Perioperative Management of Patients on Chronic Antithrombotic Therapy

Thomas L. Ortel, M.D., Ph.D.
Professor of Medicine & Pathology
Hemostasis and Thrombosis Center
Duke University Medical Center
Box 3422, Room 0563 Stead Building
Durham, NC 27710
Phone: 919-684-5350
Fax: 919-681-6160
e-mail: thomas.ortel@duke.edu
website: http://htc.medicine.duke.edu/

Supported by the Centers for Disease Control and Prevention (DD000014; DD000897) and the National Heart Lung and Blood Institute (HL087229, and HL072289).
Abstract

Perioperative management of antithrombotic therapy is a situation that occurs frequently and requires consideration of the patient, the procedure, and an expanding array of anticoagulant and antiplatelet agents. Preoperative assessment must address the individual patient’s risk for thromboembolic events, balanced against the risk for perioperative bleeding. Procedures can be separated into those with a low bleeding risk, which generally do not require complete reversal of the antithrombotic therapy, and those associated with an intermediate or high bleeding risk. For patients who are receiving warfarin who need interruption of the anticoagulant, consideration must be given to whether simply withholding the anticoagulant is the optimal approach, or whether a perioperative ‘bridge’ with an alternative agent, typically a low-molecular weight heparin, should be used. The new oral anticoagulants dabigatran and rivaroxaban have shorter effective half-lives, but they introduce other concerns for perioperative management, including prolonged drug effect in patients with renal insufficiency, limited experience with clinical laboratory testing to confirm lack of residual anticoagulant effect, and lack of a reversal agent. Antiplatelet agents must also be considered in the perioperative setting, with particular consideration given to the potential risk for thrombotic complications in patients with coronary artery stents who have antiplatelet therapy withheld.
Hematologists are frequently consulted for management recommendations for patients receiving long-term oral antithrombotic therapy who require temporary interruption of anticoagulation prior to surgery or an invasive procedure. It is currently estimated that approximately 250,000 patients in North America will require interruption of oral anticoagulant therapy each year \(^1\). The management of these patients, however, is problematic. On the one hand, disruption of oral anticoagulant therapy will expose the patient to an increased risk for thromboembolism, but the degree of risk is clearly variable among such patients. On the other hand, there is an increased risk for hemorrhagic complications if anticoagulant therapy is continued, which is affected by the type of surgery or invasive procedure that the patient will undergo. In addition, maintaining full anticoagulant therapy in the perioperative setting has the potential to inadvertently lead to an increased risk for thromboembolism in those patients who sustain a hemorrhagic event and subsequently have their anticoagulant therapy held or even reversed. For the individual patient, therefore, these issues must be considered prior to formulating management recommendations.

Although this clinical situation is not uncommon, there is relatively limited evidence available to guide therapeutic recommendations. In addition, we are entering a rapidly changing landscape, with two novel oral anticoagulants recently approved for use in patients with atrial fibrillation, and several other agents currently either under review or being studied (Table 1). These agents introduce new issues and concerns with perioperative management, and will be discussed below. In addition, there is an expanding array of antiplatelet agents in use, which also need to be considered in the perioperative period (Table 2). This article will focus on the pre-operative assessment of patients on these various antithrombotic therapies and discuss management strategies for this frequently encountered clinical situation.
Pre-operative Assessment

The perioperative management of patients who are receiving antithrombotic therapy, whether anticoagulant and/or antiplatelet, is based on an assessment of individual patient risk for thromboembolic events considered against the risk for perioperative bleeding. These issues will determine whether antithrombotic therapy can be safely held around the time of the surgery or procedure, or whether bridging therapy would need to be considered. Bridging therapy has been defined as the administration of a short-acting anticoagulant, such as a low-molecular weight heparin (LMWH) or unfractionated heparin (Table 1), during the time when a long-acting anticoagulant, such as warfarin, is being held prior to the surgery, and subsequently following the surgery or procedure until the long-acting anticoagulant is again within the target therapeutic range. Although this sounds relatively straightforward, the lack of high-quality data has led to the empiric use of a wide variety of strategies for various clinical indications.

Assessment of thromboembolic risk. Although several recent observational studies would suggest that simply interrupting warfarin therapy for a procedure is associated with an overall very low rate of postoperative thromboembolism, an individual patient’s risk of thromboembolism during a brief interruption in anticoagulant therapy is dependent on specific characteristics related to the clinical indication for anticoagulation. A suggested approach for stratifying thromboembolic risk according to the indication for anticoagulation is provided in Table 3. For patients with atrial fibrillation, the CHADS2 score, although not prospectively validated for use in the perioperative setting, is typically used for stratification. For patients with VTE, important considerations include the timing of the most recent thromboembolic event and the presence (or absence) of underlying prothrombotic risk factors. For patients with prosthetic cardiac valves, considerations include the location of the valve, type of valve, and presence of a prior stroke or transient ischemic attack.
Using this approach, patients with a >10% annual risk for thromboembolism are classified as ‘high risk’ for a thromboembolic event, patients with a 5% to 10% annual risk are classified as ‘moderate risk’, and patients with a <5% annual risk for thromboembolism are classified as ‘low risk’ 1. Individual patient characteristics may modify this risk stratification, however. For example, a patient with atrial fibrillation and a stroke that occurred several years previously might be considered a ‘higher-risk’ patient even if the CHADS2 score is less than 5, compared to a patient with a similar CHADS2 score but without a prior stroke 1.

In addition to the risk of thromboembolism present when anticoagulation is withheld, one must also consider the potential risk for thrombus formation in relation to the specific procedure or surgery that is being performed. For example, neurologic and vascular surgical procedures were associated with a higher risk for stroke in patients with atrial fibrillation than other types of procedures (e.g., urologic or orthopedic surgery) 8.

Assessment of bleeding risk. As with the evaluation of the thromboembolic risk for the individual patient, an assessment of the bleeding risk similarly needs to take into consideration patient-specific as well as surgery/procedure-specific variables. In a recent cohort study, patient-specific variables that were associated with an increased risk for bleeding included a prior bleeding history, a mechanical heart valve in the mitral position, the presence of active cancer, and thrombocytopenia 9. A bleeding risk score using these four parameters, referred to as “BleedMAP”, was shown to correlate with an increased risk for peri-procedural bleeding 9. The HAS-BLED score, which was originally developed for use in the non-perioperative setting, has recently been shown to predict bleeds during bridging of patients on chronic anticoagulation 10. This scoring system uses the presence or absence of hypertension, abnormal renal or liver function, prior stroke, bleeding history or predisposition, labile INR, elderly (age > 65 years), or drug/alcohol use concomitantly, to assess bleeding risk.
Surgical procedures differ in their risk for bleeding, although there are limited data identifying the relative risk for bleeding associated with different procedures. Procedures involving highly vascular organs, such as the liver, kidney, and spleen, have a higher risk for bleeding even in the absence of perioperative antithrombotic drug administration. Other procedures associated with an increased risk for bleeding include urologic surgery, bowel resection, and colonic polyp resection, especially for large, sessile polyps, and major surgery associated with extensive tissue injury (for example, cancer surgery, joint arthroplasty). Certain procedures, such as implantation of a pacemaker or cardioverter/defibrillator, or intracranial or spinal surgery, may not intrinsically exhibit an increased risk of hemorrhage, but even a small amount of excess bleeding in these confined locations can be associated with an adverse outcome.

Perioperative Management of Patients on Chronic Vitamin K-Antagonist Therapy

Procedures Associated with a Low Bleeding Risk. Interruption of oral anticoagulant therapy may not be necessary in patients undergoing certain procedures with a low bleeding risk. In general, interruption of warfarin is not required for minor dental procedures, including tooth extractions and endodontal procedures. Continuing warfarin with concomitant administration of a prohemostatic agent (e.g., an antifibrinolytic agent, such as tranexamic acid or aminocaproic acid used as a mouthwash prior to and following the dental work), or interrupting warfarin for only 2 to 3 days, resulting in an INR that is slightly subtherapeutic at the time of the procedure, are reasonable management strategies. Similarly, interruption of warfarin therapy is generally not necessary for patients undergoing minor skin excisions, such as treatment of basal and squamous cell skin cancers and actinic keratosis. Although a higher incidence of minor skin bleeding was reported in patients who continued warfarin compared to those who interrupted warfarin therapy, most bleeds were self-limited. In contrast to most dental and dermatologic procedures, cataract removal is generally an avascular procedure. In a recent systematic review and meta-analysis, patients who underwent cataract surgery while on vitamin
K-antagonist therapy exhibited an increased risk for bleeding (odds ratio (OR), 3.26; 95% confidence interval (CI), 1.73-6.16), but almost all bleeding events were self-limited, and none of the patients sustained compromised visual acuity due to hemorrhage 13.

**Procedures Associated with a Moderate to High Bleeding Risk.** In this clinical setting, warfarin will need to be interrupted in order to safely conduct the surgery or invasive procedure. For patients assessed as having a low risk for thromboembolic complications (Table 3), warfarin can simply be stopped prior to the procedure, typically beginning five days before, and then resumed once the procedure has been completed. The overall time that the patient will be subtherapeutic on warfarin may range from several days to a week or more, but if the risk for thromboembolism is considered low enough during this relatively brief period of time, then this approach represents the safest strategy.

Patients assessed as having a moderate to high risk for thromboembolic complications raise greater concern for the possibility of a thromboembolic event during the period of time when the INR is subtherapeutic. For these patients, a short-acting agent such as unfractionated heparin or LMWH may be used as a “bridge” during the time when the INR is subtherapeutic, to decrease the period of time when the patient is at risk for thromboembolism. The risk with this approach, however, is the potential for hemorrhage when anticoagulants are employed too near the time of the surgery or procedure, and care must be taken with the planned timing of stopping and re-starting the short-acting agent. Although conceptually this process may sound relatively simple, the devil lies in the details given the various combinations of when to stop and when to restart each agent, as well as the doses employed, and the potential for adverse outcomes that may occur with each of these strategies.

**Interruption of the vitamin K antagonist before surgery.** The current recommendation for patients taking warfarin is that it should be discontinued approximately five days before surgery
or a procedure. The elimination half-life of warfarin is 36 to 42 hours, and withholding warfarin for five days would allow sufficient time for the regeneration of functional vitamin K-dependent coagulation factors to achieve normal hemostasis (assuming normal diet and an INR that was not markedly supratherapeutic on the day withholding warfarin was started). A prospective cohort study in a non-operative setting demonstrated that a five-day period of warfarin interruption in patients with therapeutic INR’s was sufficient to allow normalization or near-normalization of the INR. A prospective, randomized trial compared withholding warfarin beginning on day -5 prior to surgery with withholding warfarin beginning on day -2 before surgery and administering 1 mg of vitamin K on day -1. For patients who withheld warfarin beginning on day -5, the mean INR on the day of surgery was 1.24 (95% CI, 1.19-1.29), but for patients who withheld warfarin beginning on day -2, the mean INR was 1.61 (95% CI, 1.50-1.71). There are no randomized trials that have compared the effects of withholding warfarin for five days prior to surgery to withholding warfarin for less than five days on perioperative bleeding outcomes.

The elimination half-lives of vitamin K antagonists other than warfarin differ, with acenocoumarol having a shorter elimination half-life (10 hours), and phenprocoumarol having a longer elimination half-life (3 to 5 days). Most studies investigating perioperative management of vitamin K antagonist therapy have studied warfarin, however, and limited data are available relevant to these other vitamin K antagonists.

Resumption of the vitamin K antagonist after surgery. For most types of surgery, vitamin K-antagonist therapy can be resumed on the evening of or the day following surgery, once post-operative bleeding has been controlled and oral intake has resumed. For patients undergoing a surgical procedure associated with a high risk of postoperative bleeding, anticoagulant therapy can be delayed for a day or two before being restarted. In general, early resumption of warfarin after surgery or a procedure is unlikely to incur an increased risk of bleeding in the
postoperative setting, given the expected delay before a therapeutic anticoagulant effect is achieved, typically ~5 to 7 days after re-starting the warfarin\textsuperscript{18,19}.

\textit{Laboratory monitoring of the INR in the perioperative setting.} Measuring the INR the day prior to surgery can be used to ensure that it will reach a target value that the surgeon or proceduralist considers safe to proceed on the day of the procedure. For patients with INR values above the target, a low-dose of oral vitamin K (1 mg) is generally sufficient to achieve the target INR and not require cancellation of the procedure\textsuperscript{20}.

\textit{Use of bridging anticoagulation.} Patients at higher risk for thromboembolism are not infrequently treated with unfractionated heparin or LMWH during the period of time that warfarin is being withheld. In a patient with normal renal function, an outpatient strategy with a LMWH is generally used. The LMWH is typically started ~36 to 48 hours after the last dose of warfarin (three days prior to surgery) and is typically stopped ~24 hours prior to the surgery. For patients undergoing a procedure associated with a higher risk for bleeding, it would be reasonable to withhold the LMWH for greater than one day prior to surgery. Similarly, for patients with impaired renal function, it would be reasonable to decrease the last dose and/or withhold the LMWH for >24 hours prior to surgery, or consider whether or not to simply avoid use of a bridging anticoagulant in the pre-operative setting. An alternative strategy for patients with significant renal insufficiency (creatinine clearance < 30 mL/min) who are at high risk for thromboembolism would be to consider the use of unfractionated heparin for bridging.

Resumption of therapeutic dose LMWH after surgery should generally be delayed for at least 24 hours following most procedures, and potentially longer after major surgery\textsuperscript{11}. In one prospective cohort study in which all patients received enoxaparin, 1.5 mg/kg daily, beginning within 12 to 24 hours after surgery, major bleeding occurred in 8 of 40 patients undergoing major surgery (20\%) and 1 of 148 patients undergoing minor surgery (0.7\%)\textsuperscript{21}. Other studies
that allowed more flexibility in either the timing of when postoperative anticoagulation was initiated, or the initial dose administered, reported a lower incidence of major bleeding (less than 5%)\textsuperscript{18}. In general, these findings would support delaying resumption of therapeutic LMWH for at least 24 hours after surgery, and possibly longer for major procedures.

For those patients who are being converted back to warfarin, typically the first dose can be administered in the early postoperative setting, as noted above. Once the INR is within the target therapeutic range, preferably on two separate measurements, the LMWH ‘bridge’ can be discontinued. For patients with a history of a prior reaction to LMWH, fondaparinux may be substituted for the LMWH, but, the longer half-life of fondaparinux needs to be considered when providing perioperative therapeutic recommendations (Table 1).

**Perioperative Management of Patients on New Oral Anticoagulants.**

The new oral anticoagulants that are currently available in North America include dabigatran, a direct thrombin inhibitor, and rivaroxaban, a direct inhibitor of factor Xa (Table 1). Other factor Xa inhibitors that are in development include apixaban and edoxaban. These agents have several important differences from warfarin and other vitamin K antagonists, primarily through their mechanisms of action on normal hemostasis\textsuperscript{22}. In particular, the new oral agents exert their anticoagulant effect by directly inhibiting the function of individual coagulation factors, with no impact on the synthesis of new zymogens. Consequently, when stopping or starting the new oral agents, the anticoagulant effect is lost and regained much more quickly than with warfarin (Table 1), which can impact bleeding risk in the peri-operative setting.

* Interruption of the new oral anticoagulants before surgery. The timing of discontinuation of dabigatran prior to surgery is impacted on by the patient’s renal function and the risk of bleeding associated with the surgical procedure\textsuperscript{23}. With normal renal function, dabigatran should be stopped ~24 hours prior to the procedure. In surgical procedures with a higher risk of bleeding
(e.g., neurosurgery, cardiovascular surgery), or with spinal anesthesia, consideration should be
given to stopping the drug 2 to 4 days prior to the procedure. As renal function declines, the
half-life of the drug prolongs, and it will need to be held for at least 2 days (with a creatinine
clearance between 30 and 50 mL/min) or longer (if creatinine clearance is ≤30 mL/min), even
for low risk procedures. Rivaroxaban is cleared to a lesser extent by the kidney (66%) 22 and in
most patients can be safely stopped within 1 to 2 days prior to the procedure 24. As with
dabigatran, however, a more conservative approach would be to consider withholding the drug
for a longer period of time in patients with significant renal impairment.

Resumption of the new oral anticoagulants after surgery. For patients undergoing major
abdominal procedures or urologic surgery, the new oral anticoagulants should not be restarted
until after all postoperative bleeding has stopped, given their rapid onset of action (Table 1).
One strategy that has been suggested is to use a lower dose of dabigatran (e.g., 75 mg) or
rivaroxaban (e.g., 10 mg) for the initial dose after surgery, followed by resumption of the usual
maintenance dose if no bleeding is encountered 24.

Laboratory testing in the perioperative setting. Although routine laboratory monitoring is not
necessary for dabigatran and rivaroxaban, some individuals may wish to use laboratory testing
to confirm the lack of any residual anticoagulant effect prior to surgery. For patients taking
dabigatran, a thrombin time prior to surgery can be helpful, since this test is particularly
sensitive to the presence of dabigatran 23. The thrombin time is extremely sensitive to
dabigatran, and in some patients a dilute thrombin time that has been calibrated to clinically
relevant concentrations of dabigatran may be preferable, if available 23. For patients taking
rivaroxaban, the sensitivities of various PT and aPTT reagents vary in their ability to detect low
levels of circulating drug 25. Anti-factor Xa chromogenic assays, similar to those used to
measure heparin levels, are being evaluated and may prove useful for patients taking
rivaroxaban 26.
Use of bridging anticoagulation. Bridging therapy with a LMWH or unfractionated heparin is not necessary with the new oral anticoagulants, given the relatively rapid clearance of the drug from the circulation, and the rapid onset of action when re-introduced (Table 1).

Perioperative Management of Patients on Chronic Antiplatelet Therapy.

Antiplatelet drugs that irreversibly inhibit platelet function include aspirin and the thienopyridines clopidogrel, ticlopidine, and prasugrel (Table 2). Ticagrelor is a direct-acting, reversibly-binding, oral P2Y₁₂ receptor antagonist that exhibits a rapid onset and offset of antiplatelet effect. Other reversible antiplatelet drugs include dipyridamole and cilostazol, and the non-steroidal anti-inflammatory agents also have a transient antiplatelet effect. Newer antiplatelet agents that are currently being studied in clinical trials include cangrelor and elinogrel. Cangrelor is an intravenous agent that has an excellent acute profile, with a rapid onset of action, a rapid offset, and a half-life of just a few minutes (Table 2). Perioperative management of these agents presents some additional challenges not encountered with the anticoagulant therapies.

Assessment of thromboembolic risk. Antiplatelet medications are used for the primary and secondary management of atherosclerotic thrombotic disease, particularly in the management of patients with stroke, acute myocardial infarction or acute coronary syndromes, or peripheral vascular disease, as well as patients undergoing percutaneous coronary intervention or cardiac surgery. Dual antiplatelet therapy with a thienopyridine in combination with aspirin has been shown to dramatically reduce the incidence of adverse events in patients receiving coronary artery stents, and premature discontinuation of antiplatelet therapy is associated with an increased risk of stent thrombosis, myocardial infarction, and death. Consequently, a recent science advisory from the American Heart Association, the American College of Cardiology, and other organizations stressed the importance of twelve months of dual antiplatelet therapy after
placement of a drug-eluting stent and that elective surgery should be postponed until after this
duration of time, if possible 30.

Assessment of bleeding risk. The assessment of bleeding risk for perioperative management of
antiplatelet therapy is similar to the concerns raised above for anticoagulant therapies.

Stopping oral antiplatelet therapy before surgery. In general, for procedures associated with a
low bleeding risk, antiplatelet therapies do not need to be withheld, similar to the
recommendations for anticoagulant therapies 1. In contrast, for procedures associated with a
moderate to high bleeding risk, a critical variable that must be considered is the individual risk
for cardiovascular events. For patients at high risk for cardiovascular complications,
consideration should be given to either continuing aspirin around the time of the procedure, or
delaying the procedure until the patient has a lower risk. For patients at low risk for
cardiovascular events, on the other hand, stopping antiplatelet therapy prior to the procedure is
reasonable 1. For patients undergoing coronary artery bypass grafting (CABG), continuing
aspirin would be appropriate, although the most recent guidelines from the American College of
Chest Physicians suggest that thienopyridine therapy should be held prior to CABG 1.

Although these therapeutic agents have relatively short half-lives, the most frequently used
agents (aspirin, clopidogrel) irreversibly inhibit platelet function, necessitating withholding their
administration for 7 to 10 days prior to surgery or an invasive procedure that requires complete
elimination of the antiplatelet effect (Table 2). No randomized trials have assessed whether
withholding antiplatelet therapy for a shorter period of time would provide a safer approach.

Resumption of antiplatelet therapy after surgery. The maximal antiplatelet effect occurs within
minutes after resumption of aspirin (Table 2). In contrast, the maximal antiplatelet effect of
clopidogrel may not be reached until after seven days of daily administration of a standard dose
(75 mg/day), but this can be shortened by administering an initial loading dose 29.
Laboratory testing of antiplatelet therapy. Several platelet function assays are available for measuring the antiplatelet effect of aspirin, clopidogrel, and the other P2Y₁₂ ADP receptor blocking agents. The clinical significance of these assays is uncertain, however, and the assay results have not been shown to correlate with clinical outcomes³¹. Consequently, laboratory testing is generally not recommended for the management of these patients.

Use of bridging antiplatelet therapy. Similar to the strategies that have been developed for the perioperative management of warfarin in patients at high risk for thromboembolic complications, strategies have also been investigated using short-acting antiplatelet agents in patients on chronic therapy with clopidogrel, given its longer onset and offset of action. The short-acting intravenous glycoprotein IIb/IIIa receptor inhibitors eptifibatide³² and tirofiban³³ have been used in small case series as ‘bridging’ antiplatelet therapy in patients requiring temporary withdrawal of clopidogrel. More recently, the non-thienopyridine adenosine triphosphate analogue cangrelor was investigated as a bridging antiplatelet agent in a prospective, randomized, double-blind, placebo-controlled multicenter trial involving patients receiving a thienopyridine who underwent CABG³⁴. A higher rate of maintenance platelet inhibition in patients treated with cangrelor compared to placebo was observed with this approach, without an increase in major bleeding prior to surgery or an increase in CABG-related bleeding³⁴. An alternative strategy that allows for ‘transient’ reversal of dual antiplatelet therapy in high-risk patients involves the use of specifically timed platelet transfusions prior to the procedure, based on the elimination half-lives of aspirin and clopidogrel (Table 2)³⁵. Additional clinical trials are needed to document the efficacy in decreasing thromboembolic complications using this strategy.

Inferior vena cava filters.

For patients with a recent VTE, it is preferable to defer all surgical procedures until at least one month, and preferably three months, of anticoagulant therapy have been administered³⁶. If this is not feasible, and major surgery needs to be performed within several weeks of an acute
episode of proximal DVT or PE, a retrievable inferior vena cava filter can be considered for use during the procedure \textsuperscript{36,37}. The filter should be removed in the postoperative setting as soon as anticoagulation can be re-established, to minimize the potential for any complications related to the device.

*Future directions.*

Several clinical trials are currently open and enrolling patients into studies designed to address some of the deficiencies noted above. For example, although bridging anticoagulation with a low-molecular weight heparin is frequently used in patients on chronic warfarin therapy who need their anticoagulation held for a procedure, there is no firm evidence that this approach actually prevents perioperative thromboembolic events. BRIDGE is a prospective randomized trial supported by the National Heart, Lung, & Blood Institute that is enrolling patients with atrial fibrillation or flutter who require temporary interruption of warfarin for a surgery or procedure. The study compares bridging with therapeutic-dose low-molecular weight heparin to placebo (clinicaltrials.gov \#NCT00786474). PERI-OP2 is a second trial that is also designed to study the safety and efficacy of low-molecular weight heparin as a bridge for patients with atrial fibrillation or prosthetic aortic valves who need anticoagulation withheld for a procedure (clinicaltrials.gov \#NCT00432796). These two studies will address the issue of efficacy and safety of bridging therapy in patients on chronic warfarin anticoagulant therapy.
Authorship

Contribution: T.L.O. performed the literature search and prepared the manuscript.

Conflict of interest disclosure: Within the past 2 years, T.L.O. has received research support from Eisai, Pfizer, GlaxoSmithKline, Daiichi Sankyo, Stago, and Instrumentation Laboratory, Inc. T.L.O. has acted as a consultant for Sanofi Aventis, Boehringer Ingelheim, Bristol Myers/Squibb, and Instrumentation Laboratory, Inc.

Correspondence: Thomas L. Ortel, M.D., Ph.D., Duke University Medical Center, Box 3422, Room 0563 Stead Building, Durham, NC, 27710. Email: thomas.ortel@duke.edu
References


Table 1. Anticoagulant agents. Relevant information for perioperative management of anticoagulant agents. Compiled from references 22,38-40.*

<table>
<thead>
<tr>
<th>Anticoagulant Therapy</th>
<th>Primary Mode of Action</th>
<th>Time to maximum effect</th>
<th>Elimination half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (racemic)</td>
<td>Inhibition of vitamin K-dependent γ-carboxylation</td>
<td>90 min for circulating drug; ~5-7 days for a therapeutic INR</td>
<td>36 to 42 hrs for circulating drug; ~5 days to normalize INR</td>
<td>Anticoagulant effect reflects alterations in circulating vitamin K-dependent factors (II, VII, IX, X), which varies from hours (factor VII) to days (factor II)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>AT-mediated inhibition of serine proteinases</td>
<td>Immediate (IV); within 6 hrs (SQ)</td>
<td>30 to 60 min</td>
<td>Effective reversal with protamine</td>
</tr>
<tr>
<td>Low-molecular weight heparin</td>
<td>AT-mediated serine proteinase inhibition</td>
<td>3 to 5 hrs</td>
<td>3 to 6 hrs</td>
<td>Renal clearance with prolonged elimination in renal failure; partial reversal with protamine</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>AT-mediated inhibition of Factor Xa</td>
<td>~2 hrs</td>
<td>17 hr</td>
<td>Renal clearance with prolonged clearance in renal failure; not reversed by protamine</td>
</tr>
<tr>
<td>Drug</td>
<td>Type of Inhibition</td>
<td>Onset (hrs)</td>
<td>Peak (hrs)</td>
<td>Duration (hrs)</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>-------------</td>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibition</td>
<td>1.25 to 3</td>
<td>12 to 14</td>
<td>Non-reversible; 80% renal clearance with prolonged elimination with renal insufficiency</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibition</td>
<td>2 to 4</td>
<td>9 to 13</td>
<td>Non-reversible; 66% renal clearance</td>
</tr>
<tr>
<td>Apixaban†</td>
<td>Direct factor Xa inhibition</td>
<td>1 to 3</td>
<td>8 to 15</td>
<td>Non-reversible; ~25% renal clearance</td>
</tr>
</tbody>
</table>

* Abbreviations: min, minutes; hr, hour; IV, intravenous; SQ, subcutaneous; AT, antithrombin; INR, international normalized ratio.

† Apixaban is currently not available for clinical use in the United States.
<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Time to maximum level</th>
<th>Elimination half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Irreversible inhibition of COX-1 and COX-2</td>
<td>30-40 min†</td>
<td>15-30 min</td>
<td>Antiplatelet effect appears within 1 hr and persists for at least 4 days after stopping therapy</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Irreversible inhibition of P2Y₁₂ ADP receptor</td>
<td>1 hr for circulating drug; 3 to 7 days for maximal antiplatelet effect</td>
<td>8 hrs for circulating drug</td>
<td>More rapid inhibition of platelet function can be achieved with a loading dose; antiplatelet effect lasts up to 10 days</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Irreversible inhibiton of P2Y₁₂ ADP receptor</td>
<td>1 to 3 hrs</td>
<td>24 to 36 hrs (after one dose)</td>
<td>Antiplatelet effect lasts for the life span of the platelet (5-7 days)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Irreversible inhibiton of P2Y₁₂ ADP receptor</td>
<td>30 min</td>
<td>7 hrs</td>
<td>Antiplatelet effect lasts 5-7 days</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Reversible inhibition of P2Y₁₂ ADP receptor</td>
<td>1.5 hrs</td>
<td>7 hrs</td>
<td>Residual antiplatelet effect decreased to 30% after ~2.5 days</td>
</tr>
<tr>
<td>Cangrelor‡</td>
<td>Reversible inhibition of P2Y₁₂ ADP receptor</td>
<td>Seconds with IV administration</td>
<td>2 to 5 min</td>
<td>Normal platelet function returns by 60 minutes after infusion is stopped</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------</td>
<td>---------------------------------</td>
<td>-----------</td>
<td>------------------------------------------</td>
</tr>
</tbody>
</table>

* Abbreviations: min, minutes; hr, hour; IV, intravenous

† Peak plasma levels shown for non-enteric-coated aspirin; peak levels are delayed up to 3 to 4 hours with enteric-coated aspirin.

‡ Cangrelor is currently being studied in clinical trials and is not available for clinical use.
Table 3. Proposed Risk Stratification Strategy for Perioperative Thromboembolism (adapted from 1,11)

<table>
<thead>
<tr>
<th>Risk Stratum for Thrombotic Events</th>
<th>Indication for Anticoagulant Therapy</th>
<th>Indication for Anticoagulant Therapy</th>
<th>Indication for Anticoagulant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mechanical Heart Valve</td>
<td>Atrial Fibrillation</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>High risk</td>
<td>• Any mitral valve prosthesis</td>
<td>• CHADS$_2$ score of 5 or 6*</td>
<td>• Recent (within 3 months) VTE</td>
</tr>
<tr>
<td></td>
<td>• Any caged-ball or tilting disc aortic valve prosthesis</td>
<td>• Recent (within 3 months) stroke or TIA</td>
<td>• “Severe” thrombophilia†</td>
</tr>
<tr>
<td></td>
<td>• Recent (within 6 months) stroke or TIA</td>
<td>• Rheumatic valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>• Bileaflet aortic valve prosthesis and $\geq$1 of the following risk factors: atrial fibrillation, prior stroke or TIA, hypertension, diabetes, CHF, age &gt;75 years</td>
<td>• CHADS$_2$ score of 3 or 4*</td>
<td>• VTE within the past 3-12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Active cancer (treated within 6 months or palliative)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• “Nonsevere” thrombophilia†</td>
</tr>
<tr>
<td>Low risk</td>
<td>• Bileaflet aortic valve prosthesis without atrial fibrillation and no</td>
<td>• CHADS$_2$ score of 0 to 2*</td>
<td>• VTE &gt;12 months previous and no other risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* The CHADS\textsubscript{2} score is calculated by the cumulative score for Congestive heart failure (1 point), Hypertension (1 point), Age >75 years (1 point), Diabetes mellitus (1 point), and prior Stroke or TIA (2 points) \textsuperscript{4}.

† “Severe” thrombophilias include deficiency of protein C, protein S, or antithrombin, antiphospholipid antibodies, or multiple abnormalities (e.g., compound heterozygosity for factor V Leiden and prothrombin G20210A). “Non-severe” thrombophilias include heterozygosity for factor V Leiden or prothrombin G20210A. The clinical relevance for these inherited risk factors in predicting risk of recurrent VTE is unclear, however \textsuperscript{43}.

Abbreviations used: TIA, transient ischemic attack; VTE, venous thromboembolism; CHF, congestive heart failure.
Perioperative management of patients on chronic antithrombotic therapy

Thomas L. Ortel