For decades, vitamin K antagonists such as warfarin were the only oral anticoagulants available. Though efficacious when used properly, these agents are associated with several limitations – including a narrow therapeutic window, unpredictable pharmacological effects, slow onset and offset of action, and numerous potential drug and food interactions – all of which lead to the need for regular coagulation monitoring and dose adjustments to maintain desired therapeutic effects.¹⁻³ Such monitoring is inconvenient for patients and costly to the health care system, and some evidence suggests that up to 50% of individuals still remain over- or under-anticoagulated.¹⁴⁻⁵

**PHARMACOKINETICS**

Dabigatran etexilate and rivaroxaban are both approved for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) surgery.⁶⁻⁷

Rivaroxaban blocks thrombin generation; the net effect of both actions is a reduction in thrombin activity and fibrin formation, events that result in inhibition of thrombus formation.⁴

**Efficacy**

Dabigatran

**Prevention of Venous Thromboembolic Events**

Three phase III randomized controlled trials (RCTs) – RE-NOVATE,¹⁰ RE-MODEL,¹¹ and REMOBLIZE¹² – comprise the primary efficacy studies for dabigatran in prevention of VTE (see Table 1). In total, the trials enrolled over 8000 patients who had undergone orthopedic surgery. All trials compared dabigatran etexilate with subcutaneous enoxaparin; in 2 of the trials,¹⁰¹¹ enoxaparin was administered once daily, and in the third,¹² it was given twice daily. The primary efficacy outcome in all trials was the composite of total VTE (venographic or symptomatic) and death from all causes during treatment; for this endpoint, dabigatran etexilate was found to be as effective as enoxaparin dosed once daily, but inferior to enoxaparin dosed twice daily.

**Uses Under Investigation**

Results from a phase II dose-finding study¹³ in patients with atrial fibrillation (AF) suggested
similar efficacy for dabigatran (150 mg twice daily) and warfarin (titrated to an international normalized ratio [INR] of 2.0–3.0) for prevention of systemic thromboembolic events. A phase III trial (RE-LY study) comparing dabigatran and warfarin in this patient population is ongoing.2,3

In addition, phase III trials comparing dabigatran with warfarin for treatment (RE-COVER study) and secondary thromboprophylaxis (RE-MEDY study) of VTE (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) are also being conducted.1

Rivaroxaban
Prevention of Venous Thromboembolic Events
The efficacy of rivaroxaban in the prevention of VTE has been demonstrated in 2 primary RCTs, RECORD1,4 and RECORD3 (see Table 1). As in the trials with dabigatran, enrolled patients (n=7072) had undergone THR or TKR surgery. Both trials compared rivaroxaban with once-daily enoxaparin. The primary efficacy outcome in both trials was the composite of DVT, nonfatal PE, or death from any cause during treatment; the overall results demonstrated that rivaroxaban was more effective than once-daily enoxaparin based on this endpoint.

While it is uncertain if rivaroxaban will be superior to enoxaparin dosed twice daily, early, non-peer-reviewed results from an additional phase III trial (RECORD4 study) comparing rivaroxaban with this regimen in patients with TKR appear promising.8

Uses Under Investigation
For treatment (and secondary prevention) of proximal DVT, 2 phase II dose-ranging studies comparing rivaroxaban with standard therapy (heparin or low molecular weight heparin followed by an oral vitamin K antagonist) have been conducted. Results demonstrated similar efficacy between rivaroxaban and the standard therapy arms in the trials.1

Phase III trials comparing rivaroxaban with warfarin are currently underway for treatment of DVT (EINSTEIN-DVT study) and PE (EINSTEIN-PE study), and prevention of stroke in patients with AF (ROCKET-AF study).3,8 A phase II dose-finding trial (ATLAS ACS TIMI 46 study) evaluating rivaroxaban alone, or in combination with ASA, or ASA and thienopyridine (e.g., clopidogrel) in patients with recent acute coronary syndrome is also being conducted.2

ADVERSE EFFECTS
As with all anticoagulants, dabigatran and rivaroxaban are associated with an increased risk of bleeding. Data from phase III studies in orthopedic surgery patients (see Efficacy, above)

TABLE 1: SUMMARY OF SELECT RCTS WITH DABIGATRAN AND RIVAROXABAN10−12,14,15

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>RE-NOVATE R, DB, DD, PG, NI, MC</td>
<td>Patients (n=3494) undergoing primary elective unilateral total hip replacement</td>
<td>DAB 220 mg OD (n=880)</td>
</tr>
<tr>
<td></td>
<td>RE-MODEL R, DB, DD, PG, NI, MC</td>
<td>Patients (n=2076) undergoing primary elective unilateral total knee replacement</td>
<td>DAB 220 mg OD (n=503)</td>
</tr>
<tr>
<td></td>
<td>RE-MOBILIZE R, DB, DD, PG, NI, MC</td>
<td>Patients (n=2615) undergoing primary elective unilateral total knee replacement</td>
<td>DAB 220 mg OD (n=604)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>RECORD1 R, DB, DD, PG, NI, MC</td>
<td>Patients (n=4541) undergoing primary elective unilateral total hip replacement</td>
<td>RIV 10 mg OD (n=1595)</td>
</tr>
<tr>
<td></td>
<td>RECORD3 R, DB, DD, PG, NI, MC</td>
<td>Patients (n=2531) undergoing primary elective total knee replacement</td>
<td>RIV 10 mg OD (n=824)</td>
</tr>
</tbody>
</table>

ARR = absolute risk reduction; BID = twice daily; DAB = dabigatran etexilate; DB = double-blind; DD = double-dummy; ENX = enoxaparin; MC = multicentre; MITT = modified intention-to-treat population; NI = non-inferiority; OD = daily; PG = parallel-group; R = randomized; RIV = rivaroxaban

* Dabigatran etexilate was started with a half dose 1−4 hours after surgery; enoxaparin was started at full dose the evening before surgery. The numbers of patients listed reflect those available for the primary efficacy analysis.
† Composite of total venous thromboembolism (deep vein thrombosis and pulmonary embolism) and all-cause mortality.
‡ Dabigatran etexilate was started with a half dose 6−12 hours after surgery; enoxaparin was started at full dose 12−24 hours after surgery. The numbers of patients listed reflect those available for the primary efficacy analysis.
§ Rivaroxaban was started 6−8 hours after surgery; enoxaparin was started 12 hours before surgery. The numbers of patients listed reflect those available for the primary efficacy analysis.
|| Rivaroxaban was started 6−8 hours after surgery; enoxaparin was started 12 hours before surgery. The numbers of patients listed reflect those available for the primary efficacy analysis.
Potential drug interaction for dabigatran and rivaroxaban, as summarized by the manufacturers, are outlined in Table 2.

### DOSAGE AND ADMINISTRATION

**Dabigatran**

The recommended dose of dabigatran for VTE prevention following TKR or THR surgery in patients with normal renal function is a single dose of 110 mg, begun within 1–4 hours of completed surgery, followed by 220 mg once daily. If treatment is not started on the day of surgery, the initial and subsequent doses should be 220 mg. The recommended duration of therapy is 10 days for TKR and 28–35 days for THR.\(^6\)

In patients with moderate renal impairment (creatinine clearance 30–50 mL/min), the initial dose is 75 mg, followed by 150 mg daily; this dose should also be considered for those over 75 years of age. Use of dabigatran is not recommended in those with severe renal impairment (creatinine clearance <30 mL/min).\(^6\)

The drug may be administered with or without food.\(^6\)

**Rivaroxaban**

The recommended dose of rivaroxaban for VTE prevention following TKR or THR surgery is 10 mg daily, begun within 6–10 hours of completed surgery. The recommended duration of therapy is 14 days for TKR and 35 days for THR. The drug may be taken with or without food.\(^7\)

### MONITORING

No routine monitoring of coagulation parameters is recommended for dabigatran or rivaroxaban.\(^6,7\)

### TABLE 2: POTENTIAL DRUG INTERACTIONS FOR DABIGATRAN AND RIVAROXABAN\(^6,7\)

<table>
<thead>
<tr>
<th>Reference drug</th>
<th>Concomitant use contraindicated/not recommended</th>
<th>Undertake concomitant use with caution</th>
</tr>
</thead>
</table>
| Dabigatran           | • Strong or potent P-glycoprotein inhibitors (e.g., quinidine, verapamil, clarithromycin)  
                        • Non-NSAID drugs that affect hemostasis (unfractionated heparin\(^*\), and heparin derivatives, LMWH, fondaparinux, bivalirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, sulfipyrazone, and vitamin K antagonists, such as warfarin)  
                        • ASA  
                        • Antacids\(^†\) | • Potent or less potent P-glycoprotein inducers (e.g., rifampin, St. John’s Wort, tenofovir)  
                        • NSAIDs  
                        • Amiodarone |
| Rivaroxaban          | • Strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir)  
                        • Anticoagulants and antithrombotics\(^†\) | • Strong inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John’s Wort)  
                        • NSAIDs, ASA, and other antiplatelet drugs (e.g., clopidogrel) |

ASA = acetylsalicylic acid; GPIIb/IIIa = glycoprotein IIb/IIIa; LMWH = low molecular weight heparins; NSAID = non steroidal anti-inflammatory drug

* Unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.
† Avoid concomitant use within 24 hours after surgery; may be used thereafter.
\(^\) Not specified in the product monograph, but most agents affecting hemostasis that are not recommended for use with dabigatran likely apply.

### AVAILABILITY AND COST

Pradax is supplied as capsules containing the equivalent of 75 mg or 110 mg of dabigatran etexilate.\(^6\) The price per package of 30 capsules from a national wholesaler is $124.34 for either strength; the price per package of 60 capsules (110 mg only) is $248.69 ($8.29/220 mg dose).

Xarelto is supplied as rivaroxaban 10 mg tablets in packages of 50;\(^7\) the price per package from a national wholesaler is $523.78 ($10.48/10 mg dose).

### SUMMARY AND CONCLUSIONS

Dabigatran and rivaroxaban are the first new oral anticoagulants available in Canada in many years. Advantages of these agents over warfarin include rapid onset of action, fixed dosing schedules, lack of need for routine monitoring, and fewer potentially significant drug and food interactions.\(^6,7\) Results from ongoing trials comparing these drugs with warfarin for secondary thromboprophylaxis and treatment of VTE and prevention of stroke in patients with AF are eagerly awaited to determine how these agents fare from an efficacy perspective.

At present, robust data regarding the long-term safety of dabigatran and rivaroxaban are unavailable. Other potential drawbacks of therapy with these agents include the lack of specific antidotes to reverse anticoagulant effects and the lack of information for use in certain patient populations (e.g., pregnant patients, those with cancer or mechanical heart valves).\(^1,6\) In addition, while routine monitoring is not necessary for most individuals, it may be useful in some instances (e.g., in those with renal or hepatic impairment or those using certain medications); currently, how to best monitor these agents is uncertain.\(^4\)

A major question – and one that is unlikely to be answered any time soon – is how dabigatran and rivaroxaban (or other agents from their respective classes) will compare with one another in head-to-head trials. Available evidence does not conclusively demonstrate superiority of one agent over the other.\(^1,16\)

The relative places in therapy of dabigatran and rivaroxaban in the near future will likely be determined by their efficacy and safety profiles as compared with warfarin for uses currently under evaluation.

### REFERENCES


ASDA = acetyl salicylic acid; GPIIb/IIIa = glycoprotein IIb/IIIa; LMWH = low molecular weight heparin; NSAID = non-steroidal anti-inflammatory drug.

### NEW PRODUCTS/PRODUCT UPDATES

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
<th>SOURCE</th>
<th>CLASSIFICATION</th>
<th>SUPPLIED/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATACAND</td>
<td>Candesartan</td>
<td>AstraZeneca Canada Inc.</td>
<td>Angiotensin II AT, receptor blocker</td>
<td>New Strength: 32 mg tablets; packages of 30</td>
</tr>
<tr>
<td>AVAMYS</td>
<td>Fluticasone furoate</td>
<td>GlaxoSmithKline Inc.</td>
<td>Corticosteroid</td>
<td>New Indication: Treatment of seasonal allergic rhinitis in patients 2 to &lt; 12 years of age</td>
</tr>
<tr>
<td>FORTEO</td>
<td>Teriperatide</td>
<td>Eli Lilly Canada Inc.</td>
<td>Bone formation agent</td>
<td>New Indication: Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men and women who are at increased risk of fracture</td>
</tr>
<tr>
<td>NATRECOR</td>
<td>Nesiritide</td>
<td>Janssen-Ortho Inc.</td>
<td>Recombinant human B-type natriuretic peptide</td>
<td>1.5 mg vials of lyophilized powder for solution; packages of 1</td>
</tr>
<tr>
<td>NEVANAC</td>
<td>Nepafenac</td>
<td>Alcon Canada Inc.</td>
<td>Nonsteroidal anti-inflammatory</td>
<td>0.1% ophthalmic suspension; bottles of 5 mL</td>
</tr>
<tr>
<td>PRADAX</td>
<td>Dabigatran etexilate</td>
<td>Boehringer Ingelheim Canada Ltd.</td>
<td>Anticoagulant</td>
<td>75 mg capsules; packages of 30 110 mg capsules; packages of 30 and 60</td>
</tr>
<tr>
<td>SEROQUEL/</td>
<td>Quetiapine fumarate</td>
<td>AstraZeneca Canada Inc.</td>
<td>Antipsychotic agent</td>
<td>New Indication: Acute management of depressive episodes associated with bipolar I and bipolar II disorder</td>
</tr>
<tr>
<td>SEROQUEL XR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XARELTO</td>
<td>Rivaroxaban</td>
<td>Bayer Inc.</td>
<td>Direct factor Xa inhibitor</td>
<td>10 mg tablets; bottles of 50</td>
</tr>
<tr>
<td>ZEFTERA</td>
<td>Ceftobiprole medocaril</td>
<td>Janssen-Ortho Inc.</td>
<td>Antibacterial agent</td>
<td>500 mg vials of lyophilized powder for solution; packages of 10</td>
</tr>
</tbody>
</table>

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