Chronic Antithrombotic Therapy and Gynecologic Surgery

ABSTRACT: Surgery can present a management dilemma for gynecologists whose patients receive chronic antithrombotic therapy because the risk of hemorrhagic complications must be balanced against the risk of thromboembolic complications. Interruption of antithrombotic therapy to reduce perioperative bleeding poses a significant risk of recurrent thromboembolic events. Patients who receive chronic antithrombotic therapy should be seen at least 7 days before a planned procedure, and each woman should be included in decision making regarding risks and benefits specific to her situation. The schedule may need to be altered if the international normalized ratio is at a high level and in patients older than 75 years of age (who may need more time to correct their international normalized ratio). The patient’s cardiologist often will have recommendations for the appropriate bridging therapy for a specific valve or stent. A discussion of the risks and benefits of different management schemes for chronic antithrombotic therapy may involve the surgeon, the patient, the anesthesiologist, and the primary care physician.

Indications for Chronic Antithrombotic Therapy

Surgery can present a management dilemma for gynecologists whose patients receive chronic antithrombotic therapy because the risk of hemorrhagic complications must be balanced against the risk of thromboembolic complications. Approximately 250,000 patients in North America are annually affected by this problem (1). Interruption of antithrombotic therapy to reduce perioperative bleeding poses a significant risk of recurrent thromboembolic events (2). With careful management, taking into account risk of hemorrhage and risk of clot, patients who receive chronic antithrombotic therapy have a less than 2% risk of venous thromboembolism or bleeding (3). The care of patients who receive antithrombotic therapy around the time of gynecologic surgery is considered in this document based on expert opinion and 2012 guidelines from the American College of Chest Physicians (ACCP), which offer clinical practice recommendations based on the best available evidence (1).

Venous thromboembolism, which includes deep venous thrombosis and pulmonary embolism; 2) current atrial fibrillation (AF), which is associated with a risk of arterial thromboembolism; and 3) the presence of a mechanical heart valve, which also carries a risk of arterial thromboembolism. Most of these patients will be managed in an outpatient setting with the administration of oral warfarin or an antiplatelet drug (or a combination of the two), or a new anticoagulant agent (see “Patients Receiving Chronic Therapy With New Anticoagulant Agents”).

Bridging Therapy

Interruption of antithrombotic therapy to reduce perioperative bleeding poses a significant risk of recurrent thromboembolic events (2). In preparation for elective surgery, patients who receive chronic antithrombotic therapy may undergo bridging therapy, in which a long-acting anticoagulant is temporarily interrupted and a shorter-acting agent is used in the perioperative period. This allows the antithrombotic therapy to be interrupted before surgery and restarted soon after surgery. The shorter acting agents are often low molecular weight (LMW) heparin or unfractionated heparin.
The decision on whether to use bridging therapy, what type of bridging therapy to use, and when to resume antithrombotic therapy is based on individualized risk assessment to determine the risk of thromboembolism and the risk of major bleeding events associated with the planned surgery. Although physicians may have different perspectives on this issue, the 2012 ACCP guidelines include the recommendation that patient preferences be considered, especially when medical recommendations are not strongly supported by evidence. A discussion of the risks and benefits of different management schemes for chronic antithrombotic therapy may involve the surgeon, the patient, the anesthesiologist, and the primary care physician. The patient’s cardiologist often will have recommendations for the appropriate bridging therapy for a specific valve or stent. Some patients may no longer need any chronic antithrombotic therapy, and the gynecologic surgeon may want to address the issue with the patient’s primary care provider as part of the preoperative surgical assessment.

**Risks Associated With Antithrombotic Therapy and Surgery**

The following sections include general considerations for the perioperative risk assessment of patients based on their clinical indication for chronic antithrombotic therapy. The CHADS₂ score (Congestive heart failure, Hypertension, Age greater than or equal to 75 years, Diabetes mellitus, and Stroke or transient ischemic attack) is used to predict the risk of stroke for patients with AF (Table 1). The CHADS₂ score is helpful in using Table 2, Table 3, and Table 4 to select management protocol (4). Patients who receive chronic antithrombotic therapy should be seen at least 7 days before a planned procedure, and each woman should be included in the decision making regarding risks and benefits specific to her situation. Patients may be stratified according to the risk of bleeding associated with the planned surgery (Table 2). For example, there may be no need to stop antithrombotic therapy for minor procedures associated with a low risk of bleeding. Patients also may be stratified based on their risk of thromboembolism (Table 2, Table 3, and Table 4). The type of thromboembolism that poses a risk also is an important consideration because the consequences of arterial thromboembolism may have more devastating sequelae compared with venous thromboembolism. There are also individual patient risk factors (eg, age, body mass index, mobility, or current cancer), some of which may not be modifiable, to incorporate into the overall risk assessment. Individual risks should be considered in upgrading or downgrading recommended protocols for managing antithrombotic therapy at the time of surgery.

**Venous Thromboembolism**

Most patients who receive chronic antithrombotic therapy for venous thromboembolism are prescribed warfarin, a vitamin K antagonist. The goal of the therapy is to achieve a standardized prothrombin time, known as the international normalized ratio (INR), in the therapeutic range of 2–3. There are no validated risk stratification schemes for patients treated with vitamin K antagonists; thus, clinician experience, perceived risk, and patient preference must be taken into account. Factors that increase the risk of recurrent venous thromboembolism are listed in Table 2. A common question is if patients with a history of venous thromboembolism more than 12 months ago should be specially treated at the time of surgery. The low rates of repeat venous thromboembolism in such patients have led to the recommendation that therapy may be avoided, unless the patient has an active neoplasm (3). Patients with cancer are at an especially high risk of venous thromboembolism, as demonstrated in the gynecologic literature and general medical literature, and the risk seems to remain increased for up to 4 weeks during the postoperative period (5). In a prospective cohort study of patients who received antithrombotic therapy for acute, subacute, or chronic venous thromboembolism, active cancer was the only independent predictor of thrombotic recurrence (hazard ratio, 4.86; 95% confidence interval, 1.6–14.5) (3).

**Atrial Fibrillation**

Chronic antithrombotic therapy is recommended for patients with AF who do not elect cardioversion, unless they are at low risk of stroke or have a specific contraindication to the use of warfarin (eg, thrombocytopenia, recent trauma or surgery, or alcoholism) (6).

**Mechanical Heart Valve**

In general, for patients with a mechanical heart valve, the patient’s cardiologist should be involved in assigning

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### Table 1. CHADS₂ Score to Predict Risk of Stroke in Patients With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age greater than or equal to 75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S Stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data from peer review organizations representing seven states were used to assemble a National Registry of Atrial Fibrillation consisting of 1,733 Medicare beneficiaries aged 65–95 years who had nonrheumatic atrial fibrillation and were not prescribed warfarin at hospital discharge. The stroke rate per 100 patient-years without antithrombotic therapy increased by a factor of 1.5 (95% confidence interval [CI], 1.3–1.7) for each 1-point increase in the CHADS₂ score: 1.9 (95% CI, 1.2–3.0) for a score of 0; 2.8 (95% CI, 2.0–3.8) for 1; 4.0 (95% CI, 3.1–5.1) for 2; 5.9 (95% CI, 4.6–7.3) for 3; 8.5 (95% CI, 6.3–11.1) for 4; 12.5 (95% CI, 8.2–17.5) for 5; and 18.2 (95% CI, 10.5–27.4) for 6. Data from Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
### Table 2. Perioperative Management of Patients With Prior Venous Thromboembolism Who Receive Antithrombotic Therapy for Venous Thromboembolism According to Risk of Recurrent Venous Thromboembolism and Risk of Bleeding With Planned Gynecologic Surgery

<table>
<thead>
<tr>
<th></th>
<th>High Risk of Thromboembolism (Venous Thromboembolism Within 3 Months, Severe Thrombophilia)</th>
<th>Moderate Risk of Thromboembolism (Venous Thromboembolism Within 3–12 Months, Nonsevere Thrombophilia)</th>
<th>Low Risk of Thromboembolism (Venous Thromboembolism More Than 12 Months Ago, No Other Risk Factors Such as Those in CHADS₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate risk of bleeding (most gynecologic surgeries)</td>
<td>Protocol A</td>
<td>Individualize: Protocol B or Protocol C</td>
<td>Protocol C</td>
</tr>
<tr>
<td>Low risk of bleeding</td>
<td>Consider continuing antithrombotic therapy through surgery or Protocol A</td>
<td>Individualize: Consider continuing antithrombotic therapy Protocol A or Protocol B</td>
<td>Protocol C</td>
</tr>
</tbody>
</table>


Protocol C. Interrupt long-term antithrombotic therapy. Do not use bridging therapy. Resume long-term anticoagulation therapy after surgery. Use mechanical prophylaxis with an intermittent compression device during surgery and until long-term antithrombotic therapy (resumed after surgery) is therapeutic.

*For patients at high risk of bleeding, consider managing the perioperative period using mechanical prophylaxis instead of LMW heparin or unfractionated heparin. Consider managing the postoperative period using subcutaneous LMW heparin or mechanical prophylaxis. In patients considered to be at high risk of bleeding, it may be reasonable to forego any LMW heparin after surgery and to simply resume long-term anticoagulation therapy.

†Consider using low-dose LMW heparin or unfractionated heparin prophylaxis during surgery in patients at low risk of bleeding.

Bridging Therapy Protocols

The goal of bridging therapy is to prevent further venous thromboembolism while avoiding bleeding. Although subcutaneous unfractionated heparin often is used for bridging therapy and may be less expensive (8, 9), most of the studies upon which to make recommendations have used LMW heparin. Types of bridging therapy include the following:

- **High dose (therapeutic dose):** Subcutaneous LMW heparin (enoxaparin, 1 mg/kg twice daily or 1.5 mg/kg once daily), or intravenous (IV) unfractionated heparin to attain an activated partial thromboplastin time that is 1.5–2 times greater than the control value.
- **Low dose (prophylactic dose):** Subcutaneous LMW heparin (enoxaparin, 30 mg twice daily or 40 mg once daily); subcutaneous unfractionated heparin (5,000–7,500 international units twice daily) is another option, although this regimen has not been studied as thoroughly as the LMW heparin regimen.

Risk based on the specific valve, stent, and comorbidities; however, the surgeon often writes the orders for the management scheme. High risk is assigned to patients with certain valve prostheses (eg, cage ball or tilting disk aortic valves) or history of stroke or transient ischemic attack within the past 6 months (Table 4) (7). Moderate risk is assigned to patients with bileaflet aortic valve prosthesis and one or more of the following risk factors: AF with prior stroke or transient ischemic attack; hypertension; diabetes; congestive heart failure; or age greater than 75 years. Low risk is assigned to patients with bileaflet aortic prosthesis without AF and no other risk factors for stroke.

Committee Opinion No. 610
### Table 3. Perioperative Management of Patients With Atrial Fibrillation Who Receive Antithrombotic Therapy According to Risk of Recurrent Arterial Thromboembolism and Risk of Bleeding With Gynecologic Surgery

<table>
<thead>
<tr>
<th>High Risk of Arterial Thromboembolism (CHADS² Score=5–6; Stroke or Transient Ischemic Attack Less Than 3 Months Ago)</th>
<th>Moderate Risk of Arterial Thromboembolism (CHADS² Score=3–4)</th>
<th>Low Risk of Arterial Thromboembolism (CHADS² Score=0–2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of bleeding (major surgery for gynecologic cancer)</td>
<td>Protocol A* or Protocol B (preferred)</td>
<td>Protocol C (preferred) or Protocol B</td>
</tr>
<tr>
<td>Moderate risk of bleeding (most gynecologic surgeries)</td>
<td>Protocol A (preferred) or Protocol B</td>
<td>Protocol B or Protocol C</td>
</tr>
<tr>
<td>Low risk of bleeding</td>
<td>Protocol A</td>
<td>Protocol B (preferred) or Protocol C</td>
</tr>
</tbody>
</table>


Protocol C. Interrupt long-term anticoagulation therapy. Do not use bridging therapy. Resume long-term anticoagulation therapy after surgery. Use mechanical prophylaxis with an intermittent compression device during surgery and until long-term anticoagulation (resumed after surgery) is therapeutic.

*Resume subcutaneous LMW heparin 48–72 hours after surgery instead of 24 hours.

### Table 4. Perioperative Management of Patients With Mechanical Heart Valves Who Receive Antithrombotic Therapy According to Risk of Arterial Thromboembolism and Risk of Bleeding With Planned Gynecologic Surgery

<table>
<thead>
<tr>
<th>High Risk of Arterial Thromboembolism (Bileaflet Aortic Valve Prosthesis, Plus One of the Following: AF With Prior Stroke or TIA; Hypertension; Diabetes; Congestive Heart Failure; Age Greater Than 75 Years)</th>
<th>Moderate Risk of Arterial Thromboembolism (Bileaflet Aortic Valve Prosthesis Without AF With Prior Stroke or TIA; Hypertension; Diabetes; Congestive Heart Failure; Age Greater Than 75 Years)</th>
<th>Low Risk of Arterial Thromboembolism (Bileaflet Aortic Valve Prosthesis Without AF With Prior Stroke or TIA; Hypertension; Diabetes; Congestive Heart Failure; Age Greater Than 75 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of bleeding (major surgery for gynecologic cancer)</td>
<td>Protocol A*</td>
<td>Protocol A or Protocol B*</td>
</tr>
<tr>
<td>Moderate risk of bleeding (most gynecologic surgeries)</td>
<td>Protocol A</td>
<td>Protocol C (preferred) or Protocol B</td>
</tr>
<tr>
<td>Low risk of bleeding</td>
<td>Protocol A</td>
<td>Protocol C Consider continuing anticoagulation therapy or Protocol B</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; TIA, transient ischemic attack.


Protocol C. Interrupt long-term anticoagulation therapy. Do not use bridging therapy. Routine perioperative thromboembolic prophylaxis should be considered. Resume long-term anticoagulation after surgery. Use mechanical prophylaxis with an intermittent compression device during surgery and until long-term anticoagulation (resumed after surgery) is therapeutic.

*Resume subcutaneous LMW heparin within 48–72 hours instead of 24 hours.
The ACCP guidelines for perioperative management of chronic antithrombotic therapy do not specify the type of bridging therapy protocol that should be used. However, the recommendations do acknowledge that although different regimens may be used, therapeutic-dose bridging regimens are the most widely studied because they offer the greatest therapeutic benefit and the least potential harm. Once a patient’s risk of thromboembolism and risk of bleeding are determined, the type of bridging therapy can be selected (Table 2, Table 3, and Table 4).

**Timing of Anticoagulation Therapy Interruption**

If interruption of vitamin K antagonist antithrombotic therapy is indicated (see Table 2, Table 3, and Table 4), administration should be stopped 5 days before surgery (eg, if surgery is scheduled on a Wednesday, the last dose is given on the previous Friday). If bridging therapy is to be used, it is begun 5 days before surgery (eg, if surgery is scheduled on a Wednesday, the first dose of bridging therapy is given on the previous Friday). Earlier cessation may be considered in patients with a higher INR, such as patients with mechanical heart valves. In all patients who receive bridging therapy, the INR should be checked the day before surgery; patients older than 75 years may benefit from this because age increases the likelihood that the INR will not normalize in the expected time span. In patients whose INR has not normalized (eg, 1.5 or higher) 1 day before surgery, administration of 1–2 mg of oral vitamin K is recommended. The INR typically is measured again the morning of surgery in all patients who receive chronic antithrombotic therapy, regardless of whether they received bridging therapy.

**Stopping Bridging Therapy**

For patients who receive therapeutic-dose bridging therapy, the last dose of subcutaneous LMW heparin should be administered 24 hours before surgery, and IV unfractionated heparin should be stopped 4–6 hours before surgery. The last prophylactic dose of subcutaneous unfractionated heparin should be administered the night before surgery. Patients should receive thromboprophylaxis during and immediately after surgery according to usual clinical practice; this may include the use of an intermittent pneumatic compression device or the administration of prophylactic doses of LMW heparin or unfractionated heparin. For patients who have a high risk of bleeding, the use of an intermittent pneumatic compression device is the preferred method of thromboprophylaxis until hemostasis is assured and bridging therapies can be started again.

**Postoperative Management**

Typically, the surgical team assumes responsibility for managing the resumption of antithrombotic therapy and the continuation of bridging therapy, if indicated. Vitamin K antagonist therapy should be resumed approximately 12–24 hours after completion of surgery (evening of or next morning) when there is adequate hemostasis. In patients who received preoperative bridging therapy with a therapeutic dose of subcutaneous LMW heparin and who underwent surgery with a high risk of bleeding, typically the therapeutic dose of subcutaneous LMW heparin should be restarted 48–72 hours after the completion of surgery. Bridging therapy (with LMW heparin or unfractionated heparin) should be continued until the vitamin K antagonist therapy has achieved an INR in the therapeutic range of 2–3. This transition back to therapeutic INR levels typically takes approximately 5 days.

**Perioperative Management of Antiplatelet Agents**

Antiplatelet agents, such as aspirin (acetylsalicylic acid [ASA]), clopidogrel, or a combination of these, are used for the primary and secondary treatment of ischemic heart disease and cerebrovascular disease. Bridging therapy typically is not recommended for patients who require antiplatelet agents alone.

Acetylsalicylic acid inhibition of platelet activity begins within minutes of administration (10), and its irreversible effect on individual platelets lasts 7–10 days. For women at moderate risk to high risk of cardiovascular (CV) events (such as those having higher CHADS2 scores) who receive ASA therapy and require noncardiac surgery, ACCP guidelines suggest continuing ASA without interruption because the benefit of CV protection that is conferred outweighs the risk of bleeding events that require intervention (11). For patients at low risk of CV events who receive ASA therapy and require noncardiac surgery, ACCP guidelines suggest stopping ASA 7–10 days before surgery. Like vitamin K antagonist therapy, ASA therapy should be restarted approximately 12–24 hours after surgery if there is adequate hemostasis.

Administration of clopidogrel should be stopped 5–7 days before the anticipated procedure if an antiplatelet effect is not desired (12, 13). Clopidogrel takes 5–10 days to attain maximal platelet inhibition, so for postoperative patients who have adequate hemostasis, an initial loading dose (300–600 mg/d) usually is given to attain antiplatelet activity within 12–15 hours after administration (14). A therapeutic-dose regimen of clopidogrel may be restarted 12–24 hours after surgery for patients who have adequate hemostasis.

Because ASA and clopidogrel have irreversible antiplatelet effects, patients being considered for elective surgery who are receiving these drugs should undergo early preoperative assessment that includes consultation with their cardiologist or appropriate perioperative specialist (eg, hematologist, anesthesiologist, or primary care provider). Women with coronary stents and vascular stents, including bare-metal or drug-eluting stents, should seek preoperative consultation with their cardiologist several weeks before a planned procedure.

Committee Opinion No. 610 5
Patients Who Receive Chronic Therapy With New Anticoagulant Agents

Several new anticoagulant agents, known as target-specific oral anticoagulant agents (or direct oral anticoagulant agents), are currently available for stroke prevention in patients with nonvalvular AF; these include direct factor Xa inhibitors (rivaroxaban and apixaban) and a direct thrombin inhibitor (dabigatran). Dabigatran also has been approved for the primary or secondary treatment of acute venous thromboembolism. Unlike traditional anticoagulant agents, target-specific oral anticoagulant agents have a rapid onset of clinical activity and a rapid rate of clearance when stopped and do not require routine laboratory monitoring. However, compared with traditional anticoagulant agents, less is known about their perioperative management.

In a Cochrane review of five randomized trials that compared target-specific oral anticoagulant agents with vitamin K antagonists, the newer drugs compared favorably with traditional warfarin in the prevention of stroke in patients who receive antithrombotic therapy for AF (15). However, it is unclear whether target-specific oral anticoagulant medications will result in fewer intracranial hemorrhages or major bleeding events compared with vitamin K antagonists. In addition, there is less known about the timing of dabigatran and rivaroxaban cessation in perioperative management compared with warfarin, which has a known length of time from last dose to clinical inactivity. Two possible perioperative cessation schemes include 1) stopping the drug 5 days before surgery and begin bridging therapy or 2) stopping the drug 1–5 days before surgery without bridging therapy. Also, these drugs have no known reversal agents, making direct factor Xa inhibitors difficult to manage in urgent or emergency situations.

As the use of target-specific oral anticoagulant agents becomes more common, more information will be available to guide their perioperative management. There are ongoing studies to evaluate the efficacy of possible reversal agents such as prothrombinase complex concentrate, either activated or inactivated, and recombinant activated factor VII (16). Preoperative consultation with the patient’s cardiologist or appropriate perioperative specialist (eg, hematologist, anesthesiologist, or primary care provider) is recommended to guide perioperative management of chronic anticoagulant therapy with these newer agents.

Emergency Surgery and Antithrombotic Therapy

Women who receive vitamin K antagonist therapy who need urgent or emergency surgery typically are given vitamin K (1–2 mg) to reverse the effects of the vitamin K antagonist, ordinarily in the inpatient setting. Furthermore, they also receive bridging therapy with IV heparin.

Conclusion

Patients who receive chronic anticoagulation therapy should be seen at least 7 days before a planned procedure to make plans for bridging therapy (if any) and the timely cessation of vitamin K antagonist therapy. The schedule may need to be altered if the INR is at a high level and in patients older than 75 years (who may need more time to correct their INR). Further coordination with cardiologists or with the patient’s antithrombotic therapy managers may be indicated before cessation of these drugs. Patients may benefit from a calendar to correctly time their bridging therapy, coordinate with caregivers, and allow training of the patient or family in subcutaneous injection techniques. Patient preferences should be considered, especially when medical recommendations are not strongly supported by evidence. A discussion of the risks and benefits of different management schemes for chronic antithrombotic therapy may involve the surgeon, the patient, the anesthesiologist, and the primary care physician.

References


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