More than 2.5 million Americans are chronically anticoagulated for indications including venous thromboembolism (VTE), mechanical heart valve(s), or atrial fibrillation (AF). Each year, ~10% of these patients require temporary interruption of anticoagulation for an invasive procedure. Defining the most appropriate management strategy for these patients requires an assessment of the periprocedural risk of thromboembolism and major hemorrhage. Bridging therapy is a recent term used to describe the application of a parenteral, short-acting anticoagulant during the interruption of warfarin. In this Clinician Update, we outline a systematic approach to defining the appropriate periprocedural strategy for anticoagulation management.

**Case 1**
A 78-year-old man is scheduled for elective colonoscopy with polypectomy next week. He is receiving chronic warfarin for stroke prevention in paroxysmal AF. He has no prior history of stroke, diabetes mellitus, or heart failure. He is treated with metoprolol both for hypertension and rate control. His international normalized ratio (INR) is well controlled on a stable warfarin dose, and he has no history of major bleeding.

**Case 2**
A 66-year-old woman was diagnosed with a first life-time right femoral-popliteal DVT 6 weeks ago. She is currently fully anticoagulated with warfarin. As part of her general medical examination, she is found to have ovarian cancer limited to her right ovary without obvious metastases. She is scheduled for total abdominal hysterectomy with bilateral oophorectomy in 5 days. Her INR is 2.2, and her creatinine clearance is 60 mL/min.

**Systematic Approach to Anticoagulants**
There is no universal strategy for periprocedural anticoagulation for patients on chronic warfarin therapy. However, a stepwise approach can be useful (Figure 1). In urgent/emergent settings, there is neither time nor opportunity for “bridging” therapy. Warfarin can be reversed with fresh-frozen plasma and parenteral vitamin K.

If the procedure is deemed elective, then the next step is to determine whether anticoagulant discontinuation is necessary. A growing list of procedures may be safely performed without anticoagulation interruption (Table 1). For these procedures, the intensity of warfarin anticoagulation is usually reduced to the lower limit of the therapeutic range.

If oral anticoagulants must be stopped, then the patient-specific thrombotic risk should be assessed to determine whether bridging therapy is required. Low-risk patients not requiring bridging therapy include the following: AF with CHADS-2 score ≤2 and no previous thromboembolism or intracardiac thrombus; bileaflet mechanical aortic valve prosthesis in sinus rhythm with no previous thromboembolism; and VTE occurring beyond 3 months in the absence of active cancer. For these patients, warfarin is stopped 4 to 5 days before the anticipated procedure. Normalization of the INR is confirmed on the morning of the procedure. Postprocedural warfarin is reinitiated on postoperative day 0 as long as hemostasis has been achieved and the patient is able to take oral medications. Postoperative variables to consider when reinitiating warfarin include the need and timing of additional surgery, administration of interacting drugs including antibiotics, and reduced nutritional intake. Consider increasing the frequency of INR monitoring. In addition, appropriate mechanical and pharmacological VTE prophylaxis should be
implemented until the patient is fully anticoagulated.

The ongoing National Institutes of Health–funded Bridge Trial will assess the safety and efficacy of bridging therapy with low molecular weight heparin (LMWH) in the setting of atrial fibrillation. This trial is poised to enroll 3626 patients with an anticipated completion date in 2014 or 2015. It is anticipated that this trial will answer the question whether AF patients with CHADS2 score of 3 to 4, but no previous stroke or thromboembolism, require bridging therapy.

When the thromboembolic risk is deemed to be moderate to high, bridging therapy with parenteral anticoagulants is justified. If feasible, LMWH given subcutaneously in the outpatient setting is preferred for patient convenience, safety, and cost. In patients with severe renal impairment (creatinine clearance 15–30 mL/min; stage IV chronic kidney disease), LMWH dose reduction and anti-Xa monitoring should be performed. For patients with stage V chronic kidney disease, intravenous unfractionated heparin should be used for this purpose. After warfarin discontinuation, a daily therapeutic dose of LMWH is initiated once the INR falls below the therapeutic range.

In patients with a history of heparin-induced thrombocytopenia, heparin products should be avoided. Alternatives
include short-acting direct thrombin inhibitor therapy such as argatroban, lepirudin, or bivalirudin. Desirudin might be particularly attractive because it can be given subcutaneously and allows outpatient management. Fondaparinux is frequently used for patients with heparin-induced thrombocytopenia but is problematic as a bridging agent given its long elimination half-life (17–21 hours).

In general, the periprocedural rate of bleeding is 2-fold higher than the risk of thrombosis (Tables 2 and 3). Bleed MAP is a recently developed risk assessment tool for defining periprocedural bleeding rates. This tool assigns 1 point for each risk factor: history of previous bleeding (Bleed), mechanical heart valve (M), active cancer (A), and low platelets (P; ≤150 000/μL). Although not yet prospectively validated, this tool offers an estimate of bleeding risk based on clinical variables and is the only score system currently available for periprocedural use.

### Recommendations for Case 1
Warfarin is stopped 5 days before the colonoscopy with polypectomy. Given the relatively low thromboembolic risk, this patient would not be bridged with LMWH either before or after the procedure. Warfarin would be reinitiated on the same day as the procedure once hemostasis is adequately achieved. In addition, it is our practice to confer with the proceduralist to make sure that the procedure was uncomplicated and that warfarin reinitiation is safe.

### Recommendations for Case 2
Warfarin is stopped 5 days before the colonoscopy with polypectomy. An inferior vena cava filter, however, would not be indicated. Warfarin would be discontinued now (5 days before surgery), and LMWH would be started tomorrow at a therapeutic once daily dose. The last dose of LMWH would be given 24 hours before surgery at half the calculated daily dose. An INR would be obtained on the morning of surgery. Postoperatively, aggressive pharmacological and mechanical DVT prophylaxis would be initiated once hemostasis is ensured. Therapeutic heparin would be withheld for at least 48 hours postoperatively to reduce the risk of bleeding. Warfarin would be reinitiated (without a loading dose) once hemostasis is achieved, provided that no potential procedures are anticipated in the near future.

### Novel Anticoagulants and Bridging
Dabigatran etexilate (Pradaxa) is an oral direct thrombin inhibitor approved by the US Food and Drug Administration for stroke prevention in nonvalvular AF. The time to peak anticoagulant effect is ~1 hour, and the drug half-life is ~15 hours, with elimination principally through the kidney (80%). Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor that is also approved by the US Food and Drug Administration for stroke prevention in nonvalvular AF and VTE prophylaxis following major joint replacement surgery. Rivaroxaban is metabolized by the liver (33%) and excreted by the kidney (66%). Elimination half-life is between 7 and 11 hours.

Our approach to the periprocedural management of patients receiving either dabigatran or rivaroxaban therapy is conservative relative to the manufacturer’s recommendations for several reasons. First, the rate of periprocedural thromboembolism is low (1%). Second, the onset of both dabigatran and rivaroxaban is rapid (1–2 hours), yet the half-life is long. Third, there is no antidote for dabigatran. Prothrombin complex concentrate has been shown to reverse rivaroxaban in healthy volunteers.

First, the surgery and anesthesia-specific (eg, neuraxial blockade) risk of bleeding must be defined (Figure 2). The proceduralist and anesthesiologist should be aware that the patient is taking a novel anticoagulant. The creatinine clearance should be reestablished to ensure that the dosing is correct. If the procedure is urgent or emergent, then increased bleeding rates should be anticipated and weighed against the consequences of procedure deferral. Mechanical interventions for hemostasis include suture, hemoclip, pressure application, coiling, cautery, and topical thrombin. For excessive bleeding, the use of hemo-static agents such as prothrombin com-

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**Table 2. Periprocedural Risk of Thromboembolism and Bleeding in Mechanical Heart Valves**

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Aortic</th>
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<td>?</td>
<td>?</td>
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<tr>
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<td>1.2</td>
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</table>

**Table 3. Periprocedural Risk of Thromboembolism and Bleeding in Atrial Fibrillation, Venous Thromboembolism, and Vascular Bypass Grafts**

<table>
<thead>
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<th>Bleed, %</th>
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<td>5.1</td>
<td>1.3</td>
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plex concentrate, Factor Eight Inhibitor Bypass Activity or recombinant factor VIIa must be weighed against the risk of thrombotic complications.21,22

For elective procedures, the first step in managing these novel anticoagulants is to assess the creatinine clearance. In patients with creatinine clearance ≥50 mL/min, we recommend discontinuing anticoagulation 4 to 5 half-lives before surgery. For patients with creatinine clearance <50 mL/min, we would extend the time of discontinuation by 24 hours. For surgeries with high bleeding risk, a normal preoperative aPTT or thrombin time provides a sensitive measure of circulating dabigatran. Assays useful to assess complete rivaroxaban clearance are not yet validated. aPTT indicates activated partial thromboplastin time; DVT, deep vein thrombosis.

Figure 2. Bridging algorithm for dabigatran. Consider alternative anticoagulants during the postoperative period when risk of bleeding is high or if postoperative bleeding occurs. "Note, aPTT and thrombin time provide a sensitive measure of circulating dabigatran. Assays useful to assess complete rivaroxaban clearance are not yet validated. aPTT indicates activated partial thromboplastin time; DVT, deep vein thrombosis.

in the near future, we suggest the use of a conventional anticoagulant therapy that can be reversed if necessary.

Periprocedural outcomes for 4591 patients with nonvalvular atrial fibrillation randomized to dabigatran (110 mg or 150 mg BID) or warfarin undergoing invasive procedures have recently been provided by the RELY investigators.23 Dabigatran was discontinued on average 2 days prior to the procedure compared to 4 days for warfarin. Timing of postprocedural reinitiation was determined by the patient’s care provider. Thirty day bleeding rates did not differ by anticoagulation allocation (3.8% [dabigatran 110 mg], 5.1% [dabigatran 150 mg] and 4.6% [warfarin]) but in general were 2 fold higher than previously reported data for warfarin (Table 2). Thromboembolism rates were low at approximately 1% for each group. While this is an important contribution, limitations of this manuscript include: retrospective design, alteration of management strategy midtrial, lack of standardized approach to anticoagulation management (particularly post-procedural re-initiation) and nonstandard definition of "major" procedure. Indeed, of the procedures performed, less than 17% would be consid-
ered major by practicing clinicians. Until further data are available for patients undergoing major procedures, our approach remains conservative.

Furthermore, it is our practice to avoid dabigatran and rivaroxaban in patients with indwelling neuraxial/epidural or deep plexus catheters because of risks of associated hematomas. After removal of neuraxial or deep plexus/peripheral catheter, the first postprocedural dose of these agents should be delayed by 24 hours.

Additional Considerations: Cancer

Patients with active cancer receiving chronic anticoagulation are prone to thrombosis and bleeding complications. Chemotherapy, central line placement, cytopenias, hormone manipulation, interacting drugs, and variable dietary intake add complexity to anticoagulation management. Periprocedural VTE (1.2% versus 0.2%) and major bleeding (3.4% versus 1.7%) are significantly higher in patients with active cancer (n=493) in comparison with those without cancer (n=1589).24 This difference is explained entirely by those patients receiving anticoagulation for cancer-associated VTE. For these patients, we recommend aggressive preoperative bridging therapy with LMWH. The last dose should be half of the total daily dose given 24 hours preoperatively. Postoperatively, LMWH is limited to prophylaxis dosing until complete hemostasis is assured. Therapeutic LMWH is avoided ≥48 hours to reduce the likelihood of major hemorrhage. Many patients with cancer-related VTE are maintained on chronic LMWH.

Disclosures

None.

References


Key Words: atrial fibrillation • deep vein thrombosis • heparin • mechanical heart valve • rivaroxaban • warfarin • dabigatran