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PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY IN CARDIOVASCULAR PATIENTS

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Abstract

Many patients with underlying cardiovascular disease require long-term anticoagulation. The perioperative or periprocedural management of patients who require temporary interruption of anticoagulant or antiplatelet medications is a common and often challenging clinical problem.[1] It requires a fine balance between the risk of thromboembolic events during anticoagulant interruption and the risk of bleeding in the setting of antithrombotic therapy administered around the time of surgery.[2] Interruption of anticoagulation is associated with an increased risk of thromboembolic events.[3] Stratifying patients into thromboembolic risk groups may be helpful in directing anticoagulation management in the perioperative setting. Bridging anticoagulation, generally with low-molecular-weight heparin (LMWH), is often an integral part of perioperative thrombosis risk reduction.[2] Perioperative anticoagulation management varies depending on the indication for anticoagulation and the anticoagulant or antiplatelet agent being used by the patient.

In this article, we review some of the general principles involved with perioperative anticoagulation and discuss the perioperative management of patients taking vitamin K antagonists (VKAs), bridging regimens for anticoagulants and antiplatelet agents, and strategies for managing patients on the newer oral anticoagulants.

Case

A 76-year-old female was evaluated prior to a planned atrial-septal defect repair. Her past medical history is significant for nonvalvular atrial fibrillation, hypertension, a single transient ischemic attack 4 months earlier, and a stable left-ventricular ejection fraction (LVEF) of 38%. She is currently on warfarin for stroke prevention. Surgery is scheduled to take place in 7 days. Part of the goal of this visit is to determine a plan for anticoagulation management around the time of surgery.

General Principles

Interruption of anticoagulation is associated with an increased risk of thromboembolic events.[3] Resulting events, such as stroke, mechanical valve thrombosis, stent thrombosis, and venous thromboembolism (VTE), are often associated with significant morbidity and mortality.[4, 5] Table 1 summarizes mortality data associated with stroke.

There is general consensus that stratifying patients into thromboembolic risk groups may be helpful in managing anticoagulation issues in the perioperative setting. Various groups have proposed thrombosis risk categories despite a lack of randomized controlled trials and validated data.[2, 6] For example, the American College of Chest Physicians (ACCP) has suggested a risk stratification model for patients on warfarin based on their clinical indication for antithrombotic therapy and presence of comorbidities. This model separates patients into high, moderate, and low perioperative thromboembolic risk groups according to their indication for antithrombotic therapy (Tables 2, 3).[2]

Mortality at 1 Year After First Stroke

Age	Men	Women
≥ 40 yrs	21%	24%
40–69 yrs	14–19%	19–20%
>70 yrs	24–25%	22–27%

Table 1. Mortality associated with stroke.[7]

Surgery or procedure-related bleeding risk should also be taken into account in determining anticoagulation strategies. While often manageable, bleeding can result in significant morbidity and mortality.[8] It can also lead to delayed resumption of antithrombotic therapy and an increased risk of thromboembolism.[9] Many cardiovascular surgeries, such as coronary artery bypass and heart valve replacement, are associated with a bleeding risk up to 7.9%.[10]

Finding an optimal balance between bleeding and thromboembolic risk is key to the appropriate perioperative management of antithrombotic therapy. In patients at high risk for thromboembolism, increased bleeding risk associated with anticoagulation is often accepted in exchange for decreased risk of morbidity and mortality associated with thrombotic events. Conversely, in patients at low risk for thromboembolism, anticoagulation and its associated bleeding risk may occasionally be avoided altogether.

Perioperative Management of Vitamin K Antagonist Therapy

Common indications for long-term oral anticoagulation include atrial fibrillation, mechanical heart valve placement, and VTE. Most patients in these categories are currently managed with warfarin, which is a vitamin K antagonist (VKA).[11] Multiple observational studies have suggested an increased risk of significant perioperative bleeding associated with the continuation of VKAs prior to surgery.[12, 13] To decrease bleeding risk, VKAs are generally stopped prior to major surgical procedures.[14]

Warfarin has a half-life of 35–45 hours.[15] It is generally recommended to hold warfarin, starting 5 days before surgery, to allow enough time for normal activity of the vitamin K-dependent

Table 2. ACCP's suggested patient risk stratification model for perioperative thromboembolism.[2]

TIA: transient ischemic attack; $CHADS_2$: Congestive heart failure-Hypertension-Age-Diabetes-Stroke; VTE: venous thromboembolism.

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	Any mechanical mitral valve prosthesis Older aortic valve prosthesis Recent stroke or TIA (within 6 months)	$CHADS_2$ score of 5 or 6 Recent stroke or TIA (within 3 months) Rheumatic valvular heart disease	Recent VTE (within 3 months) Severe thrombophilia
Moderate	Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or TIA, hypertension, diabetes, heart failure, age >75 yrs	$CHADS_2$ score of 3 or 4	VTE within the past 3–12 months Nonsevere thrombophilic conditions Recurrent VTE Active cancer
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0–2 (and no prior stroke or TIA)	Single VTE occurred >12 months ago and no other risk factors

clotting factors to resume.[16] Warfarin may need to be stopped more than 5 days before surgery in the elderly and in patients with an international normalized ratio (INR) >3.0.[17]

To mitigate the risk of thrombosis in patients who discontinue anticoagulation before surgery, anticoagulation should generally be resumed as soon as is reasonably safe. Warfarin has a delayed and gradual onset of anticoagulant activity.[16] In most cases, it is advised to resume warfarin within 12 to 24 hours after surgery, assuming the patient has normal postoperative hemostastis.[2]

Perioperative Thrombosis Risk and Bridging Anticoagulation

Various consensus groups have proposed risk categories to help guide decisions regarding bridging anticoagulation.[2, 6] A strategy of classifying patients into high, intermediate, and low risk for arterial and venous thromboembolism is presented in Table 4. Patients in the high-risk category should receive perioperative bridging anticoagulation. Patients in the low-risk category do not require perioperative bridging. For patients in the intermediate-risk group, the decision for anticoagulation should be made on a case-by-case basis, taking into consideration perioperative thromboembolic and bleeding risk, with and without bridging anticoagulation.[6]

Therapeutic-dose, subcutaneous, twice-daily low-molecular-weight heparin (LMWH) is generally recommended above other agents for bridging anticoagulation.[2] LMWHs have many advantages compared to unfractionated heparin, including an infrequent need for laboratory monitoring and availability for use in the outpatient setting.[18] LMWHs have less interaction with platelets and plasma proteins and are less likely to cause heparin-induced thrombocytopenia.[20, 21]

Table 3. Clinical classification scheme to predict stroke in the setting of atrial fibrillation.[19]

$CHADS_2$ score
Diagnosed **C**ongestive heart failure, current or past (1 point)
Hypertension (1 point)
Age >75 years (1 point)
Diabetes mellitus (1 point)
Prior ischemic **S**troke or TIA (2 points)

The elimination half–lives of common LMWHs such as enoxaparin and dalteparin are approximately 3–5 hours.[22] In patients receiving bridging anticoagulation with therapeutic-dose LMWH, the last dose should be administered 24 hours (approximately 5 elimination half-lives) before surgery or a procedure.[2, 18]

Caution should be used when resuming bridging anticoagulation after surgery. Postoperative anticoagulation should only be started if post-procedural hemostasis is normal. The timing and dose of postoperative anticoagulation is dependent on the nature of the surgery or procedure in combination with the patient's individual risk for thromboembolism and bleeding.[6]

In a study by Douketis et al., bleeding and thromboembolism events were evaluated in 650 patients who underwent a variety of surgeries or procedures.[23] These patients received bridging therapy with LMWH at therapeutic doses. LMWH was initiated at varying times after surgery or procedures based on the anticipated bleeding risk. Patients who underwent low-risk procedures, such as cardiac catheterization, resumed LMWH around 24 hours after the procedure; patients who had moderate-risk surgeries or who had inadequate postoperative hemostasis resumed LMWH 48–72 hours after surgery; and patients who had high-risk surgery were not treated postoperatively with bridging anticoagulation. Overall, the incidence of major bleeding events was 1.0% in the first week after surgery. There were no fatal bleeding events. The risk for arterial thromboembolism was less than 1%.[23] In comparison, as reported by Dunn et al., major bleeding events occurred in 20% of patients after major surgery when LMWH was initiated within 12–24 hours after surgery.[24] In patients who require bridging anticoagulation, and assuming adequate hemostasis, we suggest therapeutic-dose LMWH be resumed approximately 24 hours after minor surgical or invasive procedures and around 48–72 hours after major surgery.

Patients at high risk of VTE and related complications may benefit from insertion of temporary inferior vena cava (IVC) filters around the time of surgery.[25] Current evidence-based guidelines from the ACCP recommend IVC filter placement only in patients with proven VTE if anticoagulation therapy is not possible (e.g., excessive bleeding risk, complication from anticoagulation treatment).[26] We support the use of IVC filters in these settings. There may be additional clinical scenarios in which IVC filter placement is warranted, such as recurrent pulmonary embolism complicated by pulmonary hypertension, or high-risk trauma patients with contraindication for anticoagulation.

Perioperative Antiplatelet Drug Management

Many patients with underlying cardiovascular disease require chronic antiplatelet medications such as aspirin or clopidogrel. Indications for antiplatelet medications are varied — for example, the primary prevention of myocardial infarction (MI), secondary

Table 4. Perioperative thromboembolic risk and bridging recommendations.[2, 6] High risk: 1-year risk of arterial thromboembolism (ATE) >10%, or 1-month risk of VTE >10%; intermediate risk: 1-year risk of ATE between 4–10%, or 1-month risk of VTE between 2–10%; low risk: 1-year risk of ATE 4%, or 1-month risk of VTE <2%.

High Risk: bridging recommended

- Known thrombophilia as documented by a VTE and one or more of the following:
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
  - Factor V Leiden mutation (homozygous)
  - Antiphospholipid-antibody syndrome
- Thrombophilia suggested by recurrent thromboembolic (not atherosclerotic) events
- Thromboembolic event within the preceding 3 months
- Atrial fibrillation with one of the following:
  - $CHADS_2$ score of 5 or 6
  - Rheumatic valvular heart disease
  - Mechanical heart valve
  - Stroke or TIA within the preceding 3 months
  - History of cardioembolism
- Any mechanical mitral heart valve
- Older aortic valve
- Recently placed mechanical heart valve (<3 months)
- Mechanical heart valve and stroke or TIA within the preceding 6 months
- Acute intracardiac thrombus visualized by echocardiogram

Intermediate Risk: bridging should be considered

- VTE within the past 3–12 months
- Atrial fibrillation with one of the following:
  - $CHADS_2$ score of 3 or 4
  - Nonrheumatic valvular heart disease
- Transmural myocardial infarction within preceding month
- Bileaflet aortic valve with any of the following:
  - Atrial fibrillation
  - Prior stroke or TIA
  - Hypertension
  - Diabetes
  - Heart failure
  - Age >75 years
- Cerebrovascular disease and multiple strokes or TIAs, without risk factors for cardiac embolism
- Active cancer

Low Risk: bridging not advised

- One remote VTE >12 months ago
- Atrial fibrillation with $CHADS_2$ score of 0–2 and no prior stroke or TIA
- Bileaflet aortic valve without atrial fibrillation or stroke risk factors
- Cerebrovascular disease without recurrent strokes or TIAs

prevention of stroke, prevention of stent thrombosis — and the spectrum of risk for cardiovascular events while off of these medications is wide.[27, 28] The risk of cardiovascular events while holding antiplatelet medication should be weighed against the postoperative bleeding risk in deciding when or if to discontinue antiplatelet medications around the time of surgery.

In general, antiplatelet medications can safely be stopped preoperatively in patients at low risk for perioperative cardiovascular events such as MI or stroke. However, in patients at high risk for cardiovascular events (e.g., those with recent coronary stent placement or recent MI), the risk of holding antiplatelet drugs may outweigh the risk of major bleeding.[2] In such cases, physicians should strongly consider continuing these medications perioperatively.

Aspirin inhibits platelet function through cyclooxygenase-1 inhibition, an irreversible process with an effect lasting 7–10 days, the lifespan of a platelet.[29, 30] Approximately 50% of platelets will regain normal function 4–5 days after stopping aspirin; 90% of platelets will have normal function after 7–10 days. Clopidogrel is a thienopyridine derivative that irreversibly inhibits adenosine diphosphate receptor-mediated platelet activation and aggregation.[31] As with aspirin, 7–10 days is needed to almost completely replace affected platelets. If perioperative interruption is required, we suggest stopping both aspirin and or clopidogrel 7–10 days before a procedure or surgery.

In general, antiplatelet agents should be resumed soon after procedures. In accordance with ACCP guidelines, we suggest restarting aspirin and/or clopidogrel approximately 24 hours after surgery in the setting of adequate postoperative hemostasis.[2]

New Oral Anticoagulants

There are a number of new oral anticoagulants currently under investigation for use in a variety of clinical situations. These drugs include the direct thrombin inhibitor, dabigatran etexilate, and factor Xa inhibitors, apixaban and rivaroxaban.

The new oral anticoagulants have shown equivalent and, in some cases, superior efficacy and safety compared to VKAs and/or LMWHs for a number of clinical indications (e.g., VTE prophylaxis, treatment of acute VTE, and risk reduction of thromboembolism in atrial fibrillation).[32-36] They may also prove to be effective agents for bridging anticoagulation around the time of surgery or procedures. It is likely that these agents will have an increasingly expanded role in the management of long-term and perioperative anticoagulation.

As of the writing of this review, dabigatran etexilate is the only drug, of the previously listed agents, with FDA approval for any indication. It was approved on October 19, 2010, for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[37]

Dabigatran etexilate is an oral small-molecule direct thrombin inhibitor.[38] Direct thrombin inhibitors directly interact with and inhibit the active site of thrombin. Unlike heparin, direct thrombin inhibitors can bind to and inhibit the activity of clot-bound thrombin.[39] Dabigatran has a half-life of 12–24 hours in patients with normal renal function. Maximal anticoagulation effects are achieved at 2–3 hours after ingestion.

Routine monitoring of anticoagulant effect is not generally required or recommended. If needed, the ecarin clotting time is the best assay to use in assessing drug activity. Unfortunately, this assay is not readily available in many institutions. Thrombin time and the activated partial thromboplastin time can be used for coagulation monitoring but are not completely reliable. Bleeding

risk associated with dabigatran is somewhat mitigated by a relatively short half-life.[40]

We recommend stopping dabigatran 24 hours prior to surgery or procedures associated with low-to-moderate bleeding risk. For high-risk procedures, we recommend stopping dabigatran 2–3 days prior to surgery. For reinitiating dabigatran after surgery, assuming adequate hemostasis, we suggest that it be resumed approximately 24 hours after minor surgical or invasive procedures and between 48–72 hours after major surgery.

Case Discussion

The patient in this case is currently on appropriate anti-coagulation therapy with warfarin. However, she has a high risk of thromboembolism if not adequately anticoagulated. This is based on the diagnosis of nonvalvular atrial fibrillation with a $CHADS_2$ score of 5 (age >75, previous TIA, hypertension, and a LVEF of 38%). Warfarin should be discontinued 5 days prior to surgery. Bridging anticoagulation with therapeutic-dose subcutaneous twice-daily LMWH is recommended perioperatively. The last dose of LMWH should be given 24 hours prior to surgery, with both LMWH and warfarin to be resumed 24 hours after the procedure, assuming normal hemostasis. LMWH can be discontinued when the INR is in the therapeutic range.

Conclusion

The perioperative and periprocedural management of anti-thrombotic therapy is indeed a challenging clinical problem.[1] Over time, perioperative risk has decreased somewhat through the use of ever-evolving anticoagulant medications.[24] The goal of decreased overall risk in the perioperative period can be obtained by assessing the optimal balance between thromboembolic and bleeding risk in conjunction with the appropriate dosing and timing of perioperative anticoagulation.

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