

## New oral anticoagulants – clinical applications

Alex Gallus, Professor of Haematology, Flinders University, and SA Pathology, Flinders Medical Centre, Adelaide

### Summary

Rivaroxaban and dabigatran etexilate are oral anticoagulants that promise to be as effective as warfarin, but easier to use. The new drugs have shown similar or greater efficacy than low molecular weight heparins and comparable safety in the prevention of venous thromboembolism after hip or knee arthroplasty. Unlike other anticoagulants, routine monitoring is not required during short-term use. The drugs are also being assessed for other indications that include treatment of venous thromboembolism and preventing stroke in atrial fibrillation. Only the results of ongoing studies will tell if they can match warfarin and the heparins across their full range of clinical indications.

Key words: arthroplasty, dabigatran etexilate, rivaroxaban, thromboembolism.

(Aust Prescr 2010;33:42–7)

### Introduction

The two widely used classes of anticoagulant are the heparins, and the vitamin K antagonists such as warfarin. Heparins are best suited for short-term prevention and initial treatment of venous thromboembolism or arterial occlusion, but can be given long-term. Warfarin is the mainstay of long-term therapy and is also used for atrial fibrillation and patients with mechanical heart valves. These drugs are highly effective, but have well-known limitations in addition to the risk of bleeding. Heparins require injection or infusion. Warfarin has a narrow therapeutic window, variable dose response and multiple interactions with other drugs and concurrent illnesses, and there is a need for frequent laboratory monitoring of dose-effect.

Rivaroxaban and dabigatran etexilate are new oral anticoagulants which should be simpler to use than heparins or warfarin.<sup>1,2</sup> They have predictable oral bioavailability and pharmacokinetics, few drug interactions and are suitable for

daily dosing.<sup>3,4</sup> One dose regimen should suit most patients regardless of body weight, age and gender without the need for laboratory monitoring.

### Preventing venous thromboembolism after major joint surgery

As the Australian population ages there will be increasing demand for elective hip or knee replacement and surgery after hip fracture. As these procedures are often complicated by thromboembolism, clinical practice guidelines recommend effective anticoagulant prophylaxis for at least ten days after surgery.<sup>5</sup> Enoxaparin is the most widely used low molecular weight heparin. In Australia and Europe 40 mg is given daily, whereas in North America the dose is 30 mg 12-hourly. Despite prophylaxis, about 2.5% of patients develop symptomatic deep vein thrombosis or pulmonary embolism during the three months after major joint surgery. About two-thirds of cases occur after discharge from hospital.<sup>6,7</sup> In clinical trials subclinical deep vein thrombosis is found despite effective prophylaxis in up to 30% of patients when screening venography is done 7–10 days after surgery. The rate of clinical thromboembolism after hip replacement is reduced when prophylaxis is continued for 4–5 weeks after discharge. Selected patients who have an ongoing risk of

#### Box

#### Assessment of efficacy

- total venous thromboembolism – a composite of subclinical deep vein thrombosis detected at routine venography (the most frequent component) and confirmed clinical deep vein thrombosis, non-fatal pulmonary embolism, fatal pulmonary embolism or death from any cause (which are much less common)
- major venous thromboembolism – subclinical proximal deep vein thrombosis, symptomatic venous thromboembolism, and death related to venous thromboembolism or all-cause mortality
- clinical venous thromboembolism – non-fatal or fatal

Table 1

**Comparative efficacy and safety of rivaroxaban after elective total hip or knee replacement**

Study, surgery and patient numbers	Treatment dose and duration		Efficacy (rivaroxaban vs enoxaparin) (outcomes by the end of study treatments)			Safety (rivaroxaban vs enoxaparin)	
	Rivaroxaban	Enoxaparin	Total VTE	Major VTE	Clinical VTE	Major bleeding	Clinically relevant non-major or major bleeding
<b>RECORD1</b> Total hip replacement n=4541 (3153 evaluable for 'total VTE')	10 mg/day for 30–42 days	40 mg/day for 30–42 days	1.1% vs 3.7% RRR 70% p < 0.001 NNT = 39	0.2% vs 2.0% RRR 88% p < 0.001 NNT = 58	0.3% vs 0.5%	0.3% vs 0.1%	3.2% vs 2.5%
<b>RECORD2</b> Total hip replacement n=2509 (1733 evaluable for 'total VTE')	10 mg/day for 31–39 days	40 mg/day for 10–14 days	2.0% vs 9.3% RRR 75% p < 0.0001 NNT = 14	0.6% vs 5.1% RRR 88% p < 0.0001 NNT = 22	0.2% vs 1.2% RRR 83% p = 0.004 NNT = 101	< 0.1% vs < 0.1%	3.3% vs 2.8%
<b>RECORD3</b> Total knee replacement n=2531 (1702 evaluable for 'total VTE')	10 mg/day for 13–17 days	40 mg/day for 13–17 days	9.6% vs 18.9% RRR 49% p < 0.001 NNT = 11	1.0% vs 2.6% RRR 62% p = 0.02 NNT = 63	0.7% vs 2.0% RRR 65% p = 0.005 NNT = 77	0.6% vs 0.5%	3.3% vs 2.7%
<b>RECORD4</b> Total knee replacement n=3148 (1924 evaluable for 'total VTE')	10 mg/day for 10–14 days	30 mg 12-hourly for 10–14 days	6.9% vs 10.1% RRR 31% p = 0.012 NNT = 32	1.2% vs 2.0% RRR 40% p = 0.124	0.7% vs 1.2% RRR 42% p = 0.187	0.7% vs 0.3%	3.0% vs 2.3%

VTE venous thromboembolism

RRR relative risk reduction by rivaroxaban

NNT number of patients who need to be treated in order to prevent one thrombotic event during the relevant study period

Total VTE (the primary measure of efficacy in these trials) subclinical deep vein thrombosis found by screening venography or non-fatal symptomatic venous thromboembolism or death from any cause

Major VTE proximal deep vein thrombosis or non-fatal or fatal pulmonary embolism

Clinical VTE symptomatic deep vein thrombosis or pulmonary embolism

Rates refer to events during or soon after study treatment

Rivaroxaban dose was 10 mg once daily, starting 6–8 hours after wound closure. In RECORD 1, 2 and 3, enoxaparin 40 mg was given 12 hours before surgery and then daily from 6–8 hours after wound closure. Enoxaparin dose in RECORD4 was 30 mg twice daily, starting 12–24 hours after surgery.

thromboembolism after knee replacement may also benefit from extended prophylaxis.<sup>5</sup>

### Efficacy versus bleeding risk

Surgeons are wary of surgical bleeding after joint replacement, since wound haematoma delays recovery and may predispose to infections that can endanger the prosthesis. This adds importance to evidence regarding the balance of efficacy and risk of bleeding with the new anticoagulants.

In clinical trials the efficacy of the new drugs was assessed by the incidence of total, major and clinical venous thromboembolism (see box). The primary measure of efficacy

was the incidence of 'total venous thromboembolism'. A reduction in this composite end point has been accepted by government regulators and most guideline development groups as indicating efficacy. However, others argue that a composite of proximal vein thrombosis with clinical thromboembolism or even symptomatic pulmonary embolism alone should be the main measure. This debate is unfinished.<sup>8</sup>

Bleeding was reported as 'major' or 'clinically relevant but non-major'. The studies also reported bleeding from the wound, but this was not always considered as major bleeding if re-operation was not needed.

## Rivaroxaban

This orally active factor Xa inhibitor was compared with enoxaparin in four double-blind randomised trials for the prevention of venous thromboembolism. These were RECORD1 and RECORD2 for total hip replacement,<sup>9,10</sup> and RECORD3 and RECORD4 for total knee replacement<sup>11,12</sup> (Table 1). The rivaroxaban dose was 10 mg once daily starting 6–8 hours after wound closure. The enoxaparin dose was 40 mg once daily in RECORD 1, 2 and 3 (the studies most relevant to Australian practice) and 30 mg 12-hourly in RECORD4. Study drugs were given for about five weeks after hip replacement in RECORD1 and for about two weeks after knee replacement in RECORD3 and RECORD4. RECORD2 compared five weeks of rivaroxaban with 10–14 days of enoxaparin after hip replacement.

### *Efficacy (Table 1)*

Rivaroxaban was more effective than enoxaparin in RECORD 1, 3 and 4, when used for a similar duration. For total thromboembolism there was a statistically significant relative risk reduction of 30–70%. For major thromboembolism the risk reduction was 40–90% which was statistically significant in RECORD1 and RECORD3. Clinical venous thromboembolism during two weeks after knee replacement was reduced in RECORD3 from 2.0 to 0.7% (relative risk reduction 65%,  $p = 0.005$ ).

RECORD2, where rivaroxaban was continued for three weeks longer than enoxaparin, was primarily a comparison of treatment durations rather than an equal comparison of competing anticoagulants. It confirmed the value of post-discharge prophylaxis after hip replacement. Continuing rivaroxaban prophylaxis reduced cases of clinical venous thromboembolism within six weeks of surgery from 1.2% to 0.2% ( $p = 0.004$ ) when compared with 10–14 days of enoxaparin.<sup>10</sup>

Pooled analysis of the results of the comparisons with 40 mg once-daily enoxaparin (RECORD 1, 2 and 3) found that after two weeks symptomatic venous thromboembolism and all-cause mortality was reduced from 0.8% to 0.4% by rivaroxaban ( $p = 0.005$ ).<sup>13</sup>

### *Bleeding (Table 1)*

The rates of major or clinically relevant non-major bleeding were similar with rivaroxaban and enoxaparin 40 mg once daily. The apparent increases in bleeding were small and statistically insignificant. An overview found that rates of wound infection and re-operation due to bleeding were low and comparable.<sup>13</sup> The near absence of 'major' bleeding is explained in part by a study definition which excluded wound-related bleeding unless it was fatal or led to re-operation.

## Dabigatran etexilate

This orally active thrombin inhibitor has been compared with enoxaparin in three double-blind randomised trials (Table 2). One trial was in hip replacement (RE-NOVATE)<sup>14</sup> and two were in knee replacement (RE-MODEL and RE-MOBILIZE).<sup>15,16</sup> All compared two doses of dabigatran (220 mg once daily and 150 mg once daily) with enoxaparin. Treatment continued for 28–35 days in RE-NOVATE, 6–10 days in RE-MODEL, and 12–15 days in RE-MOBILIZE.

The studies most relevant to Australia are RE-NOVATE and RE-MODEL as dabigatran was given as a half-dose 1–4 hours after surgery, and 40 mg once-daily enoxaparin was started on the evening before surgery. In RE-MOBILIZE the initial half-dose of dabigatran was given 6–12 hours after surgery and 30 mg enoxaparin 12-hourly was started 12–24 hours after surgery.

### *Efficacy (Table 2)*

Both doses of dabigatran were statistically 'non-inferior' to enoxaparin in RE-NOVATE and RE-MODEL. In RE-MOBILIZE the total rates of venous thromboembolism with the two dabigatran regimens were significantly higher than with twice-daily enoxaparin.

### *Bleeding (Table 2)*

The rates of major or clinically relevant non-major bleeding were similar with the two dabigatran regimens and with enoxaparin. An overview showed a slight excess of bleeding with dabigatran 220 mg once daily, compared with enoxaparin 40 mg once daily, but this was not statistically significant.<sup>17</sup>

## Response to bleeding

Rivaroxaban and dabigatran etexilate have no antidote. Circulating half-lives of 9–13 hours (rivaroxaban) and 12–14 hours (dabigatran) mean the first response to bleeding should be local and supportive since the drugs will wash out quickly once treatment is withdrawn. Routine tests of coagulation are unhelpful. Recombinant factor VIIa to bypass factor Xa or thrombin inhibition may help to control massive bleeding, although clinical experience is lacking.

## Other adverse effects

Ximelagatran, the first orally active thrombin inhibitor, caused severe liver toxicity so all new oral anticoagulants are being closely watched for this and other unexpected organ effects. So far, an excess of liver effects has not been reported with rivaroxaban or dabigatran etexilate. There has not been an excess of myocardial infarction after surgery, which was another concern with ximelagatran. Other

Table 2

**Comparative efficacy and safety of dabigatran etexilate after elective total hip or knee replacement**

Study, surgery, patient numbers and treatment duration	Treatment		Efficacy (dabigatran vs enoxaparin)			Safety (dabigatran vs enoxaparin)	
	Dabigatran	Enoxaparin	Total VTE	Major VTE	Clinical VTE	Major bleeding	Clinically relevant non-major or major bleeding
<b>RE-NOVATE</b> Total hip replacement n = 3494 (2651 evaluable for efficacy) 28–35 days	220 mg once daily	40 mg once daily	6.0% vs 6.7% RRR 10.5% 'non-inferior'	3.1% vs 3.9%	1.0% vs 0.4%	2.0% vs 1.6%	6.2% vs 5.0%
	150 mg once daily		8.6% vs 6.7% RRR –28% 'non-inferior'	4.3% vs 3.9%	0.9% vs 0.4%	1.3% vs 1.6%	6.0% vs 5.0%
<b>RE-MODEL</b> Total knee replacement n = 2076 (1541 evaluable for efficacy) 6–10 days	220 mg once daily	40 mg once daily	36.4% vs 37.7% RRR 3.5% 'non-inferior'	2.6% vs 3.5%	0.15% vs 1.3%	1.5% vs 1.3%	7.4% vs 6.6%
	150 mg once daily		40.5% vs 37.7% RRR –7.4% 'non-inferior'	3.8% vs 3.5%	0.6% vs 1.3%	1.3% vs 1.3%	8.1% vs 6.6%
<b>RE-MOBILIZE</b> Total knee replacement n = 3016 (1896 evaluable for efficacy) 12–15 days	220 mg once daily	30 mg 12-hourly	31.1% vs 25.3% RRR –29% 'inferior' (p = 0.023)	3.4% vs 2.2%	0.6% vs 0.7%	0.6% vs 1.4%	3.3% vs 3.8%
	150 mg once daily		33.7% vs 25.3% RRR –33% 'inferior' (p < 0.001)	3.0% vs 2.2%	0.7% vs 0.7%	0.6% vs 1.4%	3.1% vs 3.8%

VTE venous thromboembolism

RRR relative risk reduction by dabigatran

Total VTE (the primary measure of efficacy in these trials) subclinical deep vein thrombosis found by screening venography or non-fatal symptomatic VTE or death from any cause

Major VTE proximal deep vein thrombosis or non-fatal or fatal pulmonary embolism

Clinical VTE derived from symptomatic deep vein thrombosis or pulmonary embolism or venous thromboembolism-related death reported separately in the dabigatran studies

Dabigatran doses were 220 mg once daily and 150 mg once daily, beginning after surgery with a half-dose. In RE-NOVATE and RE-MODEL, the half-dose was given 1–4 hours after surgery and the enoxaparin dose was 40 mg once daily starting on the evening before surgery. In RE-MOBILIZE, the half-dose was given 6–12 hours after surgery and 12-hourly enoxaparin 30 mg was started 12–24 hours after surgery. A new drug is considered 'non-inferior' (no less effective) than standard therapy if study outcomes meet predefined statistical targets, as in RE-NOVATE and RE-MODEL.

adverse events were equally distributed between treatment groups.

### Spinal or epidural anaesthesia

Over two-thirds of patients in these studies had surgery under regional (spinal or epidural) anaesthesia with or without a general anaesthetic, but study protocols required epidural anaesthesia to cease before the first (postoperative) dose of oral anticoagulant.

### How do the new drugs compare with each other?

There are well-known limitations to any use of results from separate clinical trial programs to estimate relative efficacy of different drugs. Nevertheless, for rivaroxaban and dabigatran, in these large studies the demographics of study populations appear similar, as were study inclusion and exclusion criteria, so results should be broadly comparable – provided comparisons are of relative and not absolute outcome rates.

With that proviso, the results with rivaroxaban appear more impressive, since 10 mg once daily started 6–8 hours after surgery was superior to enoxaparin 40 mg once daily for several outcomes with a similar risk of bleeding. The efficacy and bleeding risk of dabigatran etexilate 220 mg once daily was similar to enoxaparin 40 mg once daily. While dabigatran etexilate 150 mg once daily was formally 'non-inferior' to enoxaparin, the total rates of venous thromboembolism were consistently higher than with 220 mg once daily or with enoxaparin 40 mg once daily and bleeding rates were not reduced. However, the definitions used for 'major bleeding' differed and reported bleeding rates with enoxaparin were consistently higher in the dabigatran trials, as were the total rates of venous thromboembolism. Comparisons with enoxaparin 30 mg 12-hourly (a higher total daily dose) are less relevant to Australian clinical practice.

## Future developments

Ongoing or recently published studies include evaluating the new oral anticoagulants for acute and longer-term treatment of venous thrombosis and pulmonary embolism, and in acute coronary syndromes. Prevention of systemic embolism in atrial fibrillation is also being studied.<sup>18</sup>

## Conclusion

Both drugs are acceptable alternatives to enoxaparin 40 mg once daily for the prevention of venous thromboembolism after elective hip or knee replacement. While rivaroxaban is more effective than enoxaparin, dabigatran etexilate is no less effective. Bleeding risks are small and appear to be similar to those with enoxaparin. Attempts to draw fine distinctions about the relative safety of the two drugs are prevented by systematic differences between the two sets of study results. An advantage of the new drugs is the lack of the need for routine monitoring. Oral daily dosing will appeal especially to patients who need 3–4 weeks of continued prophylaxis after discharge from hospital.

## References

- Lohrmann J, Becker RC. New anticoagulants – the path from discovery to clinical practice. *N Engl J Med* 2008;358:2827-9.
- Eikelboom JE, Weitz JI. Dabigatran etexilate for the prevention of venous thromboembolism. *Thromb Haemost* 2009;101:2-4.
- Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005;61:873-80.
- Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007;64:292-303.
- Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381S-453S.
- White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003;90:446-55.
- Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br* 2006;88:386-91.
- Norrie J. Trials of venous thromboembolism prevention. *Lancet* 2007;370:915-7.
- Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75.
- Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9.
- Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86.
- Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-80.
- Eriksson BI, Kakkar AK, Turpie AG, Gent M, Bandel TJ, Homering M, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Joint Surg Br* 2009;91:636-44.
- Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al; RE-NOVATE Study Group. 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.
- Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-85.
- RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9.
- Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009; 101:77-85.

18. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parek A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.

*Professor Gallus has received honoraria from Astellas, Bayer, Bristol-Myers Squibb, Pfizer and Sanofi-Aventis for an advisory role on phase II and phase III clinical studies (rivaroxaban, apixaban, idrabiotaparinux and YM150), and Boehringer Ingelheim for an Australian advisory committee role.*

### Self-test questions

*The following statements are either true or false (answers on page 59)*

3. When used in the prevention of venous thromboembolism, dabigatran etexilate and rivaroxaban cause fewer bleeding complications than enoxaparin.
4. Patients given dabigatran etexilate or rivaroxaban to prevent venous thromboembolism should have their platelet count checked after one week of therapy.

## Book review

**Therapeutic Guidelines: Respiratory. Version 4.**  
Melbourne: Therapeutic Guidelines Limited; 2006.  
295 pages. Price \$39, students \$30, plus postage

**Scott Twaddell, Advanced Trainee in Respiratory and Sleep Medicine, Conjoint Fellow, University of Newcastle, John Hunter Hospital, Newcastle, NSW**

Version 4 of Therapeutic Guidelines: Respiratory continues the tradition of easy to access content and eminent readability that has become the hallmark of this series. The Respiratory Expert Group has again condensed a large volume of information into a pocket-sized quick reference manual.

Chapter 1 uses the familiar 'Getting to know your drugs' format and outlines the pharmacology, indications and importantly many of the adverse effects of common respiratory drugs. The broad content of the rest of the book covers all areas of respiratory practice from obstructive lung diseases through interstitial and pleural diseases to oxygen therapy. It also includes state-based information on access requirements to services such as domiciliary oxygen. There are clear, brief explanations of some difficult management areas, such as sleep disorders and in particular non-invasive ventilation, especially in the acute setting.

Perhaps the next version could include an expanded discussion on pulmonary artery hypertension (formerly called idiopathic pulmonary hypertension). With the advent of various treatments for pulmonary artery hypertension, these patients are increasingly managed by respiratory physicians as part of multidisciplinary teams. The brief mention of cor pulmonale secondary to chronic obstructive pulmonary disease and the use of diuretics also oversimplifies an often difficult management problem. These criticisms are slightly

unfair as this is clearly not intended to be an exhaustive text and information on specialised management of these conditions is available elsewhere.

This book will find application with students, junior doctors and their more senior colleagues. I believe it has managed to find a balance between presenting enough detail to inform decision-making while maintaining the formula of best practice standards and brevity.

*Editor's note: Information about pulmonary hypertension can be found in Therapeutic Guidelines: Cardiovascular. Version 5 (published in June 2008).*

THE MEDICINES ENVIRONMENT IS  
CHANGING DAILY.  
ARE YOU KEEPING UP?



NATIONAL MEDICINES  
SYMPOSIUM 2010  
*Medicines in people's lives*

26-28 May 2010, Melbourne  
Convention and Exhibition Centre  
[www.nms2010.org.au](http://www.nms2010.org.au)



National Prescribing Service Limited