Preoperative Management of Anticoagulation and Antiplatelet Agents

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KEYWORDS

- Anticoagulation • Antiplatelet • Warfarin • Clopidogrel • Aspirin

KEY POINTS

- Given a higher frequency of comorbidities and frailty, older adults often take anticoagulants or antiplatelet agents, which present a challenge when optimizing patients for surgery.
- Actively managing reversal of anticoagulation may reduce time to surgery and complications.
- The approach to reversal of anticoagulation requires consideration of bleeding and clotting risk.

INTRODUCTION

Anticoagulants and antiplatelet agents present a unique challenge in the preoperative management of hip fractures. Assessment of bleeding risk is an important part of perioperative management. Delaying surgery to manage the effects of these medications can increase the likelihood of adverse events, such as delirium,[1] pneumonia, pressure ulceration, and mortality.[2,3] The urgency of surgery must be balanced against the increased risk of bleeding for patients on anticoagulation and antiplatelet agents.

Four variables must be considered when deciding how to manage periprocedural anticoagulation and antiplatelet agents with the goal of optimization for surgery (Box 1). The first is the risk of thromboembolism if the anticoagulation/antiplatelet agent is discontinued. The second is the risk of bleeding from the procedure if the anticoagulation/antiplatelet agent is continued. The third variable is the effectiveness and safety of interventions, such as receiving fresh frozen plasma or vitamin K (phytonadione). Lastly, an overriding principle is the importance of timing of surgery, because

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Box 1
Issues to consider with reversal of anticoagulant or antiplatelet agent

1. Risk of thromboembolism if anticoagulation/antiplatelet is discontinued

2. Risk of bleeding from the procedure if anticoagulation/antiplatelet is continued

3. Effectiveness and safety of interventions to reverse anticoagulation

4. Timing of surgery

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those on anticoagulants or antiplatelet agents often have a large number of comorbidities.

The assessment of perioperative bleeding risk in the context of anticoagulant and antiplatelet use should take into account the procedure planned for the patient. For example, percutaneous screw fixation has a much lower risk of bleeding than total hip arthroplasty.[4] The consequences of a major bleed in a patient with a total hip arthroplasty include hematoma, infection, and possibly joint removal.

ANTICOAGULANT MANAGEMENT

For patients who are admitted on anticoagulant medication, the steps in **Box 2** should be taken. The first 3 steps must be addressed preoperatively. The fourth step should be considered preoperatively, but is implemented postoperatively, and is therefore addressed in the article on Venous Thromboembolism and Postoperative Management of Anticoagulation elsewhere in this issue by Friedman and Uy.

Medications and Reason for Use

The first question to ask when a patient presents on anticoagulation is "why are is an anticoagulant being used?" Older adults are often anticoagulated for various medical conditions, including

- Atrial fibrillation (AF)
- Thromboembolic disease (venous thromboembolism, hypercoagulable states, deep vein thrombosis, pulmonary embolism)
- Prosthetic heart valves to prevent arterial or venous thrombosis

Warfarin is the most common and most studied anticoagulant used. However, 3 novel anticoagulants are being increasingly used in the older adult population: apixaban, a factor Xa inhibitor used to prevent strokes in patients with nonvalvular AF; dabigatran, a direct thrombin inhibitor approved for stroke prevention in nonvalvular AF; and rivaroxaban, a factor Xa inhibitor used for stroke prevention in patients with nonvalvular AF and for the prevention of thrombosis after total hip and knee replacement surgery.

Box 2
Anticoagulation management steps

1. Determine why the patient is taking an anticoagulation agent

2. Determine the short-term perioperative risk of thromboembolism related to the underlying condition if anticoagulation is stopped

3. Decide how to manage the patient in preparation for surgery and the timing of surgery

4. Decide whether to bridge

Risk Assessment of Stopping Anticoagulant

The second question to ask is "what is the short-term perioperative risk related to that underlying condition and to stopping the anticoagulation?" **Table 1** lists some common conditions treated with warfarin, and the embolism risk reduction conferred by the agent (both absolute and relative risk).

Nonvalvular AF is the most common reason for anticoagulant use in this population. The risk of embolism varies according to the "CHADS$_2$" score, with point scoring as follows:

- History of congestive heart failure: 1 point
- History of hypertension: 1 point
- Age 75 years or older: 1 point
- History of diabetes mellitus: 1 point
- History of stroke or transient ischemic attack: 2 points

Total scores range from 0 to 6, with a score of 0 conferring a risk of stroke of 1.9 and a score of 6 conferring risk of stroke of score of 18.2 per 100 patient-years in patients who are not anticoagulated.[5]

How to Manage Anticoagulation in Preparation for Surgery/Timing of Surgery

The next step is determining how to manage the anticoagulant in preparation for surgery. Several agents are available for reversal, and the use depends on the medication the patient is taking and the urgency of surgery. Most hip fracture surgery is considered urgent but not emergent, and therefore aiming to reverse anticoagulation within 24 to 48 hours is acceptable.

Vitamin K antagonist: warfarin

Warfarin acts as a vitamin K antagonist and prolongs the international normalized ratio (INR), which in turn makes blood coagulate more slowly and patients more prone to bleeding. To perform a surgical repair of hip fracture, the INR should be normalized to a level as safe as possible to reduce the risk of surgical bleeding. Most expert opinions recommend achieving an INR of 1.5 or less[13–15] before surgery. An elevated INR before surgery can increase the risk of bleeding and associated complications, such as neurologic dysfunction when a spinal or epidural catheter is inserted or removed,[16] hematoma, infection, and the possible need for joint removal.

Table 1
Embolism risk reduction with warfarin in several common conditions

Condition	Risk Without Warfarin	Risk with Warfarin	RRR
DVT: first 3 mo[6]	50.0%	4.0%–10.0%	80%–90%
Recurrent VTE, hypercoagulable states, cancer[7]	15.0%/y	3.0%/y	80%
CVA with cardiac source: first 2 wk[8]	12.0%	4.0%	66%
History of CVA and AF[9]	12.0%/y	4.0%/y	67%
Nonvalvular AF[10]	4.0%–5.0%/y	1.0%–2.0%/y	65%
Myocardial infarction Ejection fraction ≤28%[11]	1.5%/y 2.3%	N/A	81%
Mechanical valve[12]	4.0%/y	0.7%–1.0%	75%–82%

Abbreviations: CVA, cerebrovascular accident; DVT, deep venous thrombosis; N/A, not applicable; RRR, relative risk reduction; VTE, venous thromboembolism.

The options available to reverse warfarin include

- Administration of vitamin K
- Use of fresh frozen plasma
- Administration of recombinant factor VIIa or prothrombin complex concentrates
- Discontinuation of warfarin with a "watch and wait" approach

The watch and wait approach is a poor option. The older and more frail a person is, the longer it will take for the warfarin to be eliminated. The half-life of warfarin is approximately a day and a half but can be significantly longer. Reversal of warfarin-associated coagulopathy with a combination of vitamin K and fresh frozen plasma in patients who have sustained a hip fracture has been shown to be safe in 2 retrospective cohort studies.[17,18] **Fig. 1** shows one suggested algorithm for managing an elevated INR in patients on warfarin on admission who are safely able to be reversed.

Oral vitamin K has been shown to be more effective than subcutaneous dosing when lowering an elevated INR value.[19] Furthermore, a meta-analysis showed that oral and intravenous vitamin K have equivalent efficacies in reducing INR values over a 24-hour period in patients with an elevated INR, and there is no optimal dose of vitamin K to lower INR values.[20] The advantage of using oral vitamin K over intravenous vitamin K is that it avoids the risk of fatal anaphylaxis.[21] Subcutaneous and intramuscular vitamin K administration is associated with erratic absorption and should be avoided.

Fresh frozen plasma is an alternative and/or adjunct to vitamin K to correct coagulopathy.[9] It is human donor plasma that contains many plasma proteins, including all of
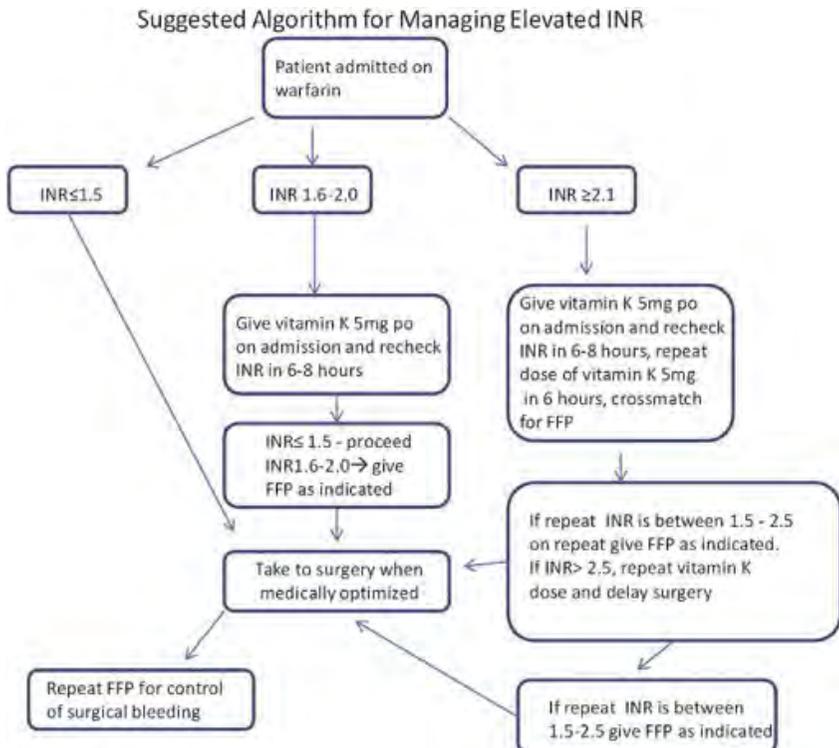

Fig. 1. Proposed algorithm for managing patients on warfarin.

the coagulation factors. One proposed formula to obtain an INR of less than 1.5 recommends

- 1 unit for an INR of 1.5 to 1.9
- 2 units for an INR of 2.0 to 3.0
- 3 units for an INR of 3.0 to 4.0
- 4 units for an INR of 4.0 to 8.0, and
- More than 4 units for an INR of greater than 8.0.[22]

Each unit of fresh frozen plasma has a volume of 190 to 240 mL. One of the challenges with fresh frozen plasma is that it only lasts approximately 6 hours, and risks include those associated with blood product transfusion (transfusion-related acute lung injury, infection) and that large volumes are often required, with the associated risk of congestive heart failure. Little evidence exists for the use of recombinant factor VIIa or prothrombin complex concentrates. Most of the studies with these products were observational in the setting of bleeding with supratherapeutic INRs. The possibility exists that they might provide an alternative to fresh frozen plasma, but more studies are necessary.[23]

There are 2 common concerns when reversing anticoagulation. The first is that a potential exists for aggressive reversal to cause increased risk of thromboembolism. The second concern is that after reversal, the patient may be warfarin-resistant and take a longer time to achieve a therapeutic level. Although it may take longer for patients to achieve a therapeutic level of warfarin after receiving reversal, this has not been shown to delay discharge.[24] Concerns about reversal should always be taken into account in the context of the clinical picture of the patient when reversing anticoagulation.

Novel Oral Anticoagulants: Dabigatran, Rivaroxaban, and Apixaban

Preoperative management of patients with AF receiving novel oral anticoagulation agents for thromboprophylaxis or stroke prevention is an important consideration for clinicians, given the increase in use of these agents.

The advantage of using these agents is their convenience, including a predictable pharmacologic profile and the lack of a need for routine monitoring, and their rapid onset of action. Nevertheless, these characteristics complicate management when surgery is needed, because the direct effect of the anticoagulant cannot be determined accurately. Therefore, determining safety for surgery can be challenging. Furthermore, no specific antidotes for reversal are currently available, limiting the ability to actively manage patients to expedite surgery, and potentially increasing the risk of preoperative blood loss.

Dabigatran

Dabigatran has an insensitive and nonlinear relationship to prothrombin time (PT) and activated partial thromboplastin time (aPTT). The aPTT may be clinically useful, because a normal aPTT is seen when the anticoagulant effect secondary to dabigatran is not present, but values often plateau at high concentrations and may underestimate supratherapeutic concentrations.[25,26] Other monitoring tests that are promising but not widely available include ecarin clotting time, hemoclot thrombin inhibitor, and thrombin clotting time. Documentation of a normal or near-normal aPTT or thrombin clotting time has been recommended to ensure that dabigatran has been adequately cleared from the circulation before surgery.

Most of dabigatran's excretion is renal (80%–85%). Given dabigatran's half-life, drug effects should decrease by approximately 50% at 12 to 18 hours after the most recent dose, and the trough levels should decrease to 25% of their previous

steady state by 24 hours after stopping dabigatran in the setting of a normal creatinine clearance exceeding 50 mL/min. In moderately severe renal dysfunction (creatinine clearance of 30–50 mL/min), which is present in many older patients, the half-life is extended to approximately 18 to 28 hours. Dabigatran is potentially dialyzable. Elective procedures or surgeries with critically high bleeding are recommended to commence between 2 and 4 days after stopping the medication.[27] Currently, no guidelines or recommendations for emergent or urgent procedures exist, and the principles should be derived from elective surgeries. Additionally, because dabigatran is cleared renally, monitoring renal function and maintaining adequate hydration are important.

Rivaroxaban and apixaban

Similarly, no standard exists to monitor direct factor Xa inhibitors. Direct factor Xa inhibitors will prolong PT, INR, and aPTT in a linear, dose-dependent fashion, and these tests can be used as a qualitative assessment of exposure to direct factor Xa inhibitors.[28] However, significant interassay variability exists.

Rivaroxaban and apixaban have less renal clearance than dabigatran. These drugs have half-lives between 9 and 12 hours, which can be longer in the elderly. Rivaroxaban can affect PT values, and this can be monitored before surgery. Some evidence suggests that rivaroxaban can be reversed with prothrombin complex concentrate, but this is not widely available, and different formulations are in use. Like dabigatran, both of these medications can have a rapid onset of action, and therefore these patients should be treated with the same approach as those treated with dabigatran.

ANTITHROMBOTIC MANAGEMENT
Aspirin

Aspirin has an antiplatelet effect because it inhibits the production of thromboxane, which binds platelet molecules together to create a patch over damaged walls of blood vessels. Aspirin is often prescribed to help prevent myocardial infarction, cerebrovascular accidents, and blood clots. The 2012 guidelines from the American College of Chest Physicians (ACCP) recommend continuing aspirin around the time of surgery for patients at moderate to high risk for cardiovascular events who are undergoing noncardiac surgery.[29] As with other agents mentioned in this article, the decision to continue or withhold aspirin should reflect a balance of the consequences of perioperative hemorrhage versus the risk of perioperative vascular complications.

Antiplatelet Agents

The approach to managing patients admitted on antiplatelets is similar to that for patients taking anticoagulants, and is outlined in **Box 3**.

Determine reason for antiplatelet use

Antiplatelet agents include clopidogrel, prasugrel, ticagrelor, and ticlopidine. Indications for these medications include treatment of symptomatic atherosclerosis in

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Box 3
Antiplatelet management steps

1. Determine why the patient is taking an antiplatelet agent

2. Determine the short-term perioperative risk associated with stopping the antiplatelet agent

3. Decide how to manage the patient in preparation for surgery and the timing of surgery

patients with acute coronary syndrome without ST segment elevation; ST elevation myocardial infarction; cerebrovascular disease; and peripheral vascular disease. The use of these agents has increased with the increase in drug-eluting coronary artery stenting procedures.

These agents work to block adenosine diphosphate receptors of subtype P2Y12 and prevent the activation of platelets and eventual cross-linking by the protein fibrin, thus preventing platelet aggregation and clot formation. Platelet inhibition can be demonstrated 2 hours after a single dose of oral clopidogrel, and the effect lasts for 5 to 9 days, which is the entire lifespan of the platelets. Less platelet aggregation may increase the risk of serious bleeding in patients undergoing surgery.

Risk assessment of stopping antiplatelet agents

The most common agent used is clopidogrel. The risk of coronary artery stent thrombosis after the premature cessation of clopidogrel is low, but stent thrombosis may be catastrophic. The ACCP recommends that for those who have undergone placement of a bare metal stent within the past 6 weeks or a drug-eluting stent in the past 6 months, both aspirin and clopidogrel should be continued perioperatively (class 2C).[29] Elective surgery should be postponed whenever possible until the minimum period of therapy with P2Y12 receptor blocker therapy is completed.

Management for surgery

Clopidogrel is different from warfarin (but similar to the newer anticoagulant agents) because no physiologic method of reversing the antithrombotic effect of this medication is known. In cases of elective surgery, clopidogrel can be discontinued well before the planned surgery, often a week before the procedure, to allow platelets to form a plug for optimal blood clotting. But in emergent or other urgent cases, such as hip fractures, the risk of increased bleeding must be carefully weighed against the benefits of the surgery.

The management of clopidogrel in patients with an acute hip fracture is often debated. One retrospective review of 21 patients showed that it was safe to operate without delay on those taking clopidogrel.[30] Another study concluded that these patients often have more comorbidities but are not at increased risk of complications such as bleeding or mortality during hip fracture repair surgery.[31] Yet another study showed that delays related to antiplatelet agents led to a higher mortality after hip fracture repair.[32]

The current challenge is to determine whether the increased risk of bleeding caused by immediate surgery is worth the risk of increased morbidity and mortality resulting from a delay of 7 to 9 days. A survey of directors of academic orthopedic programs showed a consensus for waiting 3 days or less for urgent but nonemergent surgical interventions, such as hip fractures, in patients on clopidogrel, with 23% believing that no delay was necessary. For emergent surgery, 89% believed that no delay to the operating room was indicated.[33] Recent level 2 evidence shows that patients undergoing early hip fracture surgery who are taking clopidogrel are not at a substantially increased risk for bleeding, bleeding complications, or mortality.[31] Because of the risk of bleeding, spinal anesthesia is often contraindicated in those on clopidogrel.

Additionally, no known guidelines exist for the role of platelet transfusions. Based on the reviewed physiology, one can argue that a perioperative platelet transfusion may be of some benefit, because the transfused platelets would be effective in forming a viable plug. However, the authors are unaware of any studies evaluating the effectiveness of platelet transfusion. Platelet transfusions are not standard of care and should be reserved for patients who would be expected to have bleeding problems before surgery or those who have extensive bleeding after surgery.

SUMMARY

Many patients who have sustained fragility fractures are at high risk for morbidity and mortality because of the presence of multiple comorbidities. Preoperative antithrombotic management is based on risk assessment for thromboembolic events and bleeding. Expediting time to surgery is an important goal, and therefore waiting for the INR to drift down in patients on warfarin is a poor option. Active management is less feasible in patients who are taking newer anticoagulants or antiplatelet agents. In these patients, careful monitoring and balancing of risks of thrombosis and bleeding are essential components of preoperative management.

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