MAYO CLINIC

Funambulism and the Art and Science of Periprocedural Anticoagulant Management

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Removing the anticoagulant "safety net" from a patient requiring an invasive procedure must be a deliberate decision that balances the twin goals of hemostasis and thrombus prevention. Indeed, it can feel like traversing a tightrope between 2 tall buildings, with the gravity of the procedure-specific bleeding risk on one side, and on the other, the patient-specific thrombotic propensity. And yet, these anticoagulant interruptions are common practice in medicine today. It is estimated that 6 million patients in the United States receive long-term anticoagulation, and approximately 10% of these patients require anticoagulant interruption each year for an invasive procedure.[1,2] This statistic amounts to a large number of bridges to cross for patients and physicians alike requiring this form of management.

Although there have been few randomized clinical trials of periprocedural anticoagulant management, there are a number of observational studies that can guide clinicians caring for patients taking warfarin. These studies have served as the basis for guideline statements regarding the evaluation and step-by-step management of patients with various indications for warfarin therapy.[2] The introduction of low-molecular-weight heparin (LMWH) into this practice ushered in an era of aggressive anticoagulant "bridging" for all patients taking warfarin, regardless of either the indication or the procedure being pursued. Over time, it became clear that the general mantra of "stop the clot at all costs" was perhaps too aggressive. A more judicious approach was subsequently adopted once it became apparent that thrombotic events were infrequent and the use of bridging LMWH clearly increased major bleeding events. Where warfarin is concerned, bridging LMWH is now reserved for those patients with the highest risk of thrombosis. This population includes patients with a nonbileaflet mechanical cardiac valve prosthesis, a mechanical valve prosthesis in nonaortic locations, or a bileaflet aortic valve mechanical prosthesis in those with risk factors such as prior stroke/thromboembolism, intracardiac thrombus, or atrial fibrillation. For patients with nonvalvular atrial fibrillation, bridging therapy is reserved for those with a history of stroke/thromboembolism or known intracardiac thrombosis. This general notion is supported by the BRIDGE trial, which found that in patients randomized to LMWH bridging therapy, an excess of bleeding outcomes without improved thromboembolic outcomes occurred in those with nonvalvular atrial fibrillation.[3] For venous thromboembolism indications, bridging LWMH therapy is used for patients with an acute or subacute thrombosis occurring within the preceding 3 months if surgical treatment cannot feasibly be delayed. In general, the risk of thromboembolism during the postoperative period is approximately 1% regardless of the indication for anticoagulation.[4] Low-molecular-weight heparin bridging will increase the periprocedural rate of major hemorrhage by approximately 1%. A risk stratification tool can be useful to identify those individuals at greatest risk for postoperative bleeding.[5] Hospitalization with intensive periprocedural anticoagulant management does not reduce thromboembolic events and is associated with increased bleeding complications, likely due to overaggressive postoperative heparin reinitiation.[6] In order to ensure prompt and complete drug metabolism by the time of the invasive procedure, the use of LMWH should be restricted to patients with creatinine clearance values of 30 mL/min or greater. For patients with severe chronic kidney disease, intravenous unfractionated heparin would be the preferred bridging agent.

The approval and use of direct oral anticoagulants (DOACs) have increased the complexity of decision making and management. Prescription of these agents has been impressive, with each having annual sales exceeding $1 billion. For the indication of nonvalvular atrial fibrillation, more than 60% of new prescriptions are for a DOAC. Similar trends for

Mayo Clin Proc. ■ August 2017;92(8):1176-1178 ■ http://dx.doi.org/10.1016/j.mayocp.2017.06.011
www.mayoclinicproceedings.org ■

venous thromboembolism treatment have emerged. Currently, the initiation of anticoagulant therapy, apart from the indication of mechanical heart valve prosthesis, begins with an inventory of which DOAC to initiate, rather than considering whether warfarin would still be a reasonable choice. As such, the current periprocedural management of anticoagulants now encompasses DOACs as well as warfarin. As with warfarin, there are no randomized trials specifically addressing the best management of DOAC therapy during the periprocedural period. And yet, there are a growing number of observational studies that help guide management and form the basis of societal guidelines.[2,7-10] In settings in which the periprocedural thromboembolism rates are very low, the general approach to managing the DOAC class during these interruptions is one of judicious anticoagulant withdrawal and reinitiation (Table). For the DOACs, full therapeutic anticoagulation is achieved within 1 hour of reinitiation of the drug. The lack of US Food and Drug Administration–approved reversal agents, with the exception of idarucizumab (Praxbind), underscores the need for caution with postoperative anticoagulation reinitiation. Low-molecular-weight heparin bridging has not been found to improve periprocedural outcomes for patients taking this class of anticoagulant and, as such, should be avoided for most patients.

An interesting twist in periprocedural anticoagulant management is the realization that there is a relatively large and growing list of procedures for which anticoagulants do not need to be interrupted.[11] The identification of these procedures further limits the thromboembolic risk such that anticoagulants can be continued while maintaining an acceptably low risk of major bleeding. In the current issue of *Mayo Clinic Proceedings*, Yui et al[12] add further to this list with their large retrospective cohort of patients undergoing arthrocentesis and joint injection procedures. In this study, 483 consecutive patients underwent 1050 procedures without discontinuing DOAC therapy. Bleeding events were recorded up to 14 days after the procedure. More than 20% of patients were simultaneously receiving antiplatelet in addition to DOAC therapy. Remarkably, no bleeding complications were noted.

The periprocedural anticoagulant management of patients requiring an invasive procedure

TABLE. Summary of Studies of Periprocedural Management of Direct Oral Anticoagulants and Observed Outcomes

Drug	Study/sample NVAF trials	No. of patients	Interruption		Major procedures (%)	Major bleeding (%)	Thromboembolism (%)	Death (%)
			Preop	Postop				
Apixaban[7]	ARISTOTLE	1775	No Interruption		10.2	1.58	0.40	1.37
	ARISTOTLE	2904	2-7 d	2-8 d	10.2	1.65	0.31	1.04
Dabigatran[8]	RE-LY	1546	Low bleeding risk: 24 h High bleeding risk: 2-5 d	Once hemostasis achieved	12.6	5.1	1.5	0.5
Edoxaban[9]	ENGAGE AF	4077	0-3 d	Once hemostasis achieved	NA	30 mg: 2.6 60 mg: 3.6	30 mg: 0.9 60 mg: 0.7	30 mg: 1.5 60 mg: 1.5
	ENGAGE AF	3116	4-10 d	Once hemostasis achieved	NA	30 mg: 1.2 60 mg: 1.0	30 mg: 0.9 60 mg: 0.5	30 mg: 1.0 60 mg: 1.2
Rivaroxaban[10]	ROCKET AF	2165	≥3 d	Once hemostasis achieved	18.0	0.99	0.3	0.17

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF = Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; NA = not available; NVAF = nonvalvular atrial fibrillation; Postop = postoperative; Preop = preoperative; RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy; ROCKET AF = Rivaroxaban Versus Warfarin in Acute Ischemic Stroke With Atrial Fibrillation.

may thus be a challenging one for the health care professional and is not without the risk of bleeding, thrombosis, or both for the patient. Such periprocedural anticoagulant management benefits from a clearly defined, stepwise approach that includes identifying the date and the bleeding risk of the procedure, the route and rate of anticoagulant metabolism, and whether bridging LMWH is indicated in the case of warfarin.[2,11] These steps, often referred to as the "front door," are relatively straightforward. The complicated decision making involves the "back door" reinitiation of anticoagulants once the procedure is completed. A simple rule of thumb is to wait at least 48 hours after a major procedure before restarting full-dose anticoagulants to avoid a major bleeding event.[5] If a major bleeding complication occurs, it paradoxically increases the risk of thromboembolism whereby all anticoagulants must be stopped for a period of time. During this anticoagulant "time out," the risk for thromboembolic disease is high because of a number of factors including blood product usage, elevated acute-phase reactants such as von Willebrand factor, fibrinogen and platelets, and the now unopposed thrombotic propensity for which the patient was initially prescribed anticoagulant therapy. Judicious reintroduction of anticoagulants may thus reduce thromboembolic outcomes.

The acrobatics associated with periprocedural anticoagulant management can be a dizzying "Wallenda" experience. The successful balancing of warfarin and LMWH during these procedures requires considerable thought and diligence to avoid the risks of either bleeding or thromboembolic complications. The US Food and Drug Administration approval of 4 new anticoagulant agents further adds to this complexity in decision making and management. The identification of those low-risk procedures for which anticoagulant therapy can be continued unaltered without incurring an increased risk for bleeding—as persuasively shown by Yui et al[12] when joint aspiration and injection are undertaken—thus clarifies these management uncertainties and advances this field.

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Mayo Clin Proc. ■ August 2017;92(8):1176-1178 ■ http://dx.doi.org/10.1016/j.mayocp.2017.06.011
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