REVIEW ARTICLE

Periprocedural management of patients on oral anticoagulation: focus on regional anesthesia

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KEY WORDS

direct oral anticoagulants, regional anesthesia, vitamin K antagonists

ABSTRACT

The management of anticoagulant medications in patients undergoing regional anesthesia procedures remains an evolving topic. As with all procedures, the goal is to maintain balance between bleeding and thrombotic risks when interrupting oral anticoagulants. In contrast with operating room procedures, in which the blood loss volume is probably the most important concern, for regional anesthesia procedures, it is the location of the bleeding event that takes precedence. For neuraxial anesthesia and deep plexus and peripheral nerve blocks, a lower volume bleed in an enclosed deep noncompressible area can result in transient or permanent neuronal damage. Differences exist between current guidelines for the management of oral anticoagulants, likely due to patient anatomy, practitioner experience, and standardized use of imaging modalities for different procedures.

Introduction An increasing number of patients receive chronic oral anticoagulant (OAC) therapy to mitigate the risk of thromboembolic complications due to atrial fibrillation (AF), mechanical heart valves, or history of venous thromboembolism (VTE). Internists, cardiologists, hematologists, anesthesiologists, and surgeons often care for such patients who need to undergo elective or emergent medical procedures. The balance between the risk of thromboembolism and the risk of bleeding should be carefully maintained and fine-tuned perioperatively in order to maximize benefits and minimize risks.[1,2] This review discusses the commonly used anticoagulants prescribed during the periprocedural period with a focus on appropriate considerations for regional anesthesia. Several societies have recently updated their guidelines on the subject, including the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the European Society of Anaesthesiology (ESA).[3-5]

Oral anticoagulants pharmacology Vitamin K antagonists (VKA), warfarin and acenocoumarol, block the synthesis of the vitamin K–dependent clotting factors (II, VII, IX, and X). Rapidly absorbed from the gastrointestinal tract, their blood levels peak a few hours after administration. As compared to warfarin, which has a long half-life of 36 to 42 hours, acenocoumarol has a shorter half-life of 8 to 11 hours.[6,7] The anticoagulant effect is monitored by the prothrombin time (PT) or target international normalized ratio (INR) values. An INR of less than 1.1 is considered normal in healthy patients; however, some data point towards almost normal coagulation factor levels with an INR close to 2 (30% clotting factor activity).[8]

It should be noted that the INR may not reflect a decrease in all vitamin K–dependent clotting factors simultaneously. When starting or stopping warfarin, the INR value initially mirrors the activity of factor VII (half-life, 6–8 hours), with 5 days being necessary for all coagulation factors to decrease to less than 40% or increase to more than 40%, respectively. Moreover, at the start of warfarin therapy, there is an initial prothrombotic state (conferred by decreases in levels of vitamin K–dependent natural anticoagulation factors protein C and S). Therefore, in patients who need to be rapidly therapeutically anticoagulated with warfarin, a bridging agent may be necessary for the first few days. For most indications, an INR of 2 to 3 is recommended. Patients at high thrombotic risk, such as patients with mechanical mitral valves, older generation aortic mechanical valves (Starr Edwards or ball-in-cage), and mechanical valves who recently had stroke (<6 months) should be maintained at a higher INR of 2.5 to 3.5.

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In the past decade, direct oral anticoagulants (DOACs) have been introduced to the market and have increasingly replaced VKAs for many indications. These include the direct thrombin inhibitor, dabigatran, as well as several anti–factor Xa agents such as: rivaroxaban, apixaban, edoxaban, and betrixaban (TABLE 1). As compared with warfarin, all DOACs have a rapid onset of action and peak serum level achieved within 1 to 4 hours. Moreover, all DOACs have a component of renal excretion, which affects the drugs' half-life. In addition to the traditional indications, factor Xa inhibitors (with the exception of betrixaban) have also been studied in patients with cancer, where they were found to be noninferior in comparison with low-molecular-weight heparin (LMWH).[9-11] All DOACs with their clinical indications and relevant pharmacokinetic properties are presented in TABLE 1.[12-18]

Periprocedural management of oral anticoagulants Periprocedural management of OACs relies on balancing the risk of thrombosis while temporarily stopping the OAC with the risk of bleeding incurred by the medication. While some procedures can be performed continuing the OAC, for most procedures (especially for patients undergoing neuraxial blocks [NBs]), the medication needs to be stopped in advance, as to allow for normalization of the coagulation process. For patients and / or procedures that require temporary interruption of the OAC, the risk of thrombosis could be mitigated through bridging therapy (UFH or LMWH). This is of particular importance in patients on VKAs when long half-lives of VKAs and factors II and X require the OACs to be discontinued more than a few days prior to the procedure.

Procedural bleeding risk assessment Periprocedural bleeding can be frequently categorized into 2 types, major and minor, based on the amount and location of blood loss. Major periprocedural bleeding is defined as a drop in hemoglobin greater than 2 g/dl, or need to transfuse at least 2 units of packed red blood cell, or hemodynamical instability, or bleeding into a critical site.[19] More recently, the International Society on Thrombosis and Haemostasis classified bleeding risk based on a 48-hour periprocedural time frame: 2% to 4% risk of major bleeding was defined as high bleeding risk, and less than 2%, as low bleeding risk.[20] With the exception of procedures at a very high bleeding risk in enclosed spaces (such as intracranial, intrathecal, epidural space, and posterior chamber of the eye), the volume of blood loss is the most important factor contributing to negative consequences in operating room procedures. In contrast, for regional anesthesia techniques, clinically relevant heavy bleeding is only occasionally observed in a small subset of procedures, where a large amount of blood loss may occur in anatomically deep, nonexpandable and noncompressible locations. For example, lumbar plexus blockade has been reportedly associated with rare, yet significant, retroperitoneal bleeding.

More commonly, close proximity of a vital structure causes major concern for regional anesthesia procedures. Such structures include: the spinal cord (spinal anesthesia), spinal nerve and nerve root (epidural anesthesia, paravertebral block), nerve plexus (cervical, brachial, lumbar and sacral plexus block), and nerve (major peripheral nerve such as the sciatic nerve, femoral nerve). In this context, the location of bleeding is more important than the volume of blood loss. Similar to intracranial bleeding, a relatively small bleed can have devastating consequences.[21] Neurological injury due to bleeding is mostly a secondary ischemic event, due to either hematoma compression of a vital structure and / or its feeding vessels, and / or direct injury to the feeding vessels to the vital structure. Another difference between surgery versus regional anesthesia-related bleeding is that patients undergoing regional anesthesia are frequently symptomatic before a critical blood loss occurs. The major differences between typical surgical bleeding, in which volume blood loss is more important, and regional anesthesia bleeding, in which location is more relevant, may explain the major differences in anticoagulation guidelines issued by the American College of Cardiology[19,22] and ASRA.[3,5]

The assessment of the bleeding risk in a particular patient while planning for an invasive surgical procedure should start with the severity of surgical bleeding.[23] Once the risk of surgical bleeding is deemed acceptable, the second step would be determining specific regional anesthesia options with their bleeding risk and planning for mitigation of bleeding, should it occur. As discussed above, NBs are considered high-bleeding-risk procedures by the ASRA Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy (Fourth Edition) (ASRA regional).[3] Also, in the ASRA regional guidelines, superficial easily compressible plexus or peripheral nerve blocks (PNBs) are considered low risk, whereas deep blocks are considered to have a similar bleeding risk to NB[3] (TABLE 2).

There are differences in the Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition) (ASRA pain)[5] and ASRA regional guidelines, with the similar or the same procedure being assessed differently in these 2 publications (TABLE 2).

In addition, rating of bleeding risk is not necessarily linked with guidelines. The ASRA pain guidelines classify epidural steroid injection, sympathetic and paravertebral blocks as intermediate risk procedures, and all PNB as low risk.[21] In contrast, ASRA regional deems NB (including epidural) and deep PNB / plexus blocks (such as paravertebral) as high risk, and only superficial and compressible nerve blocks are ranked as low risk.[3] Despite lower bleeding risk rating for similar procedures, most pain procedures call for

TABLE 1 Oral anticoagulants

Drug	Warfarin	Acenocoumarol	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Brand name	Marevan	Sintrom	Pradaxa	Xarelto	Eliquis	Savaysa	Bevyxxa
Mechanism	Vitamin K antagonist	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Indications	Stroke reduction in valvular and nonvalvular AF	Stroke reduction in valvular and nonvalvular AF	Stroke reduction in nonvalvular AF	Stroke reduction in nonvalvular AF	Stroke reduction in nonvalvular AF	Stroke reduction in nonvalvular AF	VTE prophylaxis in adult patients hospitalized for acute illness
	VTE treatment and prevention	VTE treatment and prevention	VTE treatment and prevention	VTE treatment and prevention	VTE treatment and prevention	VTE treatment and prevention	
	Mechanical valves	Mechanical valves	VTE prophylaxis after hip replacement surgery	VTE prophylaxis after hip replacement surgery	VTE prophylaxis after hip/knee replacement surgery		
Time to peak effect	1.5 h	1–3 h	2 h	2–4 h	1–3 h	1–2 h	3–4 h
Excretion	Hepatic, oxidative metabolism	Hepatic, oxidative metabolism	80% renal	36% renal	25% renal	35% renal	5%–7% renal
Half-life	36–42 h	8–11 h	12–14 h (CrCl >80 ml/min)	8.3 (5–9 h) (CrCl >80 ml/min)	15.1 h (CrCl >80 ml/min)	10–14 h (CrCl >80 ml/min)	19–27 h (normal CrCl)
			15 h (CrCl 50–79 ml/min)	8.7 hours (CrCl 50–80 ml/min)	14.6 hours (CrCl 50–80 ml/min)	8.4 hours (CrCl 50–80 ml/min)	No data for renal insufficiency
			18 h (CrCl 30–49 ml/min)	9 h (CrCl 30–50 ml/min)	17.6 (CrCl 30–50 ml/min)	9.4 (CrCl 30–50 ml/min)	
			27 h (CrCl 15–29 ml/min)	9.5 (CrCl 15–29 ml/min)	17.3 (CrCl 15–29 ml/min)	16.9 (CrCl 15–29 ml/min)	
			30 h (CrCl <15 ml/min)	13.2 (CrCl <15 ml/min)	No data (CrCl <15 ml/min)	No data (CrCl <15 ml/min)	
Monitoring of anticoagulant effect	Required, PT/INR	Required, PT/INR	Not required Specific tests include dilute thrombin time and ecarin clotting time	Not required Specific test: anti-Xa test calibrated for the specific anti-Xa agent			
Reversal agents	Vitamin K	Vitamin K	Idarucizumab	Andexanet alfa	Andexanet alfa	3- or 4- factor PCC	3- or 4- factor PCC
	3- or 4-factor PCC	3- or 4-factor PCC	3- or 4-factor PCC	3- or 4-factor PCC	3- or 4-factor PCC	aPCC (FEIBA)	aPCC (FEIBA)
	Fresh frozen plasma	Fresh frozen plasma	aPCC (FEIBA)	aPCC (FEIBA) Recombinant factor VII	aPCC (FEIBA) Recombinant factor VII	Andexanet alfa (off label)	Andexanet alfa (off label)
Periprocedural bridging	Recommended if high thrombotic risk		Generally not recommended due to short half-lives, predictable pharmacokinetics, and increased bleeding with bridging				
Use	On the decline			On the rise			

Abbreviations: AF, atrial fibrillation; aPCC, activated prothrombin complex concentrate; aPTT, activated thromboplastin time; CrCl, creatinine clearance; FEIBA, factor eight inhibitor bypassing activity; INR, international normalized ratio; PCC, prothrombin complex concentrate; PT, prothrombin time; VTE, venous thromboembolism

longer duration before resumption of oral anticoagulants. These discrepancies between the ASRA pain and ASRA regional guidelines may be explained as follows: pain procedures are usually performed by subspecialty trained physicians (therefore there is less variability of practice) and under direct visualization.

Although the assessment and categorization of bleeding risk in regional anesthesia, especially severe bleeding with clinically relevant consequences, have not yet been established, a systemic approach has been recently proposed and named CIA (critical, intervention, assess).[24] The CIA approach is based on the sum of 3 factors: the proximity of the regional anesthesia location to critical structures, whether an invasive intervention is need in the event of bleeding, and whether identification of bleeding can be quick and easy. Each contributing factor is scored as 0 (if absent) or 1 (if present), with the resultant CIA score ranging from 0 to 3, with 0 as low risk, 1 as intermediate risk, 2 and 3 as high risk for bleeding in regional

TABLE 2 Regional anesthesia procedures and bleeding risk

Guideline	Bleeding risk		
	Low	Intermediate	High
ASRA regional	Superficial and compressible plexus or peripheral nerve blocks	Other procedures based on compressibility, comorbidities, body habitus as well as duration and intensity of anticoagulation	Neuraxial blocks
			Deep and noncompressible plexus or peripheral nerve blocks
ASRA pain	Peripheral nerve blocks	Interlaminar ESI	Spinal cord stimulator placement
	Peripheral joint and musculoskeletal injection	Transforaminal ESI	Dorsal root ganglion stimulation
	Trigger point injection, including piriformis	Cervical facet block	Intrathecal catheter and pump implant
	Thoracic and lumbar facet block	Sympathetic blocks	Vertebral augmentation/ kyphoplasty
	Sacroiliac injection	Trigeminal ganglion block	Percutaneous decompression laminectomy
	Peripheral nerve stimulation and implant	Sphenopalatine ganglion block	Epiduroscopy and epidural decompression
	Pocket revision and implantable pulse generator/intrathecal pump replacement		
CAS	Occipital nerve block	Interscalene block	Deep cervical plexus block
	Superficial cervical plexus	Supraclavicular brachial plexus	Paravertebral block
	Axillary brachial plexus	Infraclavicular brachial plexus	Lumbar plexus block
	Median nerve block	Popliteal sciatic	Quadratus lumborum block
	Radial nerve block	Subgluteal sciatic block	Parasacral sciatic block
	Ulnar nerve block	Transgluteal sciatic block	
	Lateral femoral cutaneous nerve block	Anterior sciatic block	
	Ankle block	Femoral nerve block	
		Rectus sheath block	
		PECS block	
		TAP block	
		Erector spinae blocks	

Abbreviations: ASRA, American Society of Regional Anesthesia and Pain Medicine; CAS, Canadian Society of Anesthesiologists; ESI, epidural steroid injection; PECS, pectoralis nerve; TAP, transversus abdominis

anesthesia specifically.[24] It should be pointed out that, with the introduction of ultrasound, many regional anesthesia procedures can be performed under direct visualization. As such, the risks of venous and arterial puncture have significantly decreased. However, the risk of postoperative neurological deficits remains the same, leading to the assumption that the major risks of perioperative nerve injury may be unrelated to regional anesthesia.[25,26]

Controversy exists as to the bleeding risk classification in regional anesthetic techniques. While the ASRA's regional anesthesia bleeding risk assessment of PNBs is mostly based on anatomical considerations and data from NB, the expert consensus from the Regional Anesthesia and Acute Pain Section of the Canadian Anesthesiologists' Society takes into account the abovementioned CIA score and the absolute number of reported bleeding events for the specific plexus and nerve block discussed.[27] One caveat to this classification is that, since the total number of a specific plexus and nerve blocks performed as compared with the reported cases complicated by bleeding is unknown, the prevalence of bleeding for a certain regional procedure remains debatable. In addition, the level of expertise among proceduralists may vary among different plexus and nerve blocks, for example, an unexperienced proceduralist is more likely to start with transverse abdominal plane block rather than with anterior sciatic nerve block, which further complicates the difficulty in precise prediction of bleeding risk in regional anesthesia.

Nonetheless, the consensus from the Canadian Anesthesiologists' Society is arguably the only available classification specifically focused on PNBs and it recommends ultrasound to be used routinely to prevent complications.[28]

Classification of low bleeding risk according to the Canadian Anesthesiologists' Society Occipital block and superficial cervical plexus block are devoid of serious complications, as bleeding in that location is readily identified, therefore considered low risk. Axillary brachial plexus block, while in proximity to the axillary artery and veins, is an easily compressible site, therefore considered low risk as hematomas have been rarely noted in large studies.[29] Suprascapular as well as upper extremity PNBs (radial, median, and ulnar) are considered to be low risk, as no bleeding complications have been described. Superficial blocks such as lateral femoral cutaneous, infrainguinal fascia iliaca, and

TABLE 3 Periprocedural management of antithrombotics (continued on the next page)

Drug	2018 Interventional Pain ASRA Guidelines			2018 Regional ASRA Guidelines		ESA 2010 guidelines	
	When to discontinue		When to restart	When to discontinue	When to restart	When to discontinue	When to restart
	High and intermediate bleeding risk	Low bleeding risk					
Intravenous heparin	6 h	6 h	2 h	4–6 h before needle placement and catheter removal (normal aPTT documented)	1 h after nontraumatic needle placement and catheter removal	4–6 h	1 h
Subcutaneous heparin 5000 U twice a day	6 h	6 h	2 h for low-bleeding-risk procedures; 6–8 h for intermediate-to-high-bleeding-risk procedures	4–6 h	Immediately	4–6 h	1 h
Subcutaneous heparin 5000 U three times a day	24 h						
Subcutaneous heparin 7500–10000 U twice a day (<20000 U/d)	NA	NA	NA	12 h	NA	8–12 h	1 h
Subcutaneous heparin >10000 U/dose or >20000 U/d	NA	NA	NA	24 h	NA	NA	NA
LMWH Prophylactic dosing • Enoxaparin 30 mg twice a day • Enoxaparin 40 mg daily • Dalteparin 5000 units daily	12 h	12 h	4 h after a procedure with a low risk of bleeding	12 h before needle placement or catheter removal	Single daily dosing • First dose 12 h after needle placement • Second dose 24 h after the first dose • At least 4 h after catheter removal	12 h	4 h
			12–24 h after a procedure with an intermediate or high risk of bleeding		Twice daily dosing • Not recommended with catheter in place • At least 12 h after needle/catheter placement • 4 h after catheter removal		
LMWH Therapeutic dosing • Enoxaparin 1.5 mg/kg daily or 1 mg/kg twice a day • Dalteparin 120 units twice a day or 200 units daily • Tinzaparin 175 U/kg daily	24 h	24 h	4 h after catheter removal if the procedure had a negligible risk of bleeding	24 h	Epidural catheter contraindicated	24 h	4 h
					4 h after catheter removal and at least 24 h after needle placement		
					24 h after a low-bleeding-risk procedure		
					48–72 h after a high-bleeding-risk procedure		

TABLE 3 Periprocedural management of antithrombotics (continued from the previous page)

Drug	2018 Interventional Pain ASRA Guidelines			2018 Regional ASRA Guidelines		ESA 2010 guidelines	
	When to discontinue		When to restart	When to discontinue	When to restart	When to discontinue	When to restart
	High and intermediate bleeding risk	Low bleeding risk					
Warfarin	If on warfarin, stop for 5 d and INR ≤1.2 If not on warfarin, INR ≤1.4	Discontinuation may not be necessary if INR <3	6 h	4–5 d and normal INR	Remove catheter when INR is <1.5 Restart any time after needle placement or catheter removal	INR <1.4	After catheter removal
Dabigatran	4 d if normal renal function 5–6 d if impaired renal function	Shared assessment and risk stratification, a 2 half-life interval discontinuation may be considered	24 h	5 d before puncture, catheter manipulation or removal Alternative graded approach if renal function stable and no additional bleeding risk factors 72 h (CrCl >80 ml/min) 96 h (CrCl of 50 to 79 ml/min) 120 h (CrCl of 30 to 49 ml/min) Caution against neuraxial blocks when CrCl <30 ml/min	6 h after puncture, catheter manipulation or removal If given with catheter in place, wait 34–36 h until removal	For prophylaxis 150–220 mg, contraindicated	6 h
Rivaroxaban	3 d		24 h	3 d before puncture, catheter manipulation or removal	6 h after puncture, catheter manipulation or removal If given with catheter in place, wait 22–26 h until catheter removal	For prophylaxis, 10 mg daily 22–26 h	4–6 h
Apixaban	3 d		24 h	3 d before puncture, catheter manipulation or removal	6 h after puncture, catheter manipulation or removal If given with catheter in place, wait 26–30 h until catheter removal	For prophylaxis, 2.5 mg daily 26–30 h	4–6 h
Edoxaban	3 d		24 h	3 d before puncture, catheter manipulation or removal	6 h after puncture, catheter manipulation or removal If given with catheter in place, wait 22–28 h until catheter removal	NA	NA
Betrixaban	5–6 d	3 d	24 h	3 d before puncture, catheter manipulation or removal Contraindicated if Cr Cl <30 ml/min	5 h after puncture, catheter manipulation or removal If given with catheter in place, wait 72 h until catheter removal	NA	NA

Abbreviations: aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; ESA, European Society of Anaesthesiology; INR, international normalized ratio; LMWH, low molecular weight heparin; NA, not available; others, see TABLE 2

ankle block are easily compressible and the bleeding risk is low.[27]

Classification of intermediate bleeding risk according to the Canadian Anesthesiologists' Society Proximal upper extremity blocks such as interscalene, supra-, and infraclavicular brachial plexus blocks are considered intermediate risk with reported vascular injections in 0.63%, 0.4%, and 0.7%, respectively, of cases in retrospective reviews.[30-32] Retroclavicular brachial plexus block has been recently described and no data are available as to its intravascular puncture risk. Interfascial block such as transverse abdominal plane, iliohypogastric ilioinguinal nerve, serratus anterior, pectoral nerve (PECS), and rectus sheath are superficial; however, complications such as bleeding and hematomas have been reported.[33,34] These blocks are considered intermediate bleeding risk as well as newer blocks for which data are not available (erector spinae block).[28] Intercostal blocks present concerns similar to paravertebral blocks, although there are few reports of hematomas; as such, this block is deemed to be intermediate bleeding risk. Femoral block, despite its superficial nature, was reportedly associated with retroperitoneal hematoma formation in one report and is considered intermediate bleeding risk.[35] Other intermediate-risk lower extremity blocks include adductor canal, sciatic nerve block in most locations (popliteal, transgluteal, subgluteal, and anterior approach), obturator and suprainguinal fascia iliaca; however, evidence-based data are not available.[27]

Classification of high bleeding risk according to the Canadian Anesthesiologists' Society Deep cervical block could result in intravascular injection (vertebral artery, supra, or infrascapular artery) and hematoma could have dire consequences of airway compression.[36] As such, the Canadian Anesthesiologists' Society considers deep cervical block a high-bleeding-risk procedure, despite no complications reported during cervical block in patients undergoing carotid endarterectomy, who are frequently continued on coagulation-altering medications for the procedure.[27] Lumbar plexus block is deeply situated and despite the use of nerve stimulators and ultrasound guidance, hematomas are still occasionally reported especially in patients with multiple passes or on coagulation altering drugs.[37-42] Therefore, lumbar plexus block as well as the parasacral sciatic nerve block are deemed to be high-bleeding-risk procedures due to their proximity to vascular structures.[3,27] Quadratum lumborum is a deep block with a needle aiming to a noncompressible space; this is considered at a high bleeding risk.[43] Paravertebral blocks are generally considered high bleeding risk given the structures (nerves and vessels) present in the space as well as lack of access and compressibility of the space and difficulty in detecting pleural puncture. Though multiple reports have described it as an alternative to NB in patients deemed to be at a high risk of bleeding (either anticoagulated or thrombocytopenic), the guidelines call for the same coagulation status requirement.

Classifying procedures into low, intermediate, and high risk is only one of the facets of bleeding risk assessment. The other component should take into account patient's specific bleeding risk as it relates to comorbidities that might increase bleeding as well as concurrent administration of medications other than OACs that alter coagulation (such as herbal supplements, nonsteroidal anti-inflammatory drugs, or antiplatelet agents). The HAS BLED score is a tool available for quantifying patient bleeding risk, extrapolated from the AF literature. It takes into account several conditions: hypertension, abnormal kidney or liver function, stroke, bleeding history, labile INR, elderly (age >65), drugs or alcohol. For each category, 1 point is assigned (patients with a HAS-BLED score of >3 are considered high risk). When it relates to anticoagulation management, an OAC interruption time may need to be longer when patient's bleeding risk is high even if the procedural risk is considered low.

Thromboembolic risk and bridging

Thromboembolic risk assessment As with traditional surgical procedures, thrombotic risk while interrupting OACs should be quantified. Historically, the risks has been defined as low, intermediate, or high based on a yearly rate of less than 5%, 5% to 10%, or more than 10% of thrombotic events, respectively.[44] Patients' thrombotic risk depends on the indication for OAC. Traditionally, the $CHADS_2$ and CHA_2DS_2-VASc scores have been used in assessing the stroke risk for patients with AF. These scores take into account certain comorbidities, such as congestive heart failure, hypertension, age older than 75 years, diabetes, stroke, vascular disease, age 65 to 74 years, and female sex (each gets 1 point with the exception of age >75 years and stroke, which are assigned 2 points). CHA_2DS_2--VASc scores of 7 to 9, $CHADS_2$ of 5 to 6, or a history of recent embolic stroke (<3 months) place patients at high thrombotic risk. Similarly, patients with mechanical valves (mitral, older aortic valves, stroke / transient ischemic attack <6 months prior) as well as patient with multiple or very recent VTE events (within 3 months), or severe thrombophilias have traditionally been regarded as high risk.

Bridging while on vitamin K antagonists Historically, in order to mitigate thrombotic risk, patients on warfarin requiring temporary interruption have been bridged with heparin or LMWH in the periprocedural period. Patients at low thrombotic risk—AF with CHA_2DS_2-VASc scores of 0 to 4, VTE events more than 12 months prior, or bileaflet aortic valves without risk factors for stroke (low ejection fraction, antiphospholipid antibody syndrome, thrombophilias)—do not require bridging with LMWH or UHF. There are

controversies regarding bridging recommendations for patients in the intermediate thrombotic risk category. Traditionally, the decision for bridging has been left at the discretion of the prescribing provider; however, there is mounting evidence describing an increased surgical bleeding risk in patients bridged with LMWH with little benefit pertaining to protection against thrombosis.[45] In patients with AF at low and moderate thrombotic risk ($CHADS_2$ scores of 0–4), in the BRIDGE trial, no thrombotic benefit was detected for bridging, which was associated with increased rated of minor and major bleedings.[46] Recently, given bleeding concerns, bridging is not endorsed by guidelines published by the American Society for Hematology for patients at intermediate risk for VTE treated with warfarin.[47] Similarly, the PERIOP 2 trial that randomized patients with AF and/or mechanical valves to bridging with dalteparin or interrupting warfarin alone detected no difference in the rates of thromboembolism and bleeding between the 2 groups.[48]

The most commonly used bridging agents for VKAs are subcutaneous LMWHs (TABLE 3). Generally, LMWH is started 48 hours after warfarin discontinuation, with the last dose given at half the dose 24 hours prior to the planned surgery. Recent data suggested that the dose of bridging LMWH may be decreased in the elderly or those with renal impairment as significant anti-Xa activity was present in these patients 24 hours after the last therapeutic dose of LMWH. Intravenous UFH infusion could be an alternative; however, it requires hospital admission with frequent monitoring of activated partial thromboplastin time (aPTT).[3] For patients at risk for VTE, while bridging with a therapeutic-dose LMWH is not generally recommended for the considerations discussed above, different prophylactic (lower dose) regimens of either subcutaneous LMWH or UFH can be prescribed. Considerations for bridging regimens and regional anesthesia are discussed in TABLE 3.

Bridging while on direct oral anticoagulants In contrast with warfarin, DOACs have short half-lives and predictable pharmacokinetics; bridging therapy is generally not required or indicated.[22,49] Moreover, the recently published international multicenter PAUSE (Perioperative Anticoagulation Use for Surgery Evaluation) trial found that in patients with AF, foregoing bridging therapy was safe. In this study, using a standardized protocol for interrupting the DOAC based on procedural bleeding risk generally resulted in less than 2% major bleeding rates and less than 1% stroke rates.[50] At this time, there are no data available as to whether considerations for no bridging can apply to DOACs in patients at high VTE thrombotic risk, such as those with very recent thrombosis or active cancer.

Temporary interruption of oral anticoagulants in preparation for regional anesthesia

Vitamin K antagonists Warfarin and acenocoumarol are the most commonly used VKAs in the United States and Europe, respectively. Differences exist between their pharmacologic properties and between the ASRA pain, ASRA regional (TABLE 3), and the recent Canadian Society bleeding risk stratification.

It is widely accepted in clinical practice (as well as supported by guidelines and current evidence) that low risk bleeding procedures (whether PNBs or interventional pain procedures) may be performed safely while continuing the VKA with therapeutic INR less than 3 after careful consideration of existing comorbidities with specific weighing the risk of bleeding versus thromboembolic events.[5,27,51,52]

For procedures deemed to be at a high bleeding risk, such as NB (spinal and epidural), deep plexus (lumbar, sacral), or deep PNBs (paravertebral), warfarin is required to be discontinued for 5 days and acenocoumarol, for 3 days. In addition, a normal INR of less than 1.1 or at least an INR of less than 1.4 (the 2010 ESA guidelines) should be documented prior to procedure[44] as 7% of patients will still have an INR of less than 1.5 after off warfarin for 5 days.[53] For those patients with an INR of 1.5 to 1.9 the day prior to surgery, administration of oral vitamin K (as low as 1 mg) could further lower the INR to 1.4 in greater than 90% of cases.[54] For patients at high thrombotic risk, a bridging regimen as described above may be recommended (TABLE 3).

Decision-making for intermediate risk interventional pain procedures or PNBs remains a grey zone. A conservative approach would be to follow recommendations for high-bleeding-risk procedures. However, using an ultrasound guidance technique by an experienced provider would allow more leeway when deciding to proceed with some anticoagulant activity on board. Similarly, patients undergoing low risk procedures could, in fact, be at an increased risk if they are elderly, have a high HAS-BLED score, or take other medications that affect hemostasis (herbal medication, nonsteroidal anti-inflammatory drugs, or antiplatelet agents).

Pearls in periprocedural management of warfarin

1 Activity level of vitamin K–dependent clotting factors (II, VII, IX and X) at 40% or greater are considered adequate for hemostasis,[55] whereas activity levels of less than 20% are associated with bleeding.[56]

2 The INR has be to regularly monitored, due to narrow therapeutic index and wide variation among patients due to a variety of factors (eg, genetics, diet).[57]

3 Given the mechanism of action, while warfarin's half-life is important, its periprocedural management relies also on its effect on protein synthesis and half-lives of factors II, VII, IX and X.

4 There is an initial (first several days) dissociation between INR values and the degree of anticoagulation or hemostasis, as INR reflect mostly factor VII activity levels.

5 Approximately 5 days are necessary for all vitamin K–dependent coagulation factor activity to increase to more than 40% and the INR to normalize (required for normal hemostasis especially for high-bleeding-risk procedures such as NBs)
6 NB can be performed within 24 hours of warfarin administration without checking INR (as long as only one dose was given). Similarly, postprocedurally, a catheter can be removed within 24 hours of warfarin administration without checking an INR.
7 If patients require a bridging regimen, LMWH or UFH are discontinued or restarted postprocedurally, as per TABLE 3.
8 The resumption of warfarin may occur as soon as postoperative hemostasis has been achieved. Patients who require perioperative bridging are frequently restarted on bridging until INR is therapeutic for 48 hours (TABLE 3).

Direct oral anticoagulants While the DOACs are generally safe as far as the bleeding profile is considered, the relative risk associated with DOAC as compared with warfarin in regional anesthesia has not been systemically studied. Considerations for the management of DOACs prior to and after regional procedures as recommended by ASRA pain, ASRA / ESA regional, mostly extrapolated from the existing data on major bleedings such as hemorrhagic strokes and gastrointestinal bleeding, are detailed in TABLE 3.

Pearls in periprocedural management of direct oral anticoagulants

1 DOACs have short half-lives, therefore, in contrast to warfarin, they only need to be stopped a few days prior to the regional anesthesia and pain procedures.
2 DOACs are generally not bridged with LMWH or UFH, given their short interruption times, as well as concerns with increased bleeding with bridging.
3 All DOACs have some degree of renal excretion; as such, knowledge of the patient's renal function (creatinine clearance rather than creatinine level) as well as its impact on the drug's half-life is necessary when a tailored approach is desired for performing a regional procedure.
4 Differences exist between recommendations for DOAC management from the ASRA regional as compared with ASRA pain or the ESA guidelines.[3,5] However, there is a consensus regarding the discontinuation of DOACs for 5 half-lives prior to high-bleeding-risk procedures (see section on warfarin management), as less than 3% of residual anticoagulant effect remains.[5]
5 Low risk bleeding procedures such as compressible PNBs, performed by skilled providers and under ultrasound guidance (if applicable) could be performed without stopping the DOAC or after observing a 2 half-life interruption period, which would provide a reasonable balance between thrombosis protection while having approximately 25% residual anticoagulant on board.[5] Similarly, it is prudent for patients at a moderate / high risk of bleeding undergoing low- / moderate-risk procedures to observe a longer interruption period (5 half-lives) as recommended by the ASRA regional guidelines.
6 Recommendations from the ASRA regional guidelines regarding DOAC management err towards the conservative side, given their novelty, lack of experience, and scarcity of safety data as pertaining to regional procedures with them as compared with warfarin,
7 As compared with warfarin therapy, in which bleeding can be easily treated without major side effects, reversal agents for DOACs do not exist for all drugs, they have been recently made available on the market, and their use is not devoid of serious side effects.
8 Standard coagulation testing is not routinely performed or recommended prior to surgical procedures or regional anesthetics, which is one of the advantages of DOACs over VKAs. However, there are clinical situations in which clinicians do need to know with certainty whether an anticoagulant effect is present. The aPTT could be a qualitative indicator signaling presence of dabigatran; a normal aPTT excludes above-on therapy levels of dabigatran but does not exclude presence of therapeutic levels of the drug.[58,59] The PT is not affected by apixaban. However, a normal PT excludes above on-therapy levels of rivaroxaban and edoxaban but not on-therapy levels of rivaroxaban or above on-therapy levels of edoxaban at trough.[58-60]
9 A direct measurement of the DOAC activity is not widely used in clinical practice as tests are expensive, have long turnover times, and are not readily available in every laboratory. Moreover, the lowest level at which a surgical or invasive procedure can be safely performed is not known, but most recommendations point towards a cutoff of less than 50 ng/ml.[61] The dilute thrombin time and ecarin clotting test correlate linearly with dabigatran activity. Similarly, the activity of factor Xa inhibitors is ideally measured using an anti-Xa assay calibrated for the specific anticoagulant. If available, they could guide clinical decisions in patients needing regional procedures when less than 5 half-lives have passed since the last dose of DOAC and a regional procedure is desired or an inadvertent administration of the DOAC occurred in the presence of an indwelling epidural catheter.[3,62-64]

Urgent or emergent interventions: reversal of oral anticoagulation While regional procedures are generally elective, occasionally, NB may be desired in patients at a very high risk for general anesthesia. Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid are helpful in minimizing bleeding. Knowledge of options for reversal of commonly used OACs is necessary and could be especially useful when bleeding complications occur with inadvertent administration of OACs very close to neuraxial puncture.

The action of VKA could be countered by administration of vitamin K. The administration of vitamin K in a dose of 2.5 mg orally or intravenously (higher risk of anaphylaxis) can lead to normalization of the INR within 18 to 24 hours. Reversal of VKAs can be rapidly achieved with the administration of fresh frozen plasma (FFP) at rates of 15 ml/kg. The infusion of FFP, nonetheless, takes time and is associated with significant volume load that could be concerning in patients with compromised cardiopulmonary status. Moreover, given the short half-life of factor VII, FFP should be administered every 6 to 8 hours in order to maintain an appropriate level of coagulation factors. In addition to volume overload, patients receiving high volumes of FFP could be at risk for transfusion-associated acute lung injury. Recent advancements allow for rapid and efficient reversal of warfarin effect (within 30 minutes) following the administration of prothrombin complex concentrates (3 or 4 factor PCC). The dose of PCC is calculated based on the INR level and the factor IX content of the product. Factor IX in doses of 25, 35, and 50 U per kilogram of body weight should be administered for INRs of 2 to 4, 4 to 6, and more than 6, respectively. The advantage of PCC-mediated reversal of warfarin effects is its rapid effect, fast preparation, and small volume. However, at doses of more than 25 U/kg, there is a prothrombotic tendency directly proportional with the dose.

The need for DOAC reversal is rare due to short half-lives, and reversal should be considered only under emergency or life-threatening bleeding circumstances. There are no readily available point-of-care laboratory studies to guide the initiation or monitoring of reversal effects. These are a composite decision based on clinical scenario, pharmacodynamics, and laboratory tests.[19]

There are several options for addressing bleeding in the setting of dabigatran use. Hemodialysis is an option, specifically in patients in whom procedures or the consequences of bleeding are not immediate. When emergent reversal is needed, idarucizumab (Praxbind), a monoclonal antibody and the specific antidote for dabigatran, is the first-line treatment administered intravenously at the dose of 5 g divided in 2 vials. It leads to almost complete reversal of dabigatran action with a low risk of prothrombotic events.[65,66] Occasionally, a second idarucizumab dose is needed, if bleeding and / or a prolongation of clotting time recur within 24 hours of reversal, mostly due to redistribution of dabigatran from the extravascular space into the blood vessels.[67,68] In the absence of idarucizumab, an activated PCC such as factor VIII inhibitor bypassing activity in a dose of 50 to 80 IU/kg, 3- or 4-factor PCC in a dose of 25 to 50 U/kg, or recombinant factor VII are viable options for urgent reversal.[69]

For anti-Xa inhibitors, hemodialysis is not an option (high degree of protein binding). Andexanet alfa (Andexxa) has been approved as an antidote for rivaroxaban and apixaban associated bleeding. Andexanet is a decoy Xa protein that binds the anti-Xa, reversing its anticoagulant effect.[70,71] It is administered in a high or low dose, considering the dose of anticoagulant as well as the timing elapsed since the last dose. Andexanet should be reserved for treatment of life-threatening and neuraxial bleeding due to rivaroxaban or apixaban, given its cost as well as a high risk of thrombotic events. The Food and Drug Administration black box cautions as to a high risk of myocardial infarction, strokes, arterial, and thromboses as well as sudden death with administration of andexanet.[72] It is suggested to use 4-factor PCC 2000 U as an alternative when andexanet is not available.[69] Bleeding related with betrixaban and edoxaban could be reversed with off-label high-dose andexanet or 2000 U of 4-factor PCC.[69] Other options for all anti-Xas include recombinant factor VIIa (90 μg/kg) and aPCC (factor VIII inhibitor bypassing activity) can be used at 90 to 100 IU/kg intravenously, albeit with an increased thrombotic risks.

Current status and future directions The evaluation of patient overall health condition and past medical history is the critical step to allow providers to stratify the patient's periprocedural thrombotic and bleeding risk. Assessing thrombotic risk is a critical step in periprocedural management of VKA; however, all current recommendations and data support a no-bridging approach for the DOACs regardless of thromboembolic risk.

There is a significant amount of clinical data and pharmacodynamic reasoning backing up the current ASRA pain and ASRA regional guidelines, but there are also many unknowns. As such, clinicians should use the guideline in a more fluid rather than rigid way in conjunction with specific clinical scenarios, weighing risks and benefits. For example, the 2010 ESRA guideline specifically provided guidelines on DOACs at prophylactic doses, and recommended these to be held for 2 half-lives before an invasive procedure. This 2 half-lives requirement is consistent with the ASRA regional recommendation for catheter removal during incidental DOAC administration in the presence of an indwelling catheter. Currently, DOACs are deemed incompatible with any indwelling catheters based on limited clinical data, yet the removal of a catheter only calls for 2 half-lives rather than the 5 half-lives required for the placement of NBs. With accumulating clinical data, one would expect sufficient evidence-based knowledge to back up a differential management of patients on prophylactic as compared with therapeutic doses of DOACs.

Less data are available on the safety of various types of PNB than for NBs, which have a much longer history of clinical application. Nonetheless, it is clear that nerve injury in PNB is not the same as in NBs when it comes to bleeding around the neuronal tissues. While bleeding into a neurovascular sheath may result in significant

decreases in hematocrit levels, the expandable nature of peripheral site may decrease the chance of irreversible neural ischemia.[3] Significant blood loss, rather than neural deficits, may be the most serious complication of non-neuraxial regional techniques in the anticoagulated patient. While hemorrhagic complications following the deep plexus / deep peripheral techniques, particularly in the presence of antithrombotic therapy, are often serious and a source of major patient morbidity, most complications occurred in earlier cases with less visualized techniques such as trans-arterial for axillary brachial plexus block, with paresthesia technique and without imaging modalities such as ultrasound or fluoroscopy.[27] This could be one of the reasons why epidural anesthesia is considered intermediate risk of bleeding in the ASRA pain guidelines, as the standard of care in pain practice for epidural injection is under direct imaging-guided visualization, while in the ASRA regional guidelines, it is classified as high risk of bleeding as epidural anesthesia is mostly performed by the blind technique using body landmarks.

Although the current ASRA regional guidelines are focused on NB, they do recognize the difference between central and peripheral regional anesthesia and does allow room for adjustment based on clinical judgement for PNBs. In the authors' opinion, before a universal bleeding risk guideline specifically for PNB is made available by major governing agencies, an institution-specific guideline can be adopted as the interim, taking into consideration not only the ASRA regional guidelines, but also the local factors in a specific institution, including but not limited to regional anesthesia expertise levels of proceduralists, history of bleeding prevalence for each plexus and nerve block, and if imaging guidance is readily available. This small-scale guideline based on institutional evidence will help maintain a balance between observance of ASRA guideline principles, taking advantage of the uniqueness of PNB as compared to NB, and optimization of care in clinical practice.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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