A practice tool for the new oral anticoagulants

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Although warfarin has been the “king” of oral anticoagulation for the past few decades, its reign is now jeopardized by the recent marketing in Canada of 3 new oral anticoagulants: dabigatran (Pradaxa*), rivaroxaban (Xarelto) and apixaban (Eliquis).¹⁻³ The recent availability of these 3 new oral anticoagulants is challenging for health professionals, as they differ in many ways from warfarin and each other, including in their mechanism of action, pharmacokinetics, drug interaction profile, monitoring and dosage adjustment requirements. Despite their widespread use in the community and hospitals, many practising clinicians remain unfamiliar with how to use these medications safely.⁴

This article provides a practice tool to assist health professionals to effectively use these medications and monitor their patients. For ease of use and retrieval of the specific characteristics of these new anticoagulants, the information has been summarized and presented in tables. A total of 5 comparative tables are featured: 1) pharmacology and pharmacokinetic properties, 2) indications and dosages, 3) significant drug interactions, 4) recommendations for switching anticoagulants and 5) management in the perioperative setting. A brief discussion on laboratory monitoring and reversing the activity of these drugs is also included.

To build these tables, the product monographs of the new oral anticoagulants were reviewed thoroughly and Drugdex (from Micromedex), LexiComp and Lexi-Interact databases were consulted. A literature search was conducted using OVID MEDLINE and an internal citation database of pharmacy journals (AskSam) to identify related articles. The following search

terms (Medical Subject Headings and key words) were used: *apixaban, dabigatran, rivaroxaban, review, switching, perioperative care, perioperative setting and hemorrhage*. The literature search did not include randomized clinical trials and should not be viewed as a systematic review, as the goal was to collect key and practical prescribing information about the new oral anticoagulants, rather than assess them for their comparative efficacy and safety.

Pharmacology and pharmacokinetic properties

The new oral anticoagulants differ in their pharmacology and pharmacokinetics (Table 1). Although their onset of action and half-life are quite similar, other properties such as their respective mechanism of action, bioavailability, metabolism and clearance are different. Clinicians should be aware of these differences to ensure that each drug is used properly.

Indications and dosages

Table 2 features all indications and dosages approved by Health Canada, extracted from the most recent product monographs available at the time this article was prepared. Currently, rivaroxaban is the only new oral anticoagulant approved for the treatment of deep vein thrombosis and pulmonary embolism. However, this may change in the future, as many trials are currently being conducted for the above indication as well as others, which may lead to further approved indications from Health Canada.

With its low renal elimination, apixaban can be considered the preferred agent for elderly

*Pradaxa was originally named Pradax in Canada: the name was recently changed to align the product name with the United States and European countries (personal communication with Boehringer Ingelheim, October 3, 2012).

TABLE 1 Pharmacology and pharmacokinetic properties^{1-3,5-10}

Properties	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Prodrug	Yes; dabigatran etexilate is hydrolyzed to dabigatran by plasma and hepatic esterases (no involvement of CYP 450)	No	No
Bioavailability	6.5%	80%-100%	50%
Administration	With or without food. The capsule should be swallowed intact; it should not be opened, broken or chewed. Oral bioavailability may increase by 75% if drug pellets are administered without the capsule.	With food	With or without food
Tmax	2-3 hours	3 hours	3 hours
Half-life	12-17 hours	7-11 hours	9-14 hours
Metabolites	Conjugated with glucuronides to form metabolites with minor activity; substrate of P-glycoprotein	Transformed into inactive metabolites through CYP3A4 and CYP2J2; substrate of P-glycoprotein	Transformed into inactive metabolites mainly through CYP3A4; substrate of P-glycoprotein
Clearance	80% renal	66% renal (36% rivaroxaban + 30% inactive metabolites) 33% feces (inactive metabolites by HB route)	25% renal 56% feces (HB route)

HB, hepatobiliary; Tmax, time to obtain maximum drug concentrations in the blood.

patients or those with decreased renal function. It can be administered, although with caution, to patients with a creatinine clearance as low as 15 mL/min as opposed to dabigatran and rivaroxaban, which should not be administered to patients with a creatinine clearance less than 30 mL/min.

Significant drug interactions

Although the new oral anticoagulants are viewed as less prone to drug interactions compared with warfarin, they are still implicated in many interactions, which may require special attention and monitoring. They do not significantly induce or inhibit metabolism of other drugs; rather, it is the other drugs that can alter their anticoagulant activity. Table 3 features the most important pharmacokinetic (i.e., change of at least 50% in the anticoagulant plasma concentrations) and pharmacodynamic interactions. Many of the drug interactions quoted in the table are serious enough that concomitant therapy should

be avoided (interacting drugs are identified by an asterisk). For the less serious interactions, the reader should refer to more specialized references, as options for their management differ depending on the indication for the drug and the patient status. The options most quoted are 1) changing of the anticoagulant dose, 2) spacing the time between the administration of the 2 interacting drugs and 3) exercising more caution when the interacting drugs are administered together.^{1-3,7,8,11}

Recommendations for switching anticoagulants

Table 4 summarizes the information on the management of patients who need to switch from a parenteral anticoagulant (heparin or a low-molecular-weight heparin) or warfarin to one of the new oral anticoagulants and vice versa. The manufacturers of the new oral anticoagulants offer recommendations to ease these transitions; these recommendations are identified in the table

TABLE 2 Indications and dosages¹⁻³

	Dabigatran	Rivaroxaban	Apixaban
Usual dosage	Prevention of VTE in orthopedic surgery:		
	110 mg 1-4 hours after surgery followed by 220 mg once daily. Start with 220 mg once daily if therapy not initiated on day of surgery. In elderly >75 years, consider 150 mg once daily. Continue for 28-35 days for hip surgery and 10 days for knee surgery.	10 mg once daily, starting within 6-10 hours after surgery. Continue for 35 days for hip surgery and 14 days for knee surgery.	2.5 mg twice daily, starting 12-24 hours after surgery. Continue for 32-38 days for hip surgery and 10-14 days for knee surgery.
	Prevention of stroke and systemic embolism in patients with AFib:		
	150 mg twice daily. In the elderly ≥80 years: 110 mg twice daily.	20 mg once daily.	5 mg twice daily. Reduce to 2.5 mg twice daily if at least 2 of the 3 following factors: a) ≥80 years; b) ≤60 kg; c) serum creatinine ≥133 µmol/L
Dosage in renal failure	Treatment of DVT, pulmonary embolism and prevention of recurrences:		
		15 mg twice daily × 3 weeks, followed by 20 mg once daily. Duration of therapy is 3-6 months or longer; refer to Chest Guidelines 2012.	
	Prevention of VTE in orthopedic surgery:		
	For CrCl 30-50 mL/min: 75 mg 1-4 hours after surgery followed by 150 mg once daily thereafter. For CrCl <30 mL/min: Do NOT use.	For CrCl 30-49 mL/min: 10 mg once daily. For CrCl <30 mL/min: Do NOT use.	For CrCl ≥30 mL/min: 2.5 mg twice daily (no dosage adjustment). For CrCl 15-29 mL/min: Use with caution. For CrCl <15 mL/min: Do NOT use.
Dosage in hepatic failure* (for all indications)	Prevention of stroke and systemic embolism in patients with AFib :		
	For CrCl 30-50 mL/min: No dosage adjustment necessary. For CrCl <30 mL/min: Do NOT use.	For CrCl 30-49 mL/min: 15 mg once daily. For CrCl <30 mL/min: Do NOT use.	For CrCl 25-30 mL/min: No dosage adjustment but reduce to 2.5 mg twice daily if: serum creatinine ≥133 µmol/L and ≥80 years or ≤60 kg. For CrCl 15-24 mL/min: dosage adjustment unknown; use with caution. For CrCl <15 mL/min: Do NOT use.
	Treatment of DVT, pulmonary embolism and prevention of recurrences:		
		For CrCl 30-49 mL/min: 15 mg twice daily × 3 weeks, followed by 20 mg once daily. For CrCl <30 mL/min: Do NOT use.	

AFib, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; DVT, deep vein thrombosis; ULN, upper limit of normal; VTE, venous thromboembolic events.

*Hepatic failure: Mild: Child-Pugh class A; moderate: Child-Pugh class B; severe: Child-Pugh class C.

TABLE 3 Significant drug interactions^{1-5,7,8,11,12}

Type of interaction	Outcome	Dabigatran	Rivaroxaban	Apixaban
Pharmacokinetic	Increase of at least 50% in anticoagulant plasma concentrations	Amiodarone ^a *Dronedarone ^a *Ketoconazole ^{a,b} Quinidine ^a *Ticagrelor ^a Verapamil ^a	Clarithromycin ^{a,b} *Itraconazole ^{a,b} *Ketoconazole ^{a,b} *Posaconazole ^{a,b} *Ritonavir ^{a,b} *Voriconazole ^{a,b}	*Itraconazole ^{a,b} *Ketoconazole ^{a,b} *Posaconazole ^{a,b} * Ritonavir ^{a,b} *Voriconazole ^{a,b}
Pharmacokinetic	Decrease of at least 50% in anticoagulant plasma concentrations	*Carbamazepine ^d *Rifampin ^{c,d} *St. John's wort ^{c,d}	*Carbamazepine ^d *Phenobarbital ^d *Phenytoin ^d *Rifampin ^{c,d} *St. John's wort ^{c,d}	*Carbamazepine ^d *Phenobarbital ^d *Phenytoin ^d *Rifampin ^{c,d} *St. John's wort ^{c,d}
Pharmacodynamic	Increased risk of bleeding	ASA NSAIDs Platelet aggregation inhibitors ^e *Anticoagulants ^f *Thrombolytics ^g	ASA NSAIDs Platelet aggregation inhibitors ^e *Anticoagulants ^f *Thrombolytics ^g	ASA NSAIDs Platelet aggregation inhibitors ^e *Anticoagulants ^f *Thrombolytics ^g

ASA, aspirin; NSAIDs, nonsteroidal anti-inflammatory agents.

*Concomitant use is contraindicated or not recommended.

^aP-glycoprotein (P-gp) inhibition.

^bCYP 450 3A4 inhibition.

^cP-gp induction.

^dCYP 450 3A4 induction.

^ePlatelet aggregation inhibitors include abciximab, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlopidine and tirofiban.

^fAnticoagulants include argatroban, bivalirudin, danaparoid, fondaparinux, heparin, lepirudin, low-molecular-weight heparins (dalteparin, enoxaparin, nadroparin, tinzaparin) and warfarin. Note that when switching from one of the new oral anticoagulants to warfarin, a short period of concomitant use is acceptable to allow time to achieve therapeutic international normalized ratio.

^gThrombolytics include alteplase, reteplase and tenecteplase.

Note: (above list of drug interactions is not exhaustive)

1) P-glycoprotein (P-gp) is a transporter system located in the epithelial cells of the intestine (enterocytes). As the drug molecules diffuse through the enterocytes, P-gp picks up the drug molecules and carries them back to the luminal side of the cell, preventing them from reaching the circulation. Therefore, when a drug inhibits the P-gp pump system, it increases the systemic availability of a P-gp-sensitive drug, with a resultant enhanced activity/toxicity. Conversely, if a drug induces the P-gp system, less of the drug reaches the systemic circulation and therefore its activity will be decreased.

2) CYP 450 3A4 is an enzyme located in the liver, which metabolizes a wide variety of drugs. Inhibition will decrease the metabolism of drugs that depend on this enzyme for their elimination, thereby increasing the activity/toxicity of these agents. Conversely, if a drug induces this enzyme, the drugs that depend on this enzyme for their elimination will have a higher rate of elimination and their activity will be diminished.

as MPM (manufacturer's product monograph).¹⁻³ However, independent authors have also published their own recommendations based on their clinical experience or opinions; these recommendations are also featured in the table as LIT (the medical literature).⁴ As proposed methods from MPM and LIT may differ slightly, the final decision will depend on each patient case and the level of comfort of the prescriber. Recommendations may change as clinical experience is gained with these new drugs. Note that dabigatran and rivaroxaban should only be administered to patients with a creatinine

clearance of 30 mL/min and higher. However, if the renal function of a patient deteriorates and falls below the 30 mL/min range, some authors have offered a method to switch these patients from dabigatran or rivaroxaban to warfarin.

Management in the perioperative setting

Table 5 summarizes the information on the management of patients who are receiving a new oral anticoagulant and are scheduled for a surgery. Depending on the type of surgery (i.e., major or minor) and the associated risk

TABLE 4 Recommendations for switching anticoagulants¹⁻⁴

Dabigatran	Rivaroxaban	Apixaban
From parenteral anticoagulant to dabigatran: MPM: Start dabigatran 0-2 hours before the next dose of parenteral anticoagulant would have been due or at the time of discontinuation of intravenous heparin.	From parenteral anticoagulant to rivaroxaban: MPM: If full anticoagulation dose: Start rivaroxaban 0-2 hours before the next dose of parenteral anticoagulant would have been due or at the time of discontinuation of intravenous heparin. If prophylactic dose: Start rivaroxaban 6 hours or more after the last prophylactic dose.	From parenteral anticoagulant to apixaban: MPM: Start apixaban when the next dose of parenteral anticoagulant would have been due.
From dabigatran to parenteral anticoagulant: MPM: If dabigatran is used for VTE prophylaxis after orthopedic surgery, start parenteral anticoagulant 24 hours after the last dose of dabigatran. If dabigatran is used for prevention of stroke and systemic embolism in AFib, start parenteral anticoagulant 12 hours after the last dose of dabigatran.	From rivaroxaban to parenteral anticoagulant: MPM: Stop rivaroxaban and give first dose of parenteral anticoagulant when the next dose of rivaroxaban would have been due.	From apixaban to parenteral anticoagulant: MPM: Start parenteral anticoagulant when the next dose of apixaban would have been due.
From warfarin to dabigatran: MPM: Start dabigatran after warfarin has been stopped and INR <2.0. LIT: Start dabigatran after warfarin has been stopped and INR <2.3.	From warfarin to rivaroxaban: MPM: Start rivaroxaban after warfarin has been stopped and INR ≤2.5. LIT: Start rivaroxaban after warfarin has been stopped and INR <2.3.	From warfarin to apixaban: MPM: Start apixaban after warfarin has been stopped and INR <2.0.
From dabigatran to warfarin: MPM: a) CrCl >50 mL/min: Start warfarin 3 days before discontinuing dabigatran (i.e., 3 days of overlapping therapy*). b) CrCl 31-50 mL/min: Start warfarin 2 days before discontinuing dabigatran (i.e., 2 days of overlapping therapy*). Note: INR will not reflect warfarin activity until at least 2 days after discontinuation of dabigatran. LIT: same as a) and b) above, plus: c) CrCl 15-30 mL/min: Start warfarin 1 day before discontinuing dabigatran (i.e., 1 day of overlapping therapy*).	From rivaroxaban to warfarin: MPM: Start warfarin and discontinue rivaroxaban when INR ≥2.0. Note: Do not request an INR in the first 2 days following warfarin initiation. Blood for INR testing should be drawn just before dose of rivaroxaban to get an accurate result. LIT: a) CrCl >50 mL/min: Start warfarin 4 days before discontinuing rivaroxaban (i.e., 4 days of overlapping therapy*). b) CrCl 31-50 mL/min: Start warfarin 3 days before discontinuing rivaroxaban (i.e., 3 days of overlapping therapy*). c) CrCl 15-30 mL/min: Start warfarin 2 days before discontinuing rivaroxaban (i.e., 2 days of overlapping therapy*).	From apixaban to warfarin: MPM: Start warfarin and discontinue apixaban when INR ≥2.0. Note: Do not request an INR in the first 2 days following warfarin initiation. Blood for INR testing should be drawn just before dose of apixaban to get an accurate result.

AFib, atrial fibrillation; CrCl, creatinine clearance; INR, international normalized ratio; LIT, the medical literature⁴; MPM, manufacturer's product monograph; VTE, venous thromboembolic events.

*Overlapping therapy: This method takes into account the time for warfarin to produce a therapeutic INR and the elimination half-life of dabigatran or rivaroxaban based on patient's renal function. The starting dose of warfarin is as per usual practice or protocol.

TABLE 5 Management in the perioperative setting^{1-4,13*}

Drug and Creatinine Clearance	Preoperative [†]		Postoperative [†]	
	High Bleeding Risk: Major Surgery	Low Bleeding Risk: Minor Surgery	High Bleeding Risk: Major Surgery	Low Bleeding Risk: Minor Surgery
Dabigatran ≥80 mL/min	MPM: Stop 2 days before surgery. LIT: Last dose on day -3	MPM: Stop 24 hours before surgery. LIT: Last dose on day -2	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 2-3 days (48-72 hours) after surgery.	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 1 day (24 hours) after surgery.
50 to <80 mL/min	MPM: Stop 2-3 days before surgery. LIT: Last dose on day -3	MPM: Stop 1-2 days before surgery. LIT: Last dose on day -2	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 2-3 days (48-72 hours) after surgery.	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 1 day (24 hours) after surgery.
30 to <50 mL/min	MPM: Stop 4 days before surgery. LIT: Last dose on day -4 or day -5	MPM: Stop 2-3 days before surgery (at least >48 hours). LIT: Last dose on day -3	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 2-3 days (48-72 hours) after surgery.	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 1 day (24 hours) after surgery.
<30 mL/min	MPM: Stop at least 5 days before surgery LIT: Last dose on day -6	MPM: NA LIT: Last dose on day -4	Alternative anticoagulant should be used.	Alternative anticoagulant should be used.
Rivaroxaban ≥30 mL/min	MPM: Stop 2-4 days before surgery. LIT: Last dose on day -3	MPM: Stop at least 24 hours before surgery. LIT: Last dose on day -2	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 2-3 days (48-72 hours) after surgery.	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡] LIT: Resume 1 day (24 hours) after surgery.
<30 mL/min	LIT: Last dose on day -4	LIT: Last dose on day -3	Alternative anticoagulant should be used.	Alternative anticoagulant should be used.
Apixaban For all patients	MPM: Stop at least 48 hours before surgery.	MPM: Stop at least 24 hours before surgery.	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡]	MPM: Resume therapy when hemostasis is adequate and clinical condition allows. [‡]
>50 mL/min	LIT: Last dose on day -3	LIT: Last dose on day -2	LIT: Resume 2-3 days (48-72 hours) after surgery.	LIT: Resume 1 day (24 hours) after surgery.
30-50 mL/min	LIT: Last dose on day -4	LIT: Last dose on day -3	LIT: Resume 2-3 days (48-72 hours) after surgery.	LIT: Resume 1 day (24 hours) after surgery.

LIT, the medical literature^{4,13}; MPM, manufacturer's product monograph; NA, not available.

*As an example, if it says "Last dose on day -2," it should be interpreted as last dose of anticoagulant given on day -2, with day 0 being the day of the surgery.

†As the new oral anticoagulants have a fast onset and offset of action, bridging anticoagulation during the perioperative period with a low-molecular-weight heparin (LMWH) may not be needed. However, in some patients in whom oral medication cannot be resumed quickly after the surgery (e.g., bowel paralysis), especially in patients at moderate to high risk of thromboembolism, bridging anticoagulation with an LMWH may be desirable.¹³ In these cases, a specialized service (e.g., thrombosis, hematology or internal medicine service) should be consulted.

‡The product monograph from the manufacturer provides only this general statement.

of bleeding (i.e., high or low), the period for going off the anticoagulant during the perioperative period will vary. For example, major cardiovascular surgery, orthopedic surgery, urologic surgery and surgeries lasting 45 minutes and longer are considered high bleeding risk. Nonmajor procedures lasting less than 45 minutes, such as cholecystectomy, simple dental extractions or carpal tunnel repair, are classified as low bleeding risk.¹³ The manufacturers of the new oral anticoagulants offer recommendations for the perioperative period; as in the previous table, these recommendations are identified in the table as MPM (manufacturer's product monograph).¹⁻³ However, independent authors have also published their own recommendations based on their clinical experience and drug pharmacokinetics; these recommendations are also featured in the table as LIT (the medical literature).^{4,13} As proposed methods from product monographs and the medical literature may differ slightly, the final decision will depend on each patient, surgeon and the surgery bleeding risk. As the renal function of a patient can deteriorate and fall below 30 mL/min before surgery, some recommendations for managing patients on dabigatran and rivaroxaban in this setting have been suggested.

Laboratory monitoring and reversal of anticoagulant activity

Dabigatran, rivaroxaban and apixaban do not require routine laboratory monitoring, as their stable pharmacokinetic properties provide predictable and consistent anticoagulant activity. In addition, none of the standard coagulation tests constitutes a sensitive or accurate measure of their therapeutic activity.¹⁴ Although the lack of routine laboratory monitoring is viewed as an advantage, an assessment of the drug concentration or residual activity could be helpful in emergency situations such as

hemorrhage, urgent surgery or overdose, as well as ensuring compliance with therapy.^{14,15} Presently, laboratory investigations are being conducted to address this issue; however, final recommendations are pending, as some of the studied coagulation tests may not be available in each institution or laboratory.^{15,16}

In contrast to warfarin, there is no specific antidote for neutralizing the activity of these new oral anticoagulants.^{16,17} Minor bleeding (e.g., epistaxis, menorrhagia, ecchymosis) can be managed by holding the anticoagulant for 1 or more doses.⁴ In the case of a major bleed and/or care of a critical patient, a specialized service (e.g., thrombosis, hematology, critical care or internal medicine service) should be consulted, as management is still evolving; a case-by-case approach is recommended and may include the use of restricted and expensive blood products (e.g., recombinant factor VII, human prothrombin complex concentrates, etc.).^{4,16-18} For overdose situations, activated charcoal administered early after the ingestion has been suggested, based on an in vitro study with dabigatran.^{18,19} Also, in the case of dabigatran, its pharmacokinetic properties (low protein binding and renal excretion) allow drug removal by hemodialysis, where a 2-hour session may remove up to 62% of the drug.²⁰ Reversing the anticoagulant activity of these new drugs is still at an experimental stage, and further studies are needed before formal recommendations can be made.

To prevent excessive anticoagulation and increased risk of bleeding, the new oral anticoagulants should not be administered to patients with a creatinine clearance below 30 mL/min for dabigatran and rivaroxaban and below 15 mL/min for apixaban. In these situations, drug accumulation and risk of toxicity may exceed the benefits. The renal function of patients who are currently on these drugs should be monitored regularly.¹⁻³ ■

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