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When patients on target-specific oral anticoagulants need surgery

ABSTRACT

The target-specific oral anticoagulants (TSOACs), eg, dabigatran, rivaroxaban, and apixaban, are changing the way we manage thromboembolic disease. At the same time, many clinicians wonder how best to manage TSOAC therapy when patients need surgery. An in-depth understanding of these drugs is essential to minimize the risk of bleeding and thrombosis perioperatively.

KEY POINTS

How long before surgery to stop a TSOAC depends on the bleeding risk of the procedure and the patient's renal function.

Perioperative bridging is generally unnecessary for patients on TSOACs.

Routine coagulation assays such as the prothrombin time and activated partial thromboplastin time do not reliably reflect the degree of anticoagulation with TSOACs.

There are no specific antidotes or standardized reversal strategies for TSOACs.

TSOACs have a rapid onset of action and should only be restarted postoperatively once hemostasis has been confirmed.

MORE THAN 2.5 MILLION PATIENTS in the United States are on long-term anticoagulation therapy for atrial fibrillation, venous thromboembolic disease, or mechanical heart valves,¹ and the number is expected to rise as the population ages. Each year, about 10% of these patients undergo an invasive procedure or surgery that requires temporary interruption of anticoagulation.²

Most physicians are familiar with the perioperative management of warfarin, a vitamin K antagonist, since for decades it has been the sole oral anticoagulant available. However, many physicians lack experience with the three target-specific oral anticoagulants (TSOACs; also known as “novel” oral anticoagulants) approved so far: the direct thrombin inhibitor dabigatran (Pradaxa) and the direct factor Xa inhibitors rivaroxaban (Xarelto) and apixaban (Eliquis).

With their rapid onset of action, predictable pharmacokinetics, relatively short half-lives, and fewer drug-drug interactions than warfarin, TSOACs overcome many of the limitations of the older oral anticoagulant warfarin. In many ways, these qualities simplify the perioperative management of anticoagulation. At the same time, these new drugs also bring new challenges: caution is needed in patients with renal impairment; the level of anticoagulation is difficult to assess; and there is no specific antidote or standardized procedure to reverse their anticoagulant effect. While various periprocedural protocols for TSOAC therapy have been proposed, evidence-based guidelines are still to come.

This article first discusses the pharmacology of dabigatran, rivaroxaban, and apixaban that is pertinent to the perioperative period.

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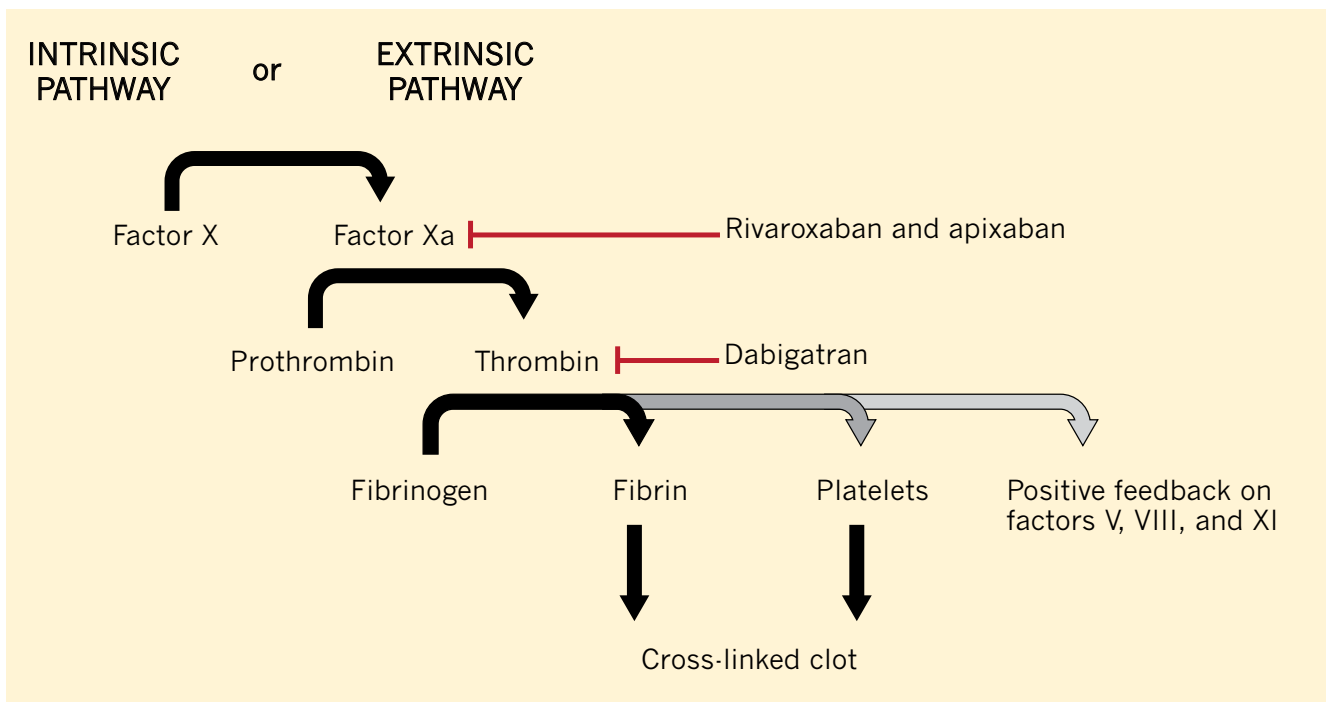


FIGURE 1. Mechanism of action of the target-specific oral anticoagulants: rivaroxaban and apixaban directly inhibit factor Xa, whereas dabigatran directly inhibits thrombin.

INFORMATION FROM REFERENCES 3, 4, 14, AND 23.

Periprocedural protocols for TSOACs have been proposed, but evidence-based guidelines are still to come

It then briefly reviews the general principles of perioperative management of anticoagulation. The final section provides specific recommendations for the perioperative management of TSOACs.

■ PHARMACOLOGY OF TARGET-SPECIFIC ORAL ANTICOAGULANTS

Dabigatran, a factor IIa inhibitor

Dabigatran is an oral direct thrombin (factor IIa) inhibitor. It exerts its anticoagulant effect by blocking the generation of fibrin, inhibiting platelet aggregation, and dampening the activity of factors V, VIII, and XI (FIGURE 1).^{3,4} From its introduction in October 2010 through August 2012, nearly 3.7 million prescriptions were dispensed to 725,000 patients in the United States.⁵

Indications for dabigatran. Dabigatran is approved in the United States and Canada for preventing stroke in nonvalvular atrial fibrillation (TABLE 1).⁶ More recently, it received US approval for treating deep vein thrombosis or pulmonary embolism after 5 to 10 days of a parenteral anticoagulant.^{7,8} It is also approved in Europe and Canada for preventing venous

thromboembolism (VTE) after total hip replacement and knee arthroplasty.^{9,10}

Dabigatran is contraindicated in patients with a mechanical heart valve, based on a phase 2 study in which it conferred a higher risk of thromboembolism and bleeding than warfarin.^{3,11}

Pharmacokinetics of dabigatran. Dabigatran is formulated as a prodrug, dabigatran etexilate, in a capsule containing multiple small pellets.¹² The capsules should not be crushed, as this significantly increases oral bioavailability. The prodrug is absorbed across the gastric mucosa and is then rapidly converted to the active form (TABLE 2).

Plasma concentrations peak within 2 hours of ingestion, which means that therapeutic anticoagulation is achieved shortly after taking the drug.

Only 35% of dabigatran is protein-bound, which allows it to be removed by hemodialysis. Nearly 85% of the drug is eliminated in the urine. It has a half-life of 13 to 15 hours in patients with normal renal function.³ However, its half-life increases to about 27 hours in patients whose creatinine clearance is less

TABLE 1

Approved indications and doses for target-specific oral anticoagulants^{3,14,23,24}

	Stroke prophylaxis in nonvalvular atrial fibrillation	VTE treatment	VTE prophylaxis after hip or knee surgery
Dabigatran	Creatinine clearance: > 30 mL/min: 150 mg twice daily 15–30 mL/min: 75 mg twice daily < 15 mL/min: avoid use	Creatinine clearance: > 30 mL/min: 150 mg twice daily ≤ 30 mL/min: avoid use	Not indicated
Rivaroxaban	Creatinine clearance: > 50 mL/min: 20 mg daily 15–50 mL/min: 15 mg daily < 15 mL/min: avoid use	Creatinine clearance: ≥ 30 mL/min: 15 mg twice daily for 21 days, then 20 mg daily < 30 mL/min: avoid use	Creatinine clearance: > 50 mL/min: 10 mg daily 30–50 mL/min: caution advised < 30 mL/min: avoid use
Apixaban	5 mg twice daily 2.5 mg twice daily if 2 of 3 criteria met: serum creatinine ≥ 1.5 mg/dL, age ≥ 80 years, or weight ≤ 60 kg AHA/ASA: Avoid use if creatinine clearance < 25 mL/min	Not indicated	Not indicated

VTE = venous thromboembolism; AHA/ASA = American Heart Association/American Stroke Association guidelines²⁴

than 30 mL/min. As a result, the dose must be reduced in patients with renal impairment (TABLE 1).

Dabigatran is not metabolized by the cytochrome P450 enzymes, but it is a substrate for P-glycoprotein, so it still has the potential for drug-drug interactions.³ Practitioners should be familiar with these potential interactions (TABLE 3), as they can result in higher- or lower-than-expected plasma concentrations of dabigatran in the perioperative period.¹³

Rivaroxaban, a factor Xa inhibitor

Rivaroxaban is an oral direct factor Xa inhibitor. It has been approved by the US Food and Drug Administration (FDA) for the prevention of stroke in nonvalvular atrial fibrillation, for VTE treatment, and for VTE prophylaxis after hip replacement or knee replacement (TABLE 1).^{14–20} It has not yet been studied in patients with hip fracture.

Pharmacokinetics of rivaroxaban. Rivaroxaban is manufactured as a tablet that is best absorbed in the stomach (TABLE 2).¹⁴ In contrast to dabigatran, it can be crushed and, for example, mixed with applesauce for patients who have trouble swallowing. It can also be mixed

with water and given via nasogastric tube; however, postpyloric administration should be avoided.

Plasma concentrations peak within a few hours after ingestion. Rivaroxaban is highly protein-bound, so it cannot be eliminated by hemodialysis.

The drug relies on renal elimination to a smaller degree than dabigatran, with one-third of the dose eliminated unchanged in the urine, one-third eliminated in the urine as inactive metabolite, and the remaining one-third eliminated in the feces. However, enough parent compound is cleared through the kidneys that the half-life of rivaroxaban increases from 8.3 hours in healthy individuals to 9.5 hours in patients whose creatinine clearance is less than 30 mL/min.²¹ As with dabigatran, the dose must be adjusted for renal impairment (TABLE 1).

Rivaroxaban has significant liver metabolism, specifically through the cytochrome P450 3A4 enzyme, and it is also a substrate of P-glycoprotein. Therefore, potential drug-drug interactions must be taken into account, as they may lead to important alterations in plasma concentrations (TABLE 3).

Dabigatran is mainly cleared through the kidneys, necessitating lower doses in renal impairment

TABLE 2

Pharmacokinetics of target-specific oral anticoagulants^{3,14,23}

	Absorption	Peak plasma concentration	% Protein-bound	% Renal elimination
Dabigatran	Stomach	2 hours	35%	85%
Rivaroxaban	Stomach	2–4 hours	90%	36%
Apixaban	Distal small bowel and ascending colon	3–4 hours	87%	27%

Apixaban, a factor Xa inhibitor

Apixaban is also an oral direct factor Xa inhibitor. It is the newest of the oral anticoagulants to be approved in the United States, specifically for preventing stroke in nonvalvular atrial fibrillation (TABLE 1).²²

Pharmacokinetics of apixaban. Apixaban is produced as a tablet that is absorbed slowly through the gastrointestinal tract, mainly the distal small bowel and ascending colon (TABLE 2).²³

Peak plasma concentrations are reached a few hours after ingestion. Like rivaroxaban, apixaban is highly protein-bound, so it cannot be removed by hemodialysis.

Apixaban is similar to rivaroxaban in that 27% of the parent compound is cleared through the kidneys, it undergoes significant hepatic metabolism through cytochrome P450 3A4, and it is a substrate for P-glycoprotein.

Drug-drug interactions must be considered as a potential source of altered drug exposure and clearance (TABLE 3).

Unlike dabigatran and rivaroxaban, dose reduction is not based on the calculated creatinine clearance. Instead, a reduced dose is required if the patient meets two of the following three criteria:

- Serum creatinine level ≥ 1.5 mg/dL
- Age ≥ 80
- Weight ≤ 60 kg (TABLE 1).

The American Heart Association/American Stroke Association guidelines further recommend against using apixaban in patients with a creatinine clearance less than 25 mL/min.²⁴

Edoxaban, a factor Xa inhibitor in development

Edoxaban (Savaysa), another factor Xa inhibitor,

is available in Japan and has been submitted for approval in the United States for treating VTE and for preventing stroke in patients with nonvalvular atrial fibrillation.

PERIOPERATIVE CONSIDERATIONS IN ANTICOAGULATION

Before addressing the perioperative management of TSOACs, let us review the evidence guiding the perioperative management of any chronic anticoagulant.

In fact, no large prospective randomized trial has clearly defined the risks and benefits of using or withholding a bridging anticoagulation strategy around surgery and other procedures, though the PERIOP 2 and BRIDGE trials are currently ongoing.^{25,26} There are some data regarding continuing anticoagulation without interruption, but they have mainly been derived from specific groups (eg, patients on warfarin undergoing cardiac pacemaker or defibrillator placement) and in procedures that pose a very low risk of bleeding complications (eg, minor dental extractions, cataract surgery, dermatologic procedures).^{2,27} Recommendations are, therefore, necessarily based on small perioperative trials and data gleaned from cohort review and from studies that did not involve surgical patients.

Ultimately, the decisions whether to discontinue oral anticoagulants and whether to employ bridging anticoagulation are based on assumptions about the risks of bleeding and the risk of thrombotic events, with similar assumptions regarding the effects of anticoagulants on both outcomes. In addition, the relative acceptance of bleeding vs thrombotic risks implicitly guides these complex decisions.

Ultimately, decisions about stopping oral anticoagulants and about bridging are based on assumptions

TABLE 3

Potential drug-drug interactions with target-specific oral anticoagulants

	Drugs that increase TSOAC levels		Drugs that decrease TSOAC levels	
	Drug class	Examples	Drug class	Examples
Dabigatran	P-glycoprotein inhibitors	Ketoconazole Dronedarone	P-glycoprotein inducers	Rifampin
Rivaroxaban, apixaban	Combined strong cytochrome P450 and P-glycoprotein inhibitors	Clarithromycin Ketoconazole Itraconazole Ritonavir	Combined strong cytochrome P450 and P-glycoprotein inducers	Carbamazepine Phenytoin Rifampin St. John's wort

TSOAC = target-specific oral anticoagulant

Perioperative bleeding risk

Many risk factors specific to the patient and to the type of surgery affect the rates and severity of perioperative bleeding.²⁸

As for patient-specific risk factors, a small retrospective cohort analysis revealed that a HAS-BLED score of 3 or higher was highly discriminating in predicting perioperative bleeding in atrial fibrillation patients receiving anticoagulation.²⁹ (The HAS-BLED score is based on hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio [INR], elderly [age > 65] and drug therapy.³⁰) However, there are no widely validated tools that incorporate patient-specific factors to accurately predict bleeding risk in an individual patient.

Therefore, the American College of Chest Physicians (ACCP) guidelines suggest coarsely categorizing bleeding risk as either low or high solely on the basis of the type of procedure.² Procedures considered “high-risk” have a risk greater than 1.5% to 2% and include urologic surgery involving the prostate or kidney, colonic polyp resections, surgeries involving highly vascular organs such as the liver or spleen, joint replacements, cancer surgeries, and cardiac or neurosurgical procedures.

Perioperative thrombotic risk

The ACCP guidelines² place patients with atrial fibrillation, VTE, or mechanical heart valves in three risk groups for perioperative thromboembolism without anticoagulation, based on their annual risk of a thrombotic event:

- High risk—annual risk of a thrombotic event > 10%
- Moderate risk—5% to 10%
- Low risk—< 5%.

Comparing the risks calculated by these methods with the real-world risk of perioperative thrombosis highlights the problem of applying nonperioperative risk calculations: the perioperative period exposes patients to a higher risk than these models would predict.³¹ Nonetheless, these risk categorizations likely have some validity in stratifying patients into risk groups, even if the absolute risks are inaccurate.

Perioperative bridging for patients taking warfarin

Many patients with atrial fibrillation, VTE, or a mechanical heart valve need to interrupt their warfarin therapy because of the bleeding risk of an upcoming procedure.

The perioperative management of warfarin and other vitamin K antagonists is challenging because of the pharmacokinetics and pharmacodynamics of these drugs. Because it has a long half-life, warfarin usually must be stopped 4 to 5 days before a procedure in order to allow not only adequate clearance of the drug itself, but also restoration of functional clotting factors to normal or near-normal levels.¹² Warfarin can generally be resumed 12 to 24 hours after surgery, assuming adequate hemostasis has been achieved, and it will again take several days for the INR to reach the therapeutic range.

The ACCP guidelines recommend using

Warfarin usually must be stopped 4 to 5 days before a procedure, and restarted 12 to 24 hours after

TABLE 4

Perioperative management of target-specific oral anticoagulants^{3,4,21,23,31–34}

	Creatinine clearance (mL/min)	Half-life (hours)	Time of discontinuation before an invasive procedure	
			Low bleeding risk ^a	High bleeding risk ^b
Dabigatran	> 50	13–15	1 day	2 days
	30–50	18	2 days	4 days
	15–30	27	2–5 days	> 5 days
Rivaroxaban	> 50	8–9	1 day	2 days
	30–50	9	1 day	2 days
	15–30	9–10	2 days	3 days
Apixaban	> 50	12	1 day	2 days
	30–50	17–18	2 days	3 days
	15–30	17–18	2 days	3 days

^aMild to moderate residual anticoagulant effect is acceptable.

^bFor example, urologic surgery involving the prostate or kidney, colonic polyp resection, surgery involving highly vascular organs such as the liver and spleen, joint replacement, cancer surgery, and cardiac and neurosurgical procedures; no or minimal residual anticoagulant effect is acceptable.

Patients on TSOACs should not routinely require perioperative bridging, regardless of thrombotic risk

the perioperative risk of thromboembolism to make decisions about the need for bridging anticoagulation during warfarin interruption.² They suggest that patients at high risk of thrombosis receive bridging with an alternative anticoagulant such as low-molecular-weight heparin or unfractionated heparin, because of the prolonged duration of subtherapeutic anticoagulation.

There has been clinical interest in using a TSOAC instead of low-molecular-weight or unfractionated heparin for bridging in the perioperative setting. Although this approach may be attractive from a cost and convenience perspective, it cannot be endorsed as yet because of the lack of information on the pros and cons of such an approach.

Patients at low thrombotic risk do not require bridging. In patients at moderate risk, the decision to bridge or not to bridge is based on careful consideration of patient-specific and surgery-specific factors.

■ PERIOPERATIVE MANAGEMENT OF TARGET-SPECIFIC ORAL ANTICOAGULANTS

As summarized above, the perioperative management strategy for chronic anticoagulation is based on limited evidence, even for drugs as

well established as warfarin.

The most recent ACCP guidelines on the perioperative management of antithrombotic therapy do not mention TSOACs.² For now, the management strategy must be based on the pharmacokinetics of the drugs, package inserts from the manufacturers, and expert recommendations.^{3,14,23,32–34} Fortunately, because TSOACs have a more favorable pharmacokinetic profile than that of warfarin, their perioperative uses should be more streamlined. As always, the goal is to minimize the risk of both periprocedural bleeding and thromboembolism.

Timing of cessation of anticoagulation

The timing of cessation of TSOACs before an elective procedure depends primarily on two factors: the bleeding risk of the procedure and the patient's renal function. Complete clearance of the medication is not necessary in all circumstances.

TSOACs should be stopped four to five half-lives before a procedure with a high bleeding risk, so that there is no or only minimal residual anticoagulant effect. The drug can be stopped two to three half-lives before a procedure with a low bleeding risk. Remember: *the half-life increases as creatinine clearance decreases.*

Specific recommendations may vary across institutions, but a suggested strategy is shown in **TABLE 4**.^{3,4,21,23,32–35} For the small subset of patients on P-glycoprotein or cytochrome P450 inhibitors or inducers, further adjustment in the time of discontinuation may be required.

Therapy does not need to be interrupted for procedures with a very low bleeding risk, as defined above.^{33,34} There is also preliminary evidence that TSOACs, similar to warfarin, may be continued during cardiac pacemaker or defibrillator placement.³⁶

Evidence from clinical trials of perioperative TSOAC management

While the above recommendations are logical, studies are needed to prospectively evaluate perioperative management strategies.

The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy), which compared the effects of dabigatran and warfarin in preventing stroke in patients with atrial fibrillation, is one of the few clinical trials that also looked at periprocedural bleeding.³⁷ About a quarter of the RE-LY participants required interruption of anticoagulation for a procedure.

Warfarin was managed according to local practices. For most of the study, the protocol required that dabigatran be discontinued 24 hours before a procedure, regardless of renal function or procedure type. The protocol was later amended and closely mirrored the management plan outlined in **TABLE 4**.

With either protocol, there was no statistically significant difference between dabigatran and warfarin in the rates of bleeding and thrombotic complications in the 7 days before or 30 days after the procedure.

A major limitation of the study was that most patients underwent a procedure with a low bleeding risk, so the analysis was likely underpowered to evaluate rates of bleeding in higher-risk procedures.

The ROCKET-AF trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) also shed light on periprocedural bleeding.¹⁵ About 15% of the participants required temporary interruption of anticoagulation for a surgical or invasive procedure.³⁸

The study protocol called for discontinuing rivaroxaban 2 days before any procedure. Warfarin was to be held for 4 days to achieve a goal INR of 1.5 or less.¹⁵

Rates of major and nonmajor clinically significant bleeding at 30 days were similar with rivaroxaban and with warfarin.³⁸ As with the RE-LY trial, the retrospective analysis was probably underpowered for assessing rates of bleeding in procedures with higher risk.

Perioperative bridging

While stopping a TSOAC in the perioperative period decreases the risk of bleeding, it naturally increases the risk of thromboembolism. However, patients on TSOACs should not routinely require perioperative bridging with an alternative anticoagulant, regardless of thrombotic risk.

Of note, dabigatran, rivaroxaban, and apixaban carry black-box warnings that discontinuation places patients at higher risk of thrombotic events.^{3,14,23} These warnings further state that coverage with an alternative anticoagulant should be strongly considered during interruption of therapy for reasons other than pathologic bleeding.

However, it does not necessarily follow that perioperative bridging is required. For example, the warning for rivaroxaban is based on the finding in the ROCKET-AF trial that patients in the rivaroxaban group had higher rates of stroke than those in the warfarin group after the study drugs were stopped at the end of the trial.³⁹ While there was initial concern that this could represent a prothrombotic rebound effect, the authors subsequently showed that patients in the rivaroxaban group were more likely to have had a subtherapeutic INR when transitioning to open-label vitamin-K-antagonist therapy.^{39,40} There was no difference in the rate of stroke or systemic embolism between the rivaroxaban and warfarin groups when anticoagulation was temporarily interrupted for a procedure.³⁸

The risks and benefits of perioperative bridging with TSOACs are difficult to evaluate, given the dearth of trial data. In the RE-LY trial, only 17% of patients on dabigatran and 28% of patients on warfarin underwent periprocedural bridging.³⁷ The selection criteria and protocol for bridging were not reported.

Use caution when relying on the aPTT to assess risk of perioperative bleeding with dabigatran

In the ROCKET-AF trial, only 9% of patients received bridging therapy despite a mean CHADS₂ score of 3.4.³⁸ (The CHADS₂ score is calculated as 1 point each for congestive heart failure, hypertension, age ≥ 75, and diabetes; 2 points for stroke or transient ischemic attack.) The decision to bridge or not was left to the individual investigator. As a result, the literature offers diverse opinions about the appropriateness of transitioning to an alternative anticoagulant.^{41–43}

Bridging does not make sense in most instances, since anticoagulants such as low-molecular-weight heparin have pharmacokinetics similar to those of the available TSOACs and also depend on renal clearance.⁴¹ However, there may be situations in which patients must be switched to a parenteral anticoagulant such as unfractionated or low-molecular-weight heparin. For example, if a TSOAC has to be held, the patient has acute renal failure, and a needed procedure is still several days away, it would be reasonable to start a heparin drip for an inpatient at increased thrombotic risk.

In patients with normal renal function, these alternative anticoagulants should be started at the time the next TSOAC dose would have been due.^{3,14,23} In patients with reduced renal function, initiation of an alternative anticoagulant may need to be delayed 12 to 48 hours depending on which TSOAC is being used, as well as on the degree of renal dysfunction. This delay would help ensure that the onset of anticoagulation with the alternative anticoagulant is timed with the offset of therapeutic anticoagulation with the TSOAC.

Although limited, information from available coagulation assays may assist with the timing of initiation of an alternative anticoagulant (see the following section on laboratory monitoring). Serial testing with appropriate coagulation assays may help identify when most of a TSOAC has been cleared from a patient.

Laboratory monitoring

Inevitably, some patients on TSOACs require urgent or emergency surgery. In certain situations, such as before an orthopedic spine procedure, in which the complications of bleeding could be devastating, it may be necessary to know if any residual anticoagulant effect is present.

Monitoring dabigatran. As one might expect, direct thrombin inhibitors such as dabigatran can prolong the prothrombin time and activated partial thromboplastin time (aPTT).^{44–47} However, the prothrombin time is not recommended for assessing the level of anticoagulation from dabigatran. Many institutions may be using a normal aPTT to rule out therapeutic concentrations of dabigatran, based on results from early in vitro and ex vivo studies.⁴⁶ While appealing from a practical standpoint, practitioners should exercise caution when relying on the aPTT to assess the risk of perioperative bleeding. A more recent investigation in patients treated with dabigatran found that up to 35% of patients with a normal aPTT still had a plasma concentration in the therapeutic range.⁴⁸

The thrombin time and ecarin clotting time are more sensitive tests for dabigatran. A normal thrombin time or ecarin clotting time indicates that no or only minimal dabigatran is present.⁴⁸ Unfortunately, these two tests often are either unavailable or are associated with long turnaround times, which limits their usefulness in the perioperative setting.

Monitoring rivaroxaban and apixaban. Factor Xa inhibitors such as rivaroxaban and apixaban can also influence the prothrombin time and aPTT (FIGURE 1).^{44–47,49,50} The aPTT is relatively insensitive to these drugs at low concentrations. It has been suggested that a normal prothrombin time can reasonably exclude therapeutic concentrations of rivaroxaban.^{45,46} However, the effects on the prothrombin time are highly variable, changing with the reagent used.^{49,50} In addition, apixaban appears to have less impact on the prothrombin time overall. The INR is not recommended for monitoring the effect of factor Xa inhibitors.

Anti-factor Xa assays likely represent the best option to provide true quantitative information on the level of anticoagulation with either rivaroxaban or apixaban. However, the assays must be specifically calibrated for each drug for results to be useful. (Anti-factor Xa assays cannot be used for heparin or low-molecular-weight heparin.) Further, most institutions do not yet have this capability. When appropriately calibrated, normal anti-factor Xa levels would exclude any effect of rivaroxaban or apixaban.

Anti-factor Xa assays are likely the best option for monitoring rivaroxaban and apixaban

Reversal of anticoagulation

If patients on TSOACs require emergency surgery or present with significant bleeding in the setting of persistent anticoagulation, it may be necessary to try to reverse the anticoagulation.

Unlike warfarin or heparin, TSOACs do not have specific reversal agents, though specific antidotes are being developed. For example, researchers are evaluating antibodies capable of neutralizing dabigatran, as well as recombinant thrombin and factor Xa molecules that could antagonize dabigatran and rivaroxaban, respectively.^{51–53}

Reversal can be attempted by neutralizing or removing the offending drug. Activated charcoal may be able to reduce absorption of TSOACs that were recently ingested,⁴⁴ and dabigatran can be removed by hemodialysis.

However, certain practical considerations may limit the use of dialysis in the perioperative period. Insertion of a temporary dialysis line in an anticoagulated patient poses additional bleeding risks. A standard 4-hour hemodialysis session may remove only about 70% of dabigatran from the plasma, which may not be enough to prevent perioperative bleeding.⁵⁴ Dabigatran also tends to redistribute from adipose tissue back into plasma after each dialysis session.⁵⁵ Serial sessions of high-flux intermittent hemodialysis or continuous renal replacement therapy may therefore be needed to counteract rebound elevations in the dabigatran concentration.

Reversal can also be attempted through activation of the coagulation cascade via other mechanisms. Fresh-frozen plasma is unlikely to be a practical solution for reversal.⁴⁴ Although it can readily replace the clotting factors depleted by vitamin K antagonists, large volumes of fresh-frozen plasma would be needed to overwhelm thrombin or factor Xa inhibition by TSOACs.

There are limited data on the use of prothrombin complex concentrates or recombinant activated factor VIIa in patients on TSOACs, though their use can be considered.⁵⁶ In a trial in 12 healthy participants, a nonactivated four-factor prothrombin complex concentrate containing factors II, VII, IX, and X immediately and completely reversed the anticoagulant effect of rivaroxaban but had no effect on dabigatran.⁵⁷ Before

2013, there were no nonactivated four-factor prothrombin complex concentrates available in the United States. The FDA has since approved Kcentra for the urgent reversal of vitamin K antagonists, meaning that the reversal of TSOACs in major bleeding events would still be off-label.⁵⁸ Giving any of the clotting factors carries a risk of thromboembolism.

Resumption of anticoagulation

TSOACs have a rapid onset of action, and therapeutic levels are reached within a few hours of administration.

Extrapolating from the ACCP guidelines, TSOACs can generally be restarted at therapeutic doses 24 hours after low-bleeding-risk procedures.² Therapeutic dosing should be delayed 48 to 72 hours after a procedure with a high bleeding risk, assuming adequate hemostasis has been achieved. Prophylactic unfractionated heparin or low-molecular-weight heparin therapy can be given in the interim if deemed safe. Alternatively, for orthopedic patients ultimately transitioning back to therapeutic rivaroxaban after hip or knee arthroplasty, prophylactic rivaroxaban doses can be started 6 to 10 hours after surgery.¹⁴

There are numerous reasons why the resumption of TSOACs may have to be delayed after surgery, including nothing-by-mouth status, postoperative nausea and vomiting, ileus, gastric or bowel resection, and the anticipated need for future procedures. Since dabigatran capsules cannot be crushed, they cannot be given via nasogastric tube in patients with postoperative dysphagia. Parenteral anticoagulants should be used until these issues resolve.

Unfractionated heparin is still the preferred anticoagulant in unstable or potentially unstable patients, given its ease of monitoring, quick offset of action, and reversibility. When patients have stabilized, TSOACs can be resumed when the next dose of low-molecular-weight heparin would have been due or when the unfractionated heparin drip is discontinued.^{3,14,23}

■ UNTIL EVIDENCE-BASED GUIDELINES ARE DEVELOPED

The development of TSOACs has ushered in an exciting new era for anticoagulant therapy. Providers involved in perioperative medicine

TSOACs do not have specific reversal agents, though antidotes are being developed

will increasingly encounter patients on dabigatran, rivaroxaban, and apixaban. However, until evidence-based guidelines are developed for these new anticoagulants, clinicians will have

to apply their knowledge of pharmacology and critically evaluate expert recommendations in order to manage patients safely throughout the perioperative period.

REFERENCES

- Douketis JD, Berger PB, Dunn AS, et al; American College of Chest Physicians. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(suppl 6):299S–339S.
- Douketis JD, Spyropoulos AC, Spencer FA, et al; American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e326S–e350S.
- Boehringer Ingelheim Pharmaceuticals, Inc. PRADAXA (dabigatran) package insert. <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/Pls/Pradaxa/Pradaxa.pdf>. Accessed August 6, 2014.
- Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM. Managing new oral anticoagulants in the perioperative and intensive care unit setting. *Anesthesiology* 2013; 118:1466–1474.
- US Food and Drug Administration (FDA). FDA drug safety communication: update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran). www.fda.gov/drugs/drugsafety/ucm326580.htm. Accessed August 6, 2014.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139–1151.
- Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361:2342–2352.
- Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013; 368:709–718.
- Eriksson BI, Dahl OE, Rosencher N, et al, Büller HR; 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; 370:949–956.
- Eriksson BI, Dahl OE, Rosencher N, 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; 5:2178–2185.
- Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013; 369:1206–1214.
- Agno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G; American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e44S–e88S.
- Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008; 36:386–399.
- Janssen Pharmaceuticals, Inc. XARELTO (rivaroxaban) package insert. www.xareltohcp.com/about-xarelto/about-xarelto.html?utm_source=google&utm_medium=cpc&utm_campaign=Branded+-+Broad&utm_term=xarelto%20rivaroxaban&utm_content=Xarelto+Rivaroxaban|mkwid|sxDpB4m_dc|pcrid|34667840494. Accessed August 6, 2014.
- Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883–391.
- EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363:2499–2510.
- EINSTEIN-PE Investigators; Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366:1287–1297.
- Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358:2765–2775.
- Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. 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; 372:31–39.
- Lassen MR, Agno W, Borris LC, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358:2776–2786.
- Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol* 2010; 70:703–712.
- Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committee and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981–992.
- Bristol-Myers Squibb Company. ELIQUIS (apixaban) package insert. www.eliquis.com/index.aspx. Accessed August 6, 2014.
- Furie KL, Goldstein LB, Albers GW, et al; American Heart Association Stroke Council; Council on Quality of Care and Outcomes Research; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; 43:3442–3453.
- ClinicalTrials.gov, US National Institutes of Health. PERIOP 2 - A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin. <http://clinicaltrials.gov/show/NCT00432796>. Accessed August 6, 2014.
- ClinicalTrials.gov, US National Institutes of Health. Effectiveness of Bridging Anticoagulation for Surgery (The BRIDGE Study). <http://clinicaltrials.gov/ct2/show/NCT00786474>. Accessed August 6, 2014.
- Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; 368:2084–2093.
- Oberweis BS, Nukala S, Rosenberg A, et al. Thrombotic and bleeding complications after orthopedic surgery. *Am Heart J* 2013; 165:427.e1–433.e1.
- Omran H, Bauersachs R, Rübenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). *Thromb Haemost* 2012; 108:65–73.
- Pisters R, Lane DA, Nieuwlaaet R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. *The Euro Heart Survey*. *Chest* 2010; 138:1093–1100.
- Kaatz S, Douketis JD, Zhou H, Gage BF, White RH. Risk of stroke after surgery in patients with and without chronic atrial fibrillation. *J Thromb Haemost* 2010; 8:884–890.
- van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010; 103:1116–1127.

33. Connolly G, Spyropoulos AC. Practical issues, limitations, and periprocedural management of the NOAC's. *J Thromb Thrombolysis* 2013; 36:212–222.
34. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood* 2012; 120:2954–2962.
35. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol* 2012; 87(suppl 1):S141–S145.
36. Rowley CP, Bernard ML, Brabham WW, et al. Safety of continuous anticoagulation with dabigatran during implantation of cardiac rhythm devices. *Am J Cardiol* 2013; 111:1165–1168.
37. Healey JS, Eikelboom J, Douketis J, et al; RE-LY Investigators. Peri-procedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 2012; 126:343–348.
38. Sherwood MW, Douketis JD, Patel MR, et al; on behalf of the ROCKET AF Investigators. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation* 2014; 129:1850–1859.
39. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol* 2013; 61:651–658.
40. Reynolds MR. Discontinuation of rivaroxaban: filling in the gaps. *J Am Coll Cardiol* 2013; 61:659–660.
41. Turpie AG, Kreutz R, Llau J, Norrving B, Haas S. Management consensus guidance for the use of rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb Haemost* 2012; 108:876–886.
42. Gallego P, Apostolakis S, Lip GY. Bridging evidence-based practice and practice-based evidence in periprocedural anticoagulation. *Circulation* 2012; 126:1573–1576.
43. Sié P, Samama CM, Godier A, et al; Working Group on Perioperative Haemostasis; French Study Group on Thrombosis and Haemostasis. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: thrombin or factor-Xa inhibitors. Recommendations of the Working Group on Perioperative Haemostasis and the French Study Group on Thrombosis and Haemostasis. *Arch Cardiovasc Dis* 2011; 104:669–676.
44. King CS, Holley AB, Moores LK. Moving toward a more ideal anticoagulant: the oral direct thrombin and factor Xa inhibitors. *Chest* 2013; 143:1106–1116.
45. Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring oral direct inhibitors (ODIs) of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost* 2013; 11:756–760.
46. Baglin T, Keeling D, Kitchen S; British Committee for Standards in Haematology. Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Committee for Standards in Haematology. *Br J Haematol* 2012; 159:427–429.
47. Mani H, Kasper A, Lindhoff-Last E. Measuring the anticoagulant effects of target specific oral anticoagulants—reasons, methods and current limitations. *J Thromb Thrombolysis* 2013; 36:187–194.
48. Hawes EM, Deal AM, Funk-Adcock D, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. *J Thromb Haemost* 2013; 11:1493–1502.
49. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost* 2010; 104:1263–1271.
50. Smythe MA, Fanikos J, Gulseth MP, et al. Rivaroxaban: practical considerations for ensuring safety and efficacy. *Pharmacotherapy* 2013; 33:1223–1245.
51. Van Ryn J, Litzenburger T, Waterman A, et al. Dabigatran anticoagulant activity is neutralized by an antibody selective to dabigatran in vitro and in vivo models. *J Am Coll Cardiol* 2011; 57:E1130.
52. Sheffield W, Lambourne M, Bhakta V, Eltringham-Smith L, Arnold D, Crowther M. Active site-mutated thrombin S195A but not active site-blocked thrombin counteracts the anticoagulant activity of dabigatran in plasma. Abstract presented at the International Society of Thrombosis and Haemostasis 2013 Congress. <http://onlinelibrary.wiley.com/doi/10.1111/jth.2013.11.issue-s2/issuetoc>. Accessed August 6, 2014.
53. Lu G, Luan P, Hollenbach SJ, et al. Reconstructed recombinant factor Xa as an antidote to reverse anticoagulation by factor Xa inhibitors (abstract). *J Thromb Haemost* 2009; 7(suppl 2):abstract OC-TH-107.
54. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; 49:259–268.
55. Singh T, Maw TT, Henry BL, et al. Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clin J Am Soc Nephrol* 2013; 8:1533–1539.
56. Kaatz S, Crowther M. Reversal of target-specific oral anticoagulants. *J Thromb Thrombolysis* 2013; 36:195–202.
57. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124:1573–1579.
58. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013; 128:1234–1243.

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