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Perioperative Management of Oral Anticoagulants: A Focus on Target-Specific Oral Anticoagulants

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Abstract

Although warfarin has historically been the dominant oral anticoagulant, newer target-specific oral anticoagulants (TSOACs) have been introduced in the marketplace in the past few years. Dabigatran, rivaroxaban, and apixaban, collectively referred to as TSOACs, have undergone extensive testing in comparison with warfarin and other anticoagulants for a variety of conditions. Compared with warfarin, the shorter time to peak effect, shorter half-life, and fewer drug–drug interactions have helped make the TSOACs attractive alternatives to warfarin for the prevention and treatment of thromboembolic disease associated with orthopedic surgery and atrial fibrillation as well as for the treatment of venous thromboembolism. However, their unique properties pose a challenge for their management in the perioperative period. This article reviews the current guideline-based approach to perioperative management of anticoagulants, the clinical data, and the recommendations supporting use of the TSOACs in the perioperative period. The article also addresses common pitfalls in their perioperative management. By understanding a few key properties of the new oral anticoagulants and with careful perioperative planning, physicians can ensure that their patients will safely undergo most surgical procedures with minimal disruption of their chronic anticoagulation.

Keywords

anticoagulants; perioperative care; warfarin; dabigatran; rivaroxaban; apixaban

Introduction

Physicians have become adept at managing patients on warfarin therapy, especially regarding scheduled and emergent surgical procedures, because of > 60 years of accumulated clinical experience with this drug. However, the introduction of 3 new target-specific oral anticoagulants (TSOACs) has necessitated a more complex approach to periprocedural and perioperative anticoagulation management. Dabigatran, rivaroxaban, and apixaban, the 3 new US Food and Drug Administration (FDA)-approved TSOACs, have

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Conflict of Interest Statement

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distinct advantages over warfarin therapy, including shorter onset and offset of action,[1] fixed dosing without the need for monitoring,[2,3] and fewer drug–drug and food–drug interactions.[2] Yet those same advantages pose new challenges when performing surgery or a procedure, including the need for revised management strategies and protocols as well as the inability to definitively measure the anticoagulant effect of the TSOACs.

Each of the 3 TSOACs has been testing in thousands of patients with atrial fibrillation (AF), venous thromboembolism (VTE), or for the prevention of VTE after an orthopedic surgery. Dabigatran has been tested and FDA approved for the prevention of stroke and systemic embolism for patients with AF.[4] It has also been tested, but not yet FDA approved, for the prevention of VTE following orthopedic surgery as well as for both acute and extended treatment of VTE.[5,6] Rivaroxaban has been tested and FDA approved for the prevention of VTE following orthopedic surgery,[7-9] stroke, and systemic embolism prevention in patients with AF,[10] as well as for the acute and extended treatment of patients with VTE.[11,12] Apixaban has been tested and FDA approved for the prevention of stroke and systemic embolism in AF.[13,14] It has also been tested recently and FDA approved for the prevention of VTE following orthopedic surgery.[15,16] Apixaban has been tested but not approved for the acute and extended treatment of VTE.[17,18]

In light of the rapid expansion of FDA-approved anticoagulants from which to choose, this article reviews the current guideline-based approach to managing perioperative anticoagulants, recommendations for managing TSOACs perioperatively, and some common pitfalls in managing patients.

Materials and Methods

The American College of Chest Physicians (ACCP) guidelines published in 2008 and 2012 for anticoagulant therapy were reviewed for relevant recommendation statements and references articles. A PubMed search using the terms *dabigatran, rivaroxaban, apixaban,* and *perioperative* was performed to collect potentially relevant publications. References from relevant publications were reviewed to identify primary sources and other related references.

Guideline-Based Care With Warfarin

Given a lack of robust randomized clinical trial experience, the ACCP has published guidelines for perioperative management of anticoagulant agents based largely on registry data and expert opinion.[19] These guidelines were published before most clinical experience with TSOACs was available in the literature, so they focus primarily on the perioperative management of warfarin and heparin-based products.

The principal decision in perioperative anticoagulant management involves an assessment of a patient's thromboembolic risk and perioperative bleeding risk. Based on these 2 factors, a decision is made to either maximize the patient's exposure to anticoagulation, often with the use of heparin bridging, or to minimize exposure to anticoagulants around the time of surgery without the use of a bridging parenteral anticoagulant (Table 1). The ACCP-suggested risk stratification schemes for thromboembolism and perioperative bleeding risk are shown in Tables 2 and 3. In general, maximizing anticoagulation around the time of a

surgery is favored only in patients with the highest risk of thromboembolism and can be considered in patients with a moderate thromboembolism risk when undergoing procedures with lower bleeding risk.

Bridging is usually performed with the administration of subcutaneous low molecular weight heparin (LMWH), which can be performed on an inpatient or outpatient basis. In specific cases, especially for patients with poor renal function, intravenous unfractionated heparin can be used.

In an effort to develop better perioperative anticoagulation guidelines, 2 trials are currently ongoing to assess the role of maximizing anticoagulation exposure with heparin bridging in AF patients treated with warfarin (BRIDGE, NCT 00786474; PERIOP-2, NCT 00432796). They will likely have an impact on the next round of ACCP guidelines.

Perioperative Management of TSOACs

Current Evidence

Warfarin, with its long effective half-life, often requires a complex management strategy of heparin or LMWH bridging when maximal anticoagulation exposure is desired for a procedure. The TSOACs, on the other hand, have much shorter half-lives (5–17 hours) and do not require such complex bridging strategies.[2] However, the shorter halflife, combined with a limited ability to measure the degree of anticoagulation, raises new issues for managing patients who will be undergoing surgery or a procedure.

Although randomized trials of perioperative TSOAC management have not yet been performed, there are some publications from clinical trials and real-world registries reporting outcomes of patients undergoing procedures or surgeries while treated with TSOACs.

A substudy of the Dabigatran Versus Warfarin in Patients with Atrial Fibrillation (RE-LY) trial compared 4591 patients undergoing ≥ 1 procedure or surgery.[20] When the twice-daily dabigatran 150-mg dose was compared with warfarin, there was no major difference in the rate of periprocedural bleeding (5.1% vs 4.6%; relative risk reduction, 1.09; 95% CI, 0.80–1.49) or a composite endpoint of thromboembolic complications (1.5% vs 1.3%; relative risk reduction, 1.29; 95% CI, 0.70–2.38). Patients treated with dabigatran had their last dose an average of 49 hours preprocedure compared with patients treated with warfarin, whose last dose was an average of 114 hours preprocedure. Periprocedural bridging was used in 17.0% of patients treated with dabigatran 150 mg and in 28.5% of warfarin patients.

A similar substudy of the Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial explored the outcomes from 321 patients who underwent either cardioversion or ablation procedures.[21] Rates of major and clinically relevant nonmajor bleeding were similar between patients treated with rivaroxaban (18.75%) and warfarin (13.04%) who underwent cardioversion or radiofrequency ablation procedures. There were also similar rates of thromboembolic compilations (3.13% vs 4.35%) between the rivaroxaban- and warfarin-treated cohorts, retrospectively.

There have been a handful of observational studies comparing dabigatran with warfarin in patients undergoing catheter-based cardiac procedures (eg, AF ablation), but the majority of these studies have compared the dabigatran 110-mg dose to warfarin (a dose not available in the United States). A recently published meta-analysis of 11 studies demonstrated no difference in the rate of major bleeding or thromboembolic events between patients treated with dabigatran and those treated with warfarin.[22] However, that study combined patients treated with both the 110-mg and 150-mg doses of dabigatran as well as including both interrupted and uninterrupted warfarin therapy patients, limiting the study's interpretation. One study comparing dabigatran 150 mg with warfarin in 404 patients with AF undergoing catheter-based ablation demonstrated no difference in either bleeding or thromboembolic events.[23] However, low event rates (6 total adverse events) limit that study's generalizability. Continuous anticoagulation was used in 17% of dabigatran patients and 80% of warfarin patients.

Other than reports of patients undergoing catheter-based cardiac ablation procedures, there have been very few reports of patients undergoing other procedures while taking TSOACs. One recent report of 176 patients treated with either dabigatran or rivaroxaban who underwent pacemaker or implantable cardioverter defibrillator demonstrated similar bleeding rates among patients treated with either TSOAC.[24] Again, small adverse event numbers (6 total bleeding events) limit the impact of this study.

Perioperative Laboratory Monitoring

Most clinicians are familiar with the international normalized ratio (INR) of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) used to monitor the effects of warfarin and heparin, respectively, because of > 60 years of accumulated clinical experience with these drugs. Most surgeons routinely use these studies to ensure that the effects of warfarin and heparin are at safe levels before proceeding with an operation.

Routine laboratory measurements for the TSOACs are not currently available. For surgeons, this means proceeding to the operating room without the reassurance that a patient's coagulation system has returned to normal prior to a procedure. This should be sufficient for most routine surgeries or procedures. However, there are circumstances when an estimate of the degree of anticoagulation in a patient taking a TSOAC is necessary. This is particularly salient when a patient requires an emergent procedure within 24 hours of the last TSOAC administration or when a patient's renal function is low enough to suspect delayed medication clearance.[25,26]

Accurate measurements of TSOAC drug concentrations or effects are not routinely available. However, strategies to demonstrate that the effect of a TSOAC agent is minimal may be useful before a procedure or surgery. For patients taking dabigatran, a normal aPTT or a normal thrombin time (TT) suggests that there is minimal to no residual anticoagulation effect.[25,26] However, TT is a very sensitive test, and an abnormal test does not necessarily indicate a clinically relevant degree of anticoagulation, especially after withholding an anticoagulant medication for 1 or 2 days. The aPTT test may also be used to estimate the degree of anticoagulation after dabigatran administration, but the relationship is curvilinear, making its interpretation more challenging for most clinicians.[26] Preliminary studies suggest

that the dilute TT (Hemoclot assay) may be one of the most reliable quantitative measures of dabigatran effect available.[27] For patients taking rivaroxaban, a normal PT (but not an INR) can signify minimal to no effective rivaroxaban in a patient's system.[26] Unfortunately, at usual doses, apixaban does not affect the PT in a reliably measurable way.[28] Both rivaroxaban and apixaban are factor Xa inhibitors and are reliably measured using anti–factor Xa assays (usually used to measure the effect of heparin or LMWH). However, those anti–factor Xa assays require recalibration before they can provide a quantitative assessment of the anticoagulant effect of either rivaroxaban or apixaban.[28,29]

Impact of Renal Function

Unlike with warfarin, where the metabolism is primarily driven by diet and liver function, the TSOACs are all at least partially excreted by the kidneys and therefore impart a greater degree of anticoagulation at lower levels of renal function.[29] In fact, the recommendation with dabigatran, rivaroxaban, and apixaban is to lower their maintenance dose when renal function is impaired. Also, all 3 TSOACs entail a degree of renal impairment beyond which their use is contraindicated.

Without the ability to easily and accurately measure the effective degree of anticoagulation in patients taking TSOACs, it is reasonable to utilize a patient's renal function when determining a safe anticoagulation-free interval prior to a surgical procedure. The RE-LY trial is the only one to have published its protocol.[20] However, this protocol was in place for only the last 7 months of the trial, diminishing the association between the published results and the protocol. For the first 2 years and 8 months of the RE-LY study, clinicians were recommended to stop dabigatran 24 hours preprocedure. In the final few months of the RE-LY trial, the protocol was amended to combine a patient's renal function with the clinician's assessment of perioperative bleeding risk in an effort to determine a customized preoperative anticoagulation-free period (between 24 hours and 5 days). In the reported substudy, there was no significant difference in the rates of bleeding or thromboembolic events between the warfarin and dabigatran patients.

Perioperative Recommendations for TSOAC Management

Many expert clinicians have published recommendations on the perioperative management of TSOAC medications. These recommendations are largely experientially driven, as few protocols have been tested and reported in a rigorous method. Our institution, in line with most published recommendations, combines a patient's renal function with the bleeding risk of a surgical procedure to determine the appropriate preoperative interval during which a TSOAC should be withheld (Table 4).[2,28,30,31] In a similar fashion to the ACCP guidelines for perioperative management of anticoagulants, our institution also recommends assessing a patient's thromboembolic risk as well when determining the preoperative anticoagulant-free interval.[19]

After a surgery or procedure, clinicians should be confident that a patient's perioperative bleeding has been appropriately managed and the risk of bleeding significantly reduced before restarting a TSOAC. Unlike warfarin, whose anticoagulant effect may be delayed for days after initiation, the full effect of TSOACs takes place within 1 to 3 hours.[29] Remember

that the concurrent use of gastric suppression (eg, proton pump inhibitors or H_2-receptor antagonists) may decrease dabigatran absorption in the gut.[31]

Because of the rapid onset and offset of the TSOACs, use of heparin or LMWH bridging is not necessary.[31] Additionally, the routine use of laboratory monitoring preoperatively is usually not needed or recommended.[26] However, in circumstances where a clinician finds a use for preoperative laboratory testing, the concurrent use of heparin or LMWH will significantly complicate interpretation.

Common Clinical Pitfalls

Given the vast clinical experience most clinicians have managing patients on warfarin therapy in the perioperative period, it is understandable that they may have difficulty easily transitioning their protocols to appropriately managing patients on TSOACs. Highlighting a few common pitfalls may help to avoid complications related to anticoagulant therapy.

One common clinical pitfall is the reliance on LMWH bridging. The TSOACs have pharmacokinetic properties similar to those of LMWH, and therefore they should not be routinely combined.[29] By using a reasonable preoperative TSOAC-free period (Table 4), surgeons can be reassured that a patient may safely undergo an operation or procedure without significant residual influence of the TSOAC medication when bleeding is of particular concern. Important exceptions include patients undergoing gastrointestinal surgeries who cannot take oral medications or patients with a concern about the effective absorption of oral medications. In these cases, careful consideration can be given to the use of LMWH or intravenous unfractionated heparin.

Another common clinical pitfall is the early resumption of TSOAC medications postoperatively. Many surgeons are comfortable restarting warfarin in the early postoperative period because they know that several days will elapse before warfarin's effect is fully manifested. However, TSOAC medications have a much more rapid onset and time to peak effect, on the order of 1 to 3 hours.[29] Therefore, we recommend that surgeons treat resumption of a TSOAC medication in the same way as they would unfractionated heparin or LMWH and not resume these medications until they are fully confident that adequate postoperative hemostasis has been achieved.

A final common clinical pitfall regarding the management of TSOACs is to assume that they have no drug–drug interactions or impairment based on renal function. This is an easy assumption to make, given frequent discussions that the TSOACs were developed to avoid the myriad of drug–drug interactions encountered with warfarin. However, rivaroxaban and apixaban are metabolized via the cytochrome P-450 pathway and all 3 TSOACs are mediated through P-glycoprotein pathways.[2,29] Therefore, TSOACs will be influenced by other medications (and herbal supplements) that affect these pathways. Important drug–drug interactions include azole antifungal medications (increased anticoagulant effect), ritonavir (increased anticoagulant effect), clarithromycin (increased anticoagulant effect), many antiepileptic medications (eg, carbamazepine and phenytoin: decreased anticoagulant effect), rifampin (decreased anticoagulant effect), and St. John's Wort (decreased anticoagulant

effect). Similarly, renal function plays a critical role in the pharmacokinetics of TSOACs and therefore should be monitored closely in the perioperative period. All 3 TSOACs have a renal function level at which their dose should be reduced or avoided until renal function improves. Use of intravenous heparin, if indicated, should replace TSOAC use until the renal function stabilizes or a transition to warfarin is possible.

An important contraindication for all TSOAC medications is their use in any patient with a mechanical heart valve replacement.[32] These patients should be managed with warfarin chronically and heparin or LMWH bridging, as indicated by the ACCP guidelines.[19]

Conclusion

Careful understanding of the pharmacokinetic and drug–drug interaction profiles of TSOAC medications is critical for the safe perioperative management of patients receiving chronic anticoagulation therapy. Assessing a patient's thromboembolic and bleeding risk can help guide anticoagulant therapy in the perioperative period. The TSOAC medications, with their relatively short time to onset and half-life, offer the ease of avoiding bridging therapy with heparin or LMWH for most patients with approved indications. Updating protocols with specific management strategies for patients treated chronically with warfarin, dabigatran, rivaroxaban, and apixaban will likely help to avoid any adverse events related to inappropriate perioperative management of anticoagulants. When in doubt, close collaboration with local experts in anticoagulation management and the surgeon is encouraged.

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Table 1

Perioperative Bridging Recommendations Based on American College of Chest Physicians Guidelines[19]

Bleeding Risk	Thromboembolism Risk		
	High	Moderate	Low
High	Bridge	No bridge	No bridge
Low	Bridge	Consider bridging	No bridge

Table 2

Thromboembolism Risk Stratification for TSOAC-Approved Indications Based on American College of Chest Physicians Guidelines[19]

Thromboembolism Risk	Anticoagulation Indication	
	Atrial Fibrillation	VTE
Low	$CHADS_2 \leq 2$ (assuming no recent stroke or TIA)	Single VTE > 12 months ago and no additional risk factors
Moderate	$CHADS_2 = 3–4$	Single VTE (3–12 months ago) or recurrent VTE
High	$CHADS_2 \geq 5$ or stroke/TIA within 3 months	Recent VTE (≤ 3 months ago)

Abbreviations: $CHADS_2$, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (1 point), diabetes mellitus (1 point), prior stroke or TIA (2 points); TIA, transient ischemic attack; TSOAC, target-specific oral anticoagulant; VTE, venous thromboembolism.

Table 3

Higher Bleeding Risk Procedures Based on American College of Chest Physicians Guidelines[19]

Urologic procedures	• Transurethral prostate resection
	• Bladder resection
	• Tumor ablation
	• Nephrectomy
	• Renal biopsy
Cardiac procedures	• Pacemaker or implantable defibrillator implantation
	• Cardiac surgery
Gastrointestinal procedures	• Colonic polyp resection (> 1–2 cm)
	• Liver or splenic surgeries
Orthopedic procedures	• Joint arthroscopy
Other procedures	• Cancer-related surgeries
	• Intracranial surgeries
	• Spinal surgery
	• Reconstructive plastic surgery

Table 4

Recommended Time to Withhold TSOACs Preprocedure[a]

	Low Thromboembolic Risk		Moderate or High Thromboembolic Risk	
	Standard Bleeding Risk	**High Bleeding Risk**	**Standard Bleeding Risk**	**High Bleeding Risk**
CrCl ≥ 50 mL/min	2 days	4 days	1 day	2 days
CrCl < 50 mL/min	4 days	5 days	2 days	3 days

Abbreviation: CrCl, creatinine clearance; TSOAC, target-specific oral anticoagulant.

[a]Adapted from the University of Michigan management guidelines, which are based on FDA-approved prescribing information.