively. The rates of major bleeding were 1.3%, 1.5% and 1.3% for patients receiving dabigatran etexilate 150 mg or 220 mg or enoxaparin, respectively, and it was noted that a late, transient rise in transaminases was observed in six patients (0.5%) who had received dabigatran.[13]

A further study on patients undergoing knee arthroplasty, the RE-MOBILIZE trial, randomly assigned patients to receive dabigatran etexilate 150 mg daily, dabigatran etexilate 220 mg daily or

2 Mechanism of action of dabigatran and current anticoagulants*



* Adapted from: Brighton TA. The direct thrombin inhibitor melagatran/ximelagatran. *Med J Aust* 2004; 181: 432-437.[10] Reproduced with permission. ◆

3 Comparison of dabigatran with warfarin and enoxaparin

Property	Warfarin	Enoxaparin	Dabigatran
Mechanism of action	Reduced synthesis of functional prothrombin and other clotting factors	Indirect inhibition of activated factor X (Xa)	Direct inhibition of thrombin
Administration	Oral	Parenteral	Oral
Onset of action	36–72 hours	3–5 hours	2–4 hours
Duration of action	48–96 hours	12 hours	24 hours
Elimination half-life	20–60 hours	4.5–7 hours	14–17 hours
Effective anticoagulant	Yes	Yes	Yes (non-inferior to enoxaparin in phase III studies)
Risk of haemorrhage	Significant	Significant	Equivalent to enoxaparin in phase III studies
Stable, predictable pharmacokinetics	No	Yes	Yes
Interactions with diet and alcohol	Yes	Some exist	Low potential
Dosing	Individualised to each patient and target international normalised ratio (INR)	Fixed dose but dependent on patient's weight	Fixed dose dependent on indication
Monitoring	INR every 2 weeks	Not monitored	No routine monitoring required
Dose adjustment	Frequent	Rarely required	Adjust dose to 150 mg in moderate renal disease (creatinine clearance 30–50 mL/min) or use with concomitant amiodarone
Use in severe liver disease	Problematic	Metabolised by hepatic route	Not studied
Use in severe renal disease	Yes	Yes (dose adjusted)	No (primarily renal excretion)
Antidote	Rapid reversal with plasma or factor replacement; slow reversal with vitamin K	Protamine sulfate (effectively reverses 60% of enoxaparin)	None available but can be removed by dialysis
Cost	Cheap	Cheap	Shown to be cost-effective (E1)*

* A cost-effectiveness study showed dabigatran to be cost-saving compared with enoxaparin in the context of the United Kingdom National Health Service.[11] ◆

subcutaneous enoxaparin 30 mg twice daily.[14] An upper limit of 9.2% for the 95% confidence interval for the risk difference found between dabigatran and enoxaparin therapies for the primary efficacy outcome, was selected as the non-inferiority margin. The dosing regimen for RE-MOBILIZE involved starting dabigatran therapy at a half dose 6–12 hours after surgery — 75 mg or 110 mg for patients assigned to receive 150 mg and 220 mg, respectively — and starting enoxaparin therapy 12–24 hours after surgery. This higher dose of enoxaparin was selected as this is consistent with North American thromboprophylaxis protocols. In RE-MOBILIZE, the primary efficacy end point was not met, as dabigatran did not demonstrate non-inferiority compared with this higher dose of enoxaparin (E2). The failure of dabigatran to achieve non-inferiority with the comparator in RE-MOBILIZE was attributed to the incidence of asymptomatic distal DVT detected at the end of therapy, as major VTE occurred at a similar rate in all groups in the study.[15] However, an important point to emerge from this study was that there was no difference in safety outcomes between either dose of dabigatran and enoxaparin, with a trend of less major bleeding in the dabigatran group (0.6%) than in the enoxaparin group (1.4%).[16]

Overall, pooled analysis of the results from these phase III studies (Box 5), which involved more than 8000 patients, showed dabigatran to be comparable to enoxaparin for prevention of VTE and VTE-related mortality after both knee and hip replacement (E2).[16] Pooled data analysis also revealed that dabigatran's safety profile was comparable to enoxaparin — incidence of major bleeding, as well as secondary safety end points such as elevation of liver enzymes and treatment-emergent acute coronary syndrome events, was similar across treatment groups (E2).

Use of dabigatran in other clinical indications

Dabigatran is currently undergoing investigation for use in other clinical indications. A recent non-inferiority study, the RE-LY trial, compared two doses of dabigatran etexilate (110 mg and 150 mg, each twice daily) with therapeutic warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation.[17] This study enrolled more than 18 000 patients, and had a median follow-up period of 2 years. It showed that dabigatran etexilate administered at a dose of 110 mg was associated with rates of stroke and systemic embolism similar to therapeutic warfarin, but with lower rates of major haemorrhage than warfarin. However, when provided at a dose of 150 mg, it was associated with statistically significant lower rates of stroke and system embolism but similar rates of major haemorrhage when compared with therapeutic warfarin.

The results of further trials, including a study assessing the use of dabigatran as a potential adjunct treatment in acute coronary syndromes (the RE-DEEM trial), are expected in the next 6 to 12 months. These may indicate the potential utility of dabigatran in different clinical applications.

Safety profile and drug interactions of dabigatran

The clinical trials performed thus far have shown, for the most part, that dabigatran demonstrates a sound safety profile, is generally

4 Summary of phase III studies of dabigatran for prophylaxis against venous thrombosis after major orthopaedic surgery

Study	RE-NOVATE[12]	RE-MODEL[13]	RE-MOBILIZE[14]
Design	Double-blind RCT	Double-blind RCT	Double-blind RCT
Type of surgery	Hip arthroplasty	Knee arthroplasty	Knee arthroplasty
Study intervention			
Control group	Enoxaparin 40 mg daily	Enoxaparin 40 mg daily	Enoxaparin 30 mg twice daily
Dabigatran groups	Dabigatran etexilate 150 mg or 220 mg daily	Dabigatran etexilate 150 mg or 220 mg daily	Dabigatran etexilate 150 mg or 220 mg daily
Treatment duration	35 ± 4 days	6–10 days	10–14 days
Number of patients			
Total number enrolled	3494	2076	2615
Enoxaparin	897	694	868
Dabigatran etexilate 150 mg	874	703	871
Dabigatran etexilate 220 mg	880	679	857
Total VTE and all-cause mortality			
Enoxaparin	6.7%	37.7%	26.5%*
Dabigatran etexilate 150 mg	8.6%	40.5%	33.8%
Dabigatran etexilate 220 mg	6.0%	36.4%	31.1%
Major VTE†			
Enoxaparin	3.9%	3.5%	2.2%
Dabigatran etexilate 150 mg	4.3%	3.8%	3.0%
Dabigatran etexilate 220 mg	3.1%	2.6%	3.4%
Major bleeding‡			
Enoxaparin	1.6%	1.3%	1.4%
Dabigatran etexilate 150 mg	1.3%	1.3%	0.6%
Dabigatran etexilate 220 mg	2.0%	1.5%	0.6%

RCT = randomised controlled trial. VTE = venous thromboembolism. * $P < 0.05$ for enoxaparin 30 mg twice daily compared with dabigatran etexilate 150 mg daily and 220 mg daily. † Major VTE defined as: proximal deep vein thrombosis, non-fatal pulmonary embolism or death from VTE. ‡ Major bleeding defined as: clinically overt bleeding associated with a > 20 g/L fall in haemoglobin level; clinically overt bleeding leading to transfusion of two or more units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. ◆

well tolerated and has few drug interactions. Ostensibly, as dabigatran is eliminated primarily by renal excretion, dose adjustment to 150 mg rather than a full dose of 220 mg is required in patients with impaired renal function, defined as creatinine clearance of 30–50 mL/min (E2). By extension, dabigatran is contraindicated in severe renal failure (creatinine clearance, < 30 mL/min).[9]

Dabigatran etexilate, the prodrug of dabigatran, is a substrate for P-glycoprotein. Accordingly, co-administration of dabigatran with strong P-glycoprotein inhibitors, such as amiodarone, quinidine, clarithromycin, verapamil and cyclosporin, should be approached with caution, and avoided if possible (E3). Additionally, close clinical surveillance is recommended for signs of bleeding or anaemia during the dabigatran treatment period. Dabigatran should not be administered concomitantly with other anticoagulants, including antithrombotics, antiplatelets and vitamin K antagonists. When dabigatran is given at recommended doses with low-dose aspirin for the prevention of cardiovascular events, there is no evidence of an excess bleeding risk[9] (E3). However, clinically monitoring patients on both aspirin and dabigatran for signs of bleeding is advisable during the treatment period.

Unlike warfarin and heparins, there is no specific antidote to dabigatran, although the drug is dialysable. This issue merits concern especially if dabigatran is used in an outpatient setting, where ensuring correct dosing is intrinsically more difficult. Consequently, the decision to treat a patient with dabigatran needs to be considered in the context of a patient's likelihood of compliance with the prescribed medication regimen.

In all the phase III clinical trials of dabigatran, there was no statistically significant difference between dabigatran and enoxaparin in the incidence of abnormal liver function (E2).[16] However,

5 Pooled analysis of venous thromboembolism (VTE) and major bleeding data from phase III studies of dabigatran[16]

	Dabigatran 150 mg	Dabigatran 220 mg	Enoxaparin
Total VTE	3.8%	3.0%	3.3%
Major bleeding*	1.1%	1.4%	1.4%

* Major bleeding defined as: clinically overt bleeding associated with a > 20 g/L fall in haemoglobin level; clinically overt bleeding leading to transfusion of two or more units of packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. ◆

6 Drug profile summary for dabigatran

Mechanism of action: Direct inhibition of thrombin, an essential enzyme for fibrin formation, platelet activation and subsequent generation of venous thromboembolism and deep vein thrombosis.

Dosage: 220 mg daily (2 capsules of 110 mg); in moderate renal impairment (or concomitant amiodarone use), dose should be adjusted to 150 mg daily (2 capsules of 75 mg); for prevention of venous thromboembolism after total knee replacement, duration of treatment should be 10 days; after total hip replacement, treatment duration is 28–35 days (E2).

Administration: Once daily, orally (taken with water, with or without food).

Indications: Approved for the prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement) (E2). Other potential indications for dabigatran (such as in atrial fibrillation, acute coronary syndromes and treatment of established thromboembolic disease) are currently being investigated (E2).

Adverse effects: Bleeding, including epistaxis, haemorrhoidal bleeding and rectal haemorrhage; wound discharge; anaemia; abnormal liver function.

Contraindications: Renal impairment (creatinine clearance, < 30 mL/min); haemorrhagic manifestations; bleeding diathesis; organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke in previous 6 months; indwelling spinal, epidural catheter, including < 2 hours after removal; hepatic impairment; concomitant treatment with strong P-glycoprotein inhibitors (eg, quinidine); initiation with oral verapamil (E2).

Precautions: Monitor for bleeding; apply precaution in patients with bleeding risk (eg, congenital or acquired coagulation disorder, thrombocytopenia, active ulcerative gastrointestinal disease, recent biopsy, major trauma, intracranial haemorrhage, and brain, spinal or ophthalmic surgery); do not use in pregnant or lactating women, or in children aged < 18 years.

Interactions: Unfractionated heparins, heparin derivatives, activated factor X (Xa) inhibitors (eg, fondaparinux), other thrombin inhibitors (eg, desirudin), antithrombotics (eg, clopidogrel, ticlopidine, dextran), and P-glycoprotein inhibitors (eg, quinidine, amiodarone, clarithromycin, cyclosporin, itraconazole, verapamil).

E2 = evidence obtained from at least one properly designed randomised controlled trial.[7] ◆

as dabigatran follows in the footsteps of ximelagatran, an earlier generation oral direct thrombin inhibitor that was abandoned due to the incidence of liver dysfunction in treated patients, prudent clinical practice would imply that liver function be regularly monitored for patients on dabigatran in case liver dysfunction is a class effectof thrombin inhibitors.

A summary of dabigatran's medicinal profile is provided in Box 6.

Conclusion

The high level of evidence in published clinical studies indicates that dabigatran is a promising anticoagulant and alternative to enoxaparin. Large-scale, international, randomised controlled trials have demonstrated that dabigatran is non-inferior to enoxaparin in the prevention of VTE after orthopaedic surgery, with a comparable safety profile (E2). In addition, as dabigatran has relatively few drug interactions (E3), it is an attractive proposition for mainstream use. Furthermore, the use of this new agent affords numerous benefits to patients and clinicians because dabigatran is orally active, does not require routine laboratory monitoring or dose adjustment, and has stable pharmacokinetics.[18] Important messages for patients are shown in Box 7.

7 Important messages for patients

- Dabigatran is a drug with similar anticlotting effects to warfarin and enoxaparin.
- Unlike warfarin, dabigatran does not require frequent blood tests for monitoring.
- Unlike enoxaparin, dabigatran does not require administration via injection.
- Dabigatran has low potential for interaction with diet and other medications.
- Dabigatran may interact with some drugs, including the cardiac medications amiodarone and verapamil, the antibiotic clarithromycin, and antifungals such as ketoconazole and itraconazole.
- Dabigatran is currently marketed in Australia under the name Pradaxa. ◆

Although dabigatran has demonstrated sound results in robust, well designed clinical trials, some issues need to be considered when using this agent. Importantly, dabigatran has no specific antidote, so clinicians must be vigilant in prescribing this drug, especially for use in an outpatient setting where the risk of overdose may be higher. Also, dabigatran cannot be used in patients treated with concomitant anticoagulants, which excludes a substantial proportion of patients who might otherwise benefit from the drug (E3). It is also a salient observation that, thus far, there have been no studies of dabigatran on pregnant or lactating women, patients with severe liver disease, or children. Further research and post-marketing surveillance of dabigatran is likely to determine how broadly the drug may be used. Additionally, the crucial issue of cost-effectiveness needs to be investigated. Although large studies indicate that dabigatran is cost-saving compared with enoxaparin (E1) in the context of the UK National Health Service,[11] the cost-effectiveness of dabigatran in Australia remains to be determined. Additionally, dabigatran is not currently listed on the Pharmaceutical Benefits Scheme.

Clinical trials investigating other clinical applications of dabigatran are underway, so its indications may soon be diversified to include atrial fibrillation and acute coronary syndromes. In the interim, however, evidence from clinical trials suggests that dabigatran is a safe, effective and viable alternative to enoxaparin for thromboprophylaxis in adults undergoing major lower limb orthopaedic surgery.

Competing interests

None identified.

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(Received 30 Jul 2009, accepted 1 Dec 2009) ❑