

# Dabigatran: oral prophylaxis for venous thromboembolism

Steve Chaplin MSc, MRPharmS and Simon Frostick MA, DM, FRCS

## KEY POINTS

- dabigatran etexilate (Pradaxa) is the prodrug of dabigatran, an orally active, reversible direct inhibitor of thrombin licensed for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or total knee replacement surgery
- available as 75mg and 110mg hard capsules (both strengths 10=£21.00, 60=£126.00)
- prophylaxis should be provided for up to four weeks after orthopaedic surgery and therefore needs to be continued at home after discharge
- dabigatran etexilate is noninferior to enoxaparin as prophylaxis in patients undergoing hip or knee replacement, with no differences in thromboses or all-cause mortality
- the incidence of major or minor bleeding events with dabigatran etexilate was similar to that with enoxaparin
- dabigatran etexilate provides effective prophylaxis for patients who have undergone hip or knee replacement without the need for continuing subcutaneous injections after hospital discharge



**Dabigatran (Pradaxa) is a new orally active antithrombotic agent licensed for VTE prophylaxis following hip and knee replacement. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects and Professor Simon Frostick comments on its place in therapy.**

In the UK, approximately two-thirds of all adults admitted to a surgical ward and 40 per cent of patients aged over 40 admitted to a medical ward are at risk of venous thromboembolism (VTE).<sup>1</sup>

It is difficult to determine the true incidence of VTE but, in the placebo arms of randomised controlled trials, the incidence was greatest in patients undergoing orthopaedic surgery (see Table 1).<sup>2</sup> Many events are asymptomatic but, again in a clinical trial setting, 2-9 per cent of patients undergoing elective knee or hip surgery experience a clinically apparent event, with 1-2 per cent developing pulmonary embolism (PE).<sup>3</sup>

The National Institute for Health and Clinical Excellence (NICE) guidance on the prevention of deep vein thrombosis (DVT) in patients undergoing elective orthopaedic surgery or surgery for hip fracture recommends, in addition to mechanical compression stockings, prophylaxis with a low-molecular-weight heparin such as enoxaparin (Clexane) or the indirect Factor Xa inhibitor fondaparinux (Arixtra) for four weeks after surgery.<sup>4</sup>

However, many patients at risk do not receive the recommended treatment: in the UK, approximately 26 per cent of surgical inpatients and 63 per cent of medical inpatients meeting 2004

(US) criteria for increased risk do not receive appropriate prophylaxis.<sup>1</sup>

One possible obstacle to delivering prophylaxis is the need for subcutaneous injection of the recommended anticoagulants. Patients are being discharged from hospital sooner and the recommended duration of prophylaxis after hip replacement is long. Patients should therefore be informed about the correct use of prophylaxis at home<sup>4</sup> and this requires additional resources to screen patients and provide training.

These problems may be overcome by a new generation of orally active anticoagulants. Several new agents acting at different points in

the coagulation cascade are now undergoing clinical trials as prophylaxis of VTE.<sup>5</sup>

### The technology

Dabigatran etexilate (Pradaxa) is the prodrug of dabigatran, an orally active, reversible direct inhibitor of thrombin, the enzyme that converts fibrinogen to fibrin and activates other factors in the coagulation cascade; it also inhibits thrombin-induced platelet aggregation.<sup>6</sup> It is licensed for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip-replacement surgery or total knee-replacement surgery.

The recommended initial dose is 110mg within one to four hours of surgery followed by 220mg once daily for 10 days after knee replacement and 28-35 days after hip replacement. In older patients (above 75 years) and those with moderate renal impairment (creatinine clearance 30-50ml per minute), these doses should be reduced to 75mg initially followed by 150mg per day.

Dabigatran is contraindicated in some patients at increased risk of bleeding, *ie* impaired haemostasis, organic lesion at increased risk of bleeding or active bleeding, and patients undergoing anaesthesia with postoperative indwelling epidural catheters. It is also contraindicated in severe renal impairment or hepatic disease likely to affect survival. It should be avoided in patients taking quinidine.

### Clinical trials

Two clinical trials – the RE-MODEL trial,<sup>7</sup> in patients undergoing total knee replacement, and the RE-NOVATE trial, in patients undergoing total hip replacement – form the key evidence base for primary prevention of VTE with dabigatran.<sup>8</sup>

Both were double-blind randomised noninferiority trials comparing dabigatran etexilate 150mg and 220mg per day with enoxaparin 40mg once daily. The doses of dabigatran etexilate were not stratified by age and therefore do not correspond exactly with the licensed regimens. The use of elastic stockings and low-dose aspirin was permitted.

The primary end-point was a composite of total venous thromboembolic events (symptomatic or venographic DVT and/or symptomatic PE) and all-cause mortality. Neither trial reported rates of adherence with oral or subcutaneous regimens.

#### RE-MODEL trial<sup>7</sup>

A total of 2101 patients, mean age 67-68 years, were treated for 6-10 days until mandatory venography, after which treatment was continued at the clinician's discretion, median duration eight days; follow-up was at three months. Venography was inadequate or not performed in 560 patients, leaving 1541 for the efficacy analysis.

The incidence of the primary end-point was 36.4 per cent with dabigatran etexilate 220mg per day, 40.5 per cent with 150mg per day and 37.7 per cent with enoxaparin (see Table 2). Both doses of dabigatran etexilate were noninferior to enoxaparin. There were also no differences in major VTE, VTE-related mortality or the composite VTE end-point.

#### RE-NOVATE trial<sup>8</sup>

A total of 3494 patients, mean age 63-65, were treated for 28-35 days until mandatory venography, median duration of treatment 33 days; median follow-up was 94 days. Venography was not performed or inadequate in 843 patients, leaving 2651 for the efficacy analysis.

Specialty	Incidence (% patients)
cardiac	14
general	24
gynaecology	16
neurological	20
orthopaedic – elective hip	44
orthopaedic – hip fracture	37
orthopaedic – elective knee	27
orthopaedic – mixed	47
urological	10
mixed	22

**Table 1.** Incidence of DVT in the placebo arms of randomised trials of thromboprophylaxis, by hospital specialty<sup>2</sup>

The primary end-point occurred in 6.0 per cent of patients assigned to dabigatran etexilate 220mg per day, 8.6 per cent with 150mg per day and 6.7 per cent with enoxaparin (see Table 2). Both doses of dabigatran etexilate were noninferior to enoxaparin. There were no significant differences in secondary end-points.

### Adverse effects

There were no differences between either dose of dabigatran etexilate and enoxaparin in the incidence of major (1-2 per cent) or minor (6-10 per cent) bleeding events in both trials. Adverse-event profiles were similar and the rates of adverse events leading to treatment discontinuation did not differ (4-8 per cent). There were no differences in the incidence of liver enzyme elevation, though the numbers were small.

### Summary

Dabigatran etexilate is an orally active direct thrombin inhibitor for the primary prevention of VTE in patients undergoing total knee or hip replacement. Two large clinical trials have shown that it is as effective as subcutaneous enoxaparin, with a comparable risk of major bleeding episodes and other adverse events.

	Dabigatran		Enoxaparin
	220mg	150mg	
<i>RE-MODEL trial</i>			
% (95% CI)	36.4 (32.2-40.8)	40.5 (36.3-44.7)	37.7 (33.5-41.9)
p-value*	0.0003	0.017	
<i>RE-NOVATE trial</i>			
% (95% CI)	6.0 (4.5-7.6)	8.6 (6.7-10.4)	6.7 (5.1-8.3)
p-value*	<0.0001	<0.0001	
*p-value for noninferiority vs enoxaparin			

**Table 2.** Primary outcomes (composite of total VTE events and all-cause mortality) from the RE-MODEL<sup>7</sup> and RE-NOVATE<sup>8</sup> noninferiority trials of dabigatran vs enoxaparin

Neither trial presented evidence of an advantage in treatment adherence with oral over subcutaneous administration.

**References**

1. Cohen AT, Tapson VF, Bergmann J-F, *et al.* Venous thromboembolism and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;371:387-94.

2. National Collaborating Centre for Acute Care. *Venous thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery.* April 2007. www.nice.org.uk/nicemedia/pdf/VTEFullGuide.pdf; accessed 21.4.08.

3. Gillespie W, Murray D, Gregg PJ, *et al.* Risks and benefits of prophylaxis against venous thromboembolism in orthopaedic surgery. *J Bone Joint Surg-Br* 2000;82-B:475-9.

4. National Institute for Health and Clinical Excellence. *Venous thromboembolism.* Clinical Guideline No. 46. April 2007. www.nice.org.uk/nicemedia/pdf/CG046NICEguideline.pdf; accessed 21.4.08.

5. Bates SM, Weitz JI. New anticoagulants: beyond heparin, low-molecular weight heparin and warfarin. *Br J Clin Pharmacol* 2005;144:1017-28.

6. European Medicines Agency. *Pradaxa European Public Assessment Report. Scientific discussion.* April 2008. www.emea.europa.eu/hums/human/epar/p.htm; accessed 21.4.08.

7. Eriksson BI, Dahl OE, Rosencher N, *et al.* Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemostasis* 2007;5:2178-85.

8. Eriksson BI, Dahl OE, Rosencher N, *et al.* Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56.

*By Steve Chaplin, a pharmacist who specialises in writing on therapeutics*

**Place in therapy**

Dabigatran is a new orally-active antithrombotic agent that has recently been licensed for prophylaxis against VTE (DVT and PE) in patients undergoing lower-limb arthroplasty surgery (hip and knee replacement). Historically, it has been shown that lower-limb arthroplasty is associated with a high prevalence of VTE, including its most devastating effect, that of fatal PE.

Over the last 10 years or so, a considerable body of evidence has demonstrated that for patients undergoing total hip replacement surgery, prophylaxis needs to be continued for at least 35 days. Orthopaedic surgeons in the UK have given their patients prophylaxis against VTE, but recently there has been a move towards using aspirin, which has never been shown to be effective against venous thrombosis but is an oral agent that is easy to take.

Recommending out-of-hospital and extended prophylaxis has cost implications for PCTs, particularly if it is necessary for a district nurse to attend patients to administer injectable drugs such as enoxaparin.

The advent of dabigatran is therefore a major step forward in providing effective prophylaxis for orthopaedic patients. Unlike the only other orally effective agent, warfarin, dabigatran does not need monitoring and appears to be safe in the vast majority of patients, as shown by the lack of side-effects

seen in all trials that have been completed (phases II and III). The phase III clinical trials on hip and knee replacement patients have very clearly shown that dabigatran is as effective as enoxaparin and has a similar safety profile in terms of bleeding, liver and cardiac problems. It is hoped that the results of other trials will be just as successful, *eg* in stroke patients, but the results of these studies are still some months away. However, we can look forward to orthopaedic patients receiving an effective agent for an adequate length of time and administered in a simple way.

seen in all trials that have been completed (phases II and III).

The phase III clinical trials on hip and knee replacement patients have very clearly shown that dabigatran is as effective as enoxaparin and has a similar safety profile in terms of bleeding, liver and cardiac problems.

It is hoped that the results of other trials will be just as successful, *eg* in stroke patients, but the results of these studies are still some months away. However, we can look forward to orthopaedic patients receiving an effective agent for an adequate length of time and administered in a simple way.

*By Simon Frostick, professor of orthopaedics, University of Liverpool*