Perioperative Management of Antithrombotic Therapy in Common Otolaryngologic Surgical Procedures: State of the Art Review

Wayne D. Hsueh, MD1, Peter H. Hwang, MD2, and Waleed M. Abuzeid, MD1

Abstract

Objective. The perioperative management of patients undergoing otolaryngologic procedures is increasingly complicated by the use of newer antithrombotic agents. Furthermore, with advances in anesthesia and surgical technique, otolaryngologists are presented with the challenge of operating on patients with advanced comorbid diseases. The objective of this review is to provide evidence-based recommendations on perioperative antithrombotic management for common otolaryngologic procedures.

Data Sources. PubMed/MEDLINE.

Review Methods. Selected literature on patient-specific thromboembolic risk, rate of bleeding complications in otolaryngologic procedures, and the interruption of antithrombotic therapy is reviewed and interpreted by expert opinion.

Conclusions. By stratifying patients into either low thromboembolic risk (≤5%) or high thromboembolic risk (>5%) and interpreting this in the context of procedural bleed risk and potential clinical consequences in the event of a bleed, otolaryngologists can make evidence-based decisions to determine the appropriate perioperative management of antithrombotic therapy.

Implications for Practice. When the perioperative management of antithrombotic therapy is being decided, 3 critical factors must be considered systematically: the patient’s inherent thromboembolic risk, the risk and potential consequences of bleeding related to the procedure, and the timing of interruption of thromboembolic therapy.

Keywords

anticoagulation, antithrombotics, perioperative management

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The perioperative management of patients undergoing otolaryngologic procedures is increasingly complicated by comorbid conditions necessitating anticoagulant or antiplatelet therapies. These comorbidities include atrial fibrillation, cardiac valve replacement, venous thromboembolism, and the presence of coronary stents. Approximately 10% of patients on antithrombotic agents must interrupt their therapy to undergo surgery.1 In these patients, a therapeutic dilemma exists: continuing antithrombotic therapy increases the risk of perioperative bleeding, while interrupting therapy increases the risk of thromboembolism. Further complicating the issue is the introduction of a newer generation of anticoagulants.

There is a paucity of prospective data comparing the efficacy and safety of antithrombotic regimens. The ultimate goal is to balance and minimize the risk of thromboembolic events and hemorrhage in the perioperative period. This review provides evidence-based suggestions on perioperative antithrombotic management for common otolaryngologic procedures. These recommendations are intended to augment the clinical decision-making process but, secondary to the paucity of specialty-specific data, should not be considered clinical practice guidelines.

Methods

The PubMed/MEDLINE database from 1960 to 2015 was searched for all relevant peer-reviewed publications. Manuscripts pertaining to the determination of thromboembolic risk in patients were reviewed. A second search identified manuscripts reporting bleeding risk associated with common otolaryngologic procedures. A third literature search was directed toward literature investigating antithrombotic agents, including drugs introduced over the past 5 years, and drug-specific recommendations regarding interruption of therapy. The data obtained were

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Prosthetic heart valve without high-risk features

Prosthetic heart valve within 3 mo of surgery or with high-risk features

Heart failure, hypertension, age of scores carrying increased thromboembolic risk: congestive ischemic attack is given 2 points.2 A CHADS2 score of 0 to

Annual risk. ’’Moderate to high risk’’ patients have an annual risk >5% (Table 1).2-6 Risk stratification is influenced by underlying pathology and associated disease-related risk assessments. Common factors that increase thromboembolic risk include atrial fibrillation, presence of a prosthetic heart valve, venous thromboembolism, and presence of coronary stents.

Atrial Fibrillation. Atrial fibrillation accounts for the highest percentage of patients in whom perioperative anticoagulation must be addressed. The significance of this issue is demonstrated by the Randomized Evaluation of Long-term Anticoagulant Therapy trial, which included 4591 patients with nonvalvular atrial fibrillation who underwent elective procedures during a 2-year period, with an overall perioperative thromboembolic risk of 1.2%.7

Due to a wide variation in stroke risk related to comorbidities in patients with atrial fibrillation, stratification systems are used to quantify thromboembolic risk. In the CHADS2 system, scores range from 0 to 6, with higher scores carrying increased thromboembolic risk: congestive heart failure, hypertension, age of ≥75 years, and diabetes are each assigned 1 point, and prior stroke or transient ischemic attack is given 2 points.2 A CHADS2 score of 0 to 2 places patients in the low-risk category and predicts the stroke rate per 100 patient-years as 1.9 to 4.2.8

In the more recent CHA2DS2-VASc, the maximum score is 9 and includes added points for vascular disease, female sex, and age from 65 to 74 years, each of which is worth 1 point. Patients who are ≥75 years of age receive 2 points.3 A CHA2DS2-VASc score from 0 to 4 places a patient at low risk for a thromboembolic event with a predicted adjusted stroke rate from 0% to 4%.3,9 A CHA2DS2-VASc score ≥5 predicts an adjusted stroke rate from 6.7% to 15.2%.

Typically, the CHA2DS2-VASc score is interpreted during the preoperative clearance process for patients with atrial fibrillation to determine overall thromboembolic risk and, based on the overall risk stratification, to provide recommendations for perioperative anticoagulant management.

Prosthetic Heart Valve. Patients with prosthetic heart valves are required to be on long-term anticoagulation, usually warfarin, due to their inherently high risk of a thromboembolic event. The risk of thromboembolism is highest in the first 3 months after prosthetic heart valve replacement or repair, with a risk of 3.6% to 10%, declining to <4% after 90 days.10,11 Whenever possible, elective procedures should be delayed for at least 3 months after valve surgery.12

Based on the 2006 American College of Cardiology / American Heart Association valvular disease guidelines, the 2012 European Society of Cardiology valvular guidelines, and the 2012 American College of Chest Physicians guidelines, the presence of any one of the following features, in the setting of a prosthetic heart valve, places patients at high risk for thromboembolism: atrial fibrillation, prior thromboembolism, left ventricular ejection fraction <35%, mitral or tricuspid valve placement, ≥2 prosthetic valves, or older aortic ball or tilting disc valves. This latter category includes Lillehei-Kaster, Omnicience, Starr-Edwards, or Bjork Shiley replacement valves.1,11,14 Importantly, patients without any of the above risk factors are considered low risk. Those with newer low thrombogenic prostheses, such as the Carbomedics, Medtronic Hall, St Jude Medical, and ON-X devices, are also considered low risk assuming the absence of any of the aforementioned risk factors.4,5,14

Venous Thromboembolism. The risk of thromboembolism is greatest in the period immediately following a thromboembolic event, and it declines over time. Patients with a recent thromboembolic event are likely to benefit from delaying the procedure until they are out of the high-risk period.15

For venous thromboembolism, the greatest risk for recurrent thrombosis, thrombus propagation, and embolization is within the initial 3 to 4 weeks—approximately 1% risk per day—and then diminishes over the next 2 months.16,17 Without anticoagulation, the early risk of thromboembolic event recurrence is approximately 50%; however, with

<table>
<thead>
<tr>
<th>Table 1. Thromboembolic Risk Stratification.</th>
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<tbody>
<tr>
<td>Low Thromboembolic Risk (≤5%)</td>
</tr>
<tr>
<td>Atrial fibrillation with a CHADS2 score of 0-2</td>
</tr>
<tr>
<td>Atrial fibrillation with a CHADS2-VASc score of 0-4</td>
</tr>
<tr>
<td>Prosthetic heart valve without high-risk features</td>
</tr>
<tr>
<td>Venous thromboembolism after 3 mo of anticoagulation treatment</td>
</tr>
<tr>
<td>Coronary stents after 1 y of antiplatelet therapy</td>
</tr>
</tbody>
</table>

*High-risk features include atrial fibrillation, prior thromboembolism, left ventricular ejection fraction <35%, mitral or tricuspid valve placement, ≥2 prosthetic valves, and older aortic ball or tilting disc valves (eg, Lillehei-Kaster, Omnicience, Starr-Edwards, Bjork Shiley).
warfarin, the risk is reduced to 10% after 1 month and 5% after 3 months. In essence, patients who have had a newly diagnosed venous thromboembolism within 3 months of the surgical date should be managed as high risk.

**Coronary Stents.** Patients with coronary stents often require dual antiplatelet therapy with aspirin and a second antiplatelet agent. The American College of Cardiology and the American Heart Association recommend antiplatelet therapy for at least 1 month after bare-metal stent and up to 1 year after drug-eluting stent implantation based on the anticipated time for stent endothelialization, a physiologic process that reduces thrombosis risk. The risk of stent thrombosis is highest in the first month after implantation, which can precipitate a myocardial infarction with mortality rates from 20% to 45%. Consequently, the general consensus is to delay elective surgery for at least 1 year after stent placement. If the surgery cannot be postponed, aspirin must be continued during the perioperative period for patients with drug-eluting stents. Any patient with a coronary stent placed within 1 year of the proposed surgical date should be managed as high risk.

**Assessment of Bleeding Risk**

The risk of bleeding associated with a procedure is primarily determined by the type of procedure, age, and the use of antithrombotics. Overall risk is significantly influenced by comorbidities, including renal disease, hepatic dysfunction, and malignancy. The stratification of perioperative bleeding risk has not been standardized. The American Academy of Otolaryngology—Head and Neck Surgery does not provide guidelines on antithrombotic management. However, a recent review in the *New England Journal of Medicine* proposed that high-risk procedures be defined as those with a bleeding risk exceeding 1.5% among patients not receiving antithrombotic agents. This threshold, in the absence of evidence-based literature, provides a basis from which procedural bleeding risk can be estimated. The consequences of a potential bleed must be considered as part of procedural risk stratification. Specifically, procedures that may result in hemorrhage into the intraocular or intracranial spaces or that could result in airway compromise should be considered high risk regardless of the relative risk of a bleeding event. Furthermore, procedures that may warrant the transfusion of blood products should also be considered high risk. Applying these principles, we have categorized a variety of common otolaryngologic procedures as “low risk” or “high risk” (Table 2).

### Table 2. Bleeding Risks of Common Procedures in Otolaryngology.

<table>
<thead>
<tr>
<th>Low Bleeding Risk (≤1.5%) AND Lower Potential for Major Sequelae</th>
<th>High Bleeding Risk (&gt;1.5%) OR Higher Potential for Major Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tympanoplasty</td>
<td>Endoscopic sinus surgery</td>
</tr>
<tr>
<td>Diagnostic nasopharyngoscopy or laryngoscopy</td>
<td>Transsphenoidal pituitary surgery</td>
</tr>
<tr>
<td>Fine-needle aspiration biopsy</td>
<td>Rhinoplasty and/or septoplasty</td>
</tr>
<tr>
<td>Vocal fold injections</td>
<td>Inferior turbinate reduction</td>
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<tr>
<td></td>
<td>Tracheotomy</td>
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<tr>
<td></td>
<td>Thyroidectomy</td>
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<tr>
<td></td>
<td>Parotidectomy</td>
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<tr>
<td></td>
<td>Laryngectomy</td>
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<tr>
<td></td>
<td>Tonsillectomy and adenoidectomy</td>
</tr>
</tbody>
</table>

**Low-Risk Procedures: ≤1.5% Bleeding Rate and Lower Potential for Major Sequelae.** Common low-risk procedures include tympanoplasty, diagnostic nasopharyngoscopy and laryngoscopy, fine-needle aspiration biopsy, and vocal fold injections. There are no publications reporting the rates of posttympanoplasty hemorrhage or bleeding after diagnostic nasopharyngoscopy or laryngoscopy, suggesting that the bleeding risk is exceedingly low. Additionally, there are few reported cases of fine-needle aspiration biopsy complicated by compressive hematoma. In a series of 2592 patients admitted emergently for thyroidectomy over 7 years, only 1 patient had an acute hemorrhage after diagnostic fine-needle aspiration. There have been no reported bleeding complications from vocal fold injection. Indeed, in a series of 460 vocal fold injections over 1 year, the incidence of hemorrhage was zero.

**High-Risk Procedures: >1.5% Bleeding Rate or Higher Potential for Major Sequelae.** Common high-risk procedures include endoscopic sinus surgery, transsphenoidal pituitary surgery, rhinoplasty, septoplasty, inferior turbinate reduction, tracheotomy, thyroidectomy, parotidectomy, laryngectomy, tonsillectomy, and adenoidectomy.

May et al reviewed complications of endoscopic sinus surgery in 2108 patients. In this cohort, hemorrhage requiring transfusion occurred in 0.19% of cases and epistaxis in 0.6%. The investigators also conducted a meta-analysis incorporating 2583 cases with a transfusion rate of 0.19%. Ramakrishnan et al recently analyzed a national insurance database to evaluate the incidence of complications in endoscopic sinus surgery. In their cohort of 58,752 patients, 0.76% experienced a hemorrhage requiring transfusion.
Across the literature, reported postoperative hemorrhage rates range from 0.1% to 1.3%. Although most bleeds related to endoscopic sinus surgery are of minimal consequence, significant bleeding-related complications are described. For example, intraorbital hemorrhage may occur in 0.07% of cases and can lead to vision loss. Although these risks are of low incidence, their consequences may be severe. Consequently, endoscopic sinus surgery should be considered a high-risk procedure.

Endoscopic transsphenoidal pituitary resections are associated with a higher risk of bleeding than that of endoscopic sinus surgery, with rates from 0.8% to 3.4%. Capabianca et al reviewed 146 cases and reported bleeding complications in 2.7% of patients. Similarly, Charalampaki et al reviewed 150 cases and found that 2.6% of patients had significant bleeding complications. A national survey of 939 neurosurgeons demonstrated a 2.9% rate of residual tumor hemorrhage and a 3.4% rate of postoperative epistaxis requiring intervention. In the same study, the lead author reported his personal experience of 638 cases, in which 2.2% experienced postoperative bleeding complications. These data suggest that transsphenoidal pituitary surgery is of high bleeding risk.

Rhinoplasty has reported bleeding rates of 2% to 4%. Miller reported postoperative epistaxis that required repacking in 2.3% of cases. In cosmetic rhinoplasties, postoperative hemorrhage occurs in approximately 2% of patients. Goldwyn reviewed 780 cases undergoing elective nasal surgery under local anesthesia and reported excessive bleeding in 3.6%, and severe bleeding in 0.9%. The majority of rhinoplasty-related epistaxis is easily controlled, without the need for operative intervention. Episodes of epistaxis that are more severe can typically be managed conservatively with silver nitrate cauterization, topical hemostatic sealants, and nasal packing. However, rhinoplasty is also associated with a low risk of orbital hematoma. This risk is particularly evident in cases necessitating osteotomies. The potential consequences of such a bleed may be significant and should be considered during risk stratification.

Septoplasty is associated with a low absolute risk of bleeding. Quinn et al performed a systematic review of complications from septoplasty incorporating 17 studies with a total of 2079 participants. The overall hematoma rate was 0.7%, consistent with other published studies. The use of intranasal packing did not change bleeding risk postoperatively. The most feared bleeding complication in septoplasty is septal hematoma. Left untreated or in situations where treatment is delayed, septal hematoma can result in dissolution of the septal cartilage and, subsequently, severe nasal deformity. Although the risk of bleeding in septoplasty is <1.5%, the potential consequences are significant, and this procedure should be considered high risk.

The bleeding risk of inferior turbinate reduction depends on the method used. Electrocautery has been shown to have a rate of delayed hemorrhage from 6% to 9%. Partial turbinates resections range from <1% to 10%. Submucous resection has a reported postoperative bleeding rate of 5.3% to 26%. Overall, the bleeding risk of inferior turbinate reduction remains relatively high regardless of technique, suggesting that this procedure is high risk.

Tracheotomy is associated with postoperative bleeding rates of 0.7% to 2.6% in the literature. Halum et al reviewed 1175 tracheotomy procedures and found that the most common early complication was postoperative bleeding, with an incidence of 2.6%. Although posttracheotomy bleeding can range from mild stomal oozing to catastrophic tracheoinnominate fistulas, the potential for resultant airway compromise exists in all scenarios. When this is considered with reported bleeding rates that exceed 1.5%, tracheotomy should be stratified as high risk.

Head and neck open procedures are generally classified as high-risk procedures. To illustrate, the incidence of postoperative hematoma from thyroidectomies ranges from 0.1% to 4.7%. Bergenfelz et al reviewed 3660 thyroid operations in a Scandinavian database from 2004 to 2006 and found that 2.1% of operations were complicated by rebleeding with compressive hematoma. Matory and Spiro found that of 504 thyroidectomy cases, 1.6% had postoperative bleeding. However, numerous studies have reported an incidence <1.5% for neck hematomas secondary to thyroidectomy. Given this wide range of risks and, critically, the possibility of airway compression secondary to the development of a neck hematoma, thyroidectomy should be considered a procedure at high risk for bleeding.

Matory and Spiro noted that, among head and neck surgical procedures, parotidectomy was associated with the highest rate of significant postoperative bleeding, with an incidence of 2.7%. Lacourreye and colleagues reported a hemorrhage rate of 1.7% across 229 parotidectomy cases. In contrast, in a separate study spanning 10 years and incorporating 271 parotidectomy patients, Lin et al found a 1% hemorrhage rate. Similarly, Klintworth et al showed only a 0.8% rate of secondary bleeding in 934 parotidectomy patients, but this was offset by an elevated incidence of postoperative hematoma of 6.1%. Like that of thyroidectomy, the bleeding risk of parotidectomy spans the low- and high-risk stratification threshold. The most conservative approach is to consider this surgery of high bleeding risk.

The reported postoperative bleeding rates associated with laryngectomy exceed 2%. Herranz et al showed that of 471 patients undergoing total laryngectomy, with or without neck dissection, 2.8% were complicated by postoperative hemorrhage. This is consistent with other published postoperative hemorrhage rates of 2% to 3%. Thus, laryngectomy should be stratified as a procedure with high bleeding risk.

The risk of postoperative hemorrhage associated with tonsillectomy and adenoidectomy demonstrates a bimodal distribution. The risk of hemorrhage is highest in the immediate postoperative period, termed primary bleeding, with a second peak approximately 1 week after surgery, designated as secondary bleeding. A retrospective analysis of 15,218 patients demonstrated a primary bleeding incidence of...
Low, 1% to 8.1%, although the majority of studies indicate an incidence between 1% and 4%.\textsuperscript{91-93} Due to the potentially high rate of secondary bleeding, tonsillectomy should be classified as a procedure with a high bleeding risk.

### Planning Perioperative Interruption of Antithrombotic Therapy

Following accurate determination of a patient’s underlying thromboembolic risk, the procedural bleeding risk, and the potential consequences in the event of a bleed, an informed adjustment of perioperative antithrombotic medications can be made with the goal of achieving a risk-benefit balance between increased thromboembolic risk and reducing bleed risk (Table 3). The reduction of bleed risk is dependent on allowing sufficient time for dissipation of the anticoagulation effect. This duration depends on the pharmacokinetics of the antithrombotic agent and on patient factors that affect drug clearance, such as renal or hepatic function. Antithrombotic agents can be safely restarted once the postoperative bleeding risk is deemed low, typically on postoperative day 2 or 3. A notable exception to this recommendation is warfarin, which can be started on postoperative day 1 given the extended time required for the serum concentration to achieve the therapeutic window.

### Warfarin

Warfarin (Coumadin) impairs coagulation by preventing the synthesis of vitamin K–dependent factors II, VII, IX, and X and proteins C and S. The anticoagulant effects of warfarin are monitored by measuring serum prothrombin time, which is standardized across institutions using the international normalized ratio (INR). An INR of 2.0 to 3.5 indicates therapeutic anticoagulation. An INR \( \leq 1.5 \) is subtherapeutic and should not increase bleeding risk.\textsuperscript{6,96} Approximately 93% of patients with therapeutic levels of warfarin will have an INR <1.5 five days after stopping warfarin based on its half-life of 36 to 42 hours.\textsuperscript{97,98} Thus, discontinuing warfarin 5 days prior to surgery with a preoperative target INR \( \leq 1.5 \) is considered safe for high-risk procedures.\textsuperscript{6,99}

The INR should be checked the day before surgery, and if \( >1.5 \), consideration should be given for administration of low-dose vitamin K (1-2 mg).\textsuperscript{100} However, in patients with mechanical heart valves, vitamin K should not be administered, as it will significantly delay the ability to reanticoagulate with warfarin, markedly increasing the risk of a thromboembolic event.\textsuperscript{113} If warfarin is continued through the procedure because the patient’s thromboembolic risk is deemed too high, an INR of approximately 2.5 is advisable.\textsuperscript{30} Warfarin can be reversed within hours by administering intravenous vitamin K and fresh-frozen plasma.\textsuperscript{99} If volume overload is a concern, prothrombin complex concentrates can achieve the same effect.\textsuperscript{101} Since warfarin takes several days to achieve therapeutic levels, we recommend restarting it the evening of postoperative day 0, assuming there are no anticipated bleeding issues or need for reoperation.\textsuperscript{6,30}

### Direct Thrombin Inhibitors

Dabigatran (Pradaxa) is an oral direct thrombin inhibitor that reversibly blocks the function of thrombin (factor II) in converting fibrinogen to fibrin. Although routine coagulation studies have not been validated for monitoring, a normal activated partial thromboplastin time (aPTT) can rule out any residual effect of dabigatran.\textsuperscript{102} Based on its half-life of 12 to 14 hours in patients with normal renal function, dabigatran should be discontinued 2 days preoperatively in patients with a creatinine clearance \( \geq 50 \) mL/min and 4 days preoperatively if creatinine clearance is \(<50 \) mL/min.\textsuperscript{103,104}

In the Randomized Evaluation of Long-term Anticoagulant Therapy trial, patients with nonvalvular atrial fibrillation were randomized to warfarin or dabigatran for stroke prevention.\textsuperscript{7} In patients who underwent elective surgery, dabigatran was discontinued 49 hours prior to surgery and warfarin, 114 hours. The perioperative thromboembolic risk was 1.2%, with no difference in bleeding risk between anticoagulants. Thus, dabigatran can be safely discontinued prior to surgery in patients with atrial fibrillation, and it shortens interruption of anticoagulation as compared with warfarin. In life-threatening bleeding, dabigatran reversal with hemodialysis or charcoal hemoperfusion can be considered.\textsuperscript{105}

Desirudin (Iprivask) is a subcutaneous direct thrombin inhibitor that has an elimination half-life of 2 hours and should be discontinued 10 hours preoperatively.\textsuperscript{30} Argatroban is an intravenously administered direct thrombin inhibitor used primarily in heparin-induced thrombocytopenia. It has a half-life of 50 minutes and should be discontinued 4 hours prior to surgery.\textsuperscript{106,107}

### Table 3. Recommendations for Perioperative Management of Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Thromboembolic Risk</th>
<th>Low Bleeding Risk (( \leq 1.5 )) AND Lower Potential for Major Sequelae</th>
<th>High Bleeding Risk (( &gt;1.5 )) OR Higher Potential for Major Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low, ( \leq 5% )</td>
<td>Hold antithrombotic therapy if possible. If not, proceeding with surgery without holding antithrombotic therapy should be safe.</td>
<td>Hold antithrombotic therapy.</td>
</tr>
<tr>
<td>Moderate to high, ( &gt;5% )</td>
<td>Continue antithrombotic therapy.</td>
<td>Hold antithrombotic therapy. Consider waiting for the thromboembolic risk to decrease before surgery.</td>
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</tbody>
</table>
Direct thrombin inhibitors can be resumed 2 to 3 days postoperatively after hemostasis has been achieved due to their rapid onset of action and lack of reliable reversal agents.30

Direct Factor Xa Inhibitors. Rivaroxaban (Xarelto) and Apixaban (Eliquis) are orally administered direct factor Xa inhibitors that reversibly block the conversion of prothrombin to thrombin by factor Xa. A normal anti–factor Xa activity level determines if the anticoagulant has been cleared from the circulation. Dosing is based on creatinine clearance, with an elimination half-life of 7 to 11 hours with normal renal function. These agents should be discontinued 2 days prior to surgery in patients with a creatinine clearance ≥60 mL/min and 4 to 5 days preoperatively if creatinine clearance is <60 mL/min.96,108

Fondaparinux (Arixtra) is a subcutaneously administered direct factor Xa inhibitor with a half-life of 17 hours. It has been associated with acceptable rates of bleeding when discontinued >36 hours prior to coronary artery bypass grafting.30,109 Based on these findings, fondaparinux can be safely discontinued 2 days prior to otolaryngologic surgery.

Direct factor Xa inhibitors can be resumed 2 to 3 days postoperatively after hemostasis has been achieved, due to their rapid onset of action and lack of reliable reversal agents.30

Heparin. Unfractionated heparin can be administered intravenously or subcutaneously, and it activates antithrombin, leading to inhibition of factors IIa, IXa, Xa, XIa, and XIIa. The effects can be monitored by using aPTT. When given intravenously, unfractionated heparin has a half-life of 60 to 90 minutes, and it can be stopped 4 to 6 hours prior to surgery.6,110 Subcutaneous unfractioned heparin can be given up to 12 hours preoperatively. In cases of severe bleeding, protamine sulfate is a highly effective reversal agent.

Low molecular weight heparins (LMWH), such as enoxaparin (Lovenox) and dalteparin (Fragmin), are subcutaneously administered and lead to antithrombin activation through targeted anti–factor Xa activity. This obviates the need for aPTT monitoring and reduces the risk of heparin-induced thrombocytopenia. LMWH has a half-life of 4 hours. The last dose should be given 24 hours preoperatively at 50% of the total daily dose.6

LMWH and unfractionated heparin are often used for bridging when longer-acting anticoagulants, typically warfarin, are interrupted. Bridging can be done preoperatively, postoperatively, or both. The efficacy of bridging protocols is uncertain. One meta-analysis demonstrated no significant difference in thromboembolism rates in patients receiving bridging versus those who were not bridged. However, the bridging cohort experienced a threefold increase in major bleeding.111 Until ongoing randomized trials investigating bridging therapy protocols are published, no definitive recommendations on bridging therapy exist.112

Resumption of heparin products should occur 48 hours postoperatively based on the results of the Prospective Perioperative Enoxaparin Cohort Trial, which demonstrated a two- to fourfold increased bleed risk with therapeutic heparin, most often on postoperative day 0.113

Antiplatelet Agents. Aspirin exhibits its antithrombotic effect through the irreversible inhibition of cyclooxygenase, resulting in the suppression of thromboxane A2, which activates and aggregates platelets. Low-dose aspirin (81 mg) alone does not significantly increase the risk of clinically relevant bleeding after surgery and can be safely continued.114–116

Newer antiplatelet agents that inhibit the adenosine diphosphate receptor P2Y12 include clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), and ticlopidine (Ticlid).117 These also prevent the activation and aggregation of platelets, thereby interrupting the clotting cascade. Clopidogrel, prasugrel, and ticagrelor should be discontinued 5 to 7 days prior to surgery, and ticlopidine should be suspended for 10 to 14 days.30,118 Antiplatelet agents can be restarted within 24 hours postoperatively.30

Implications for Practice

Positive surgical outcomes in otolaryngology necessitate well-managed perioperative care. Antithrombotic therapies often complicate the perioperative picture. The decision to interrupt antithrombotic therapy is dependent on the risk of perioperative bleeding if the antithrombotic therapy were to be continued, balanced against the thromboembolic risk if the therapy were interrupted. When the perioperative management of antithrombotic therapy is being decided, 3 critical factors must be considered systematically: the patient’s inherent thromboembolic risk, the risk and potential consequences of bleeding related to the surgical procedure, and the timing of interruption of thromboembolic therapy.

The major factors influencing the risk of a thromboembolic event are atrial fibrillation, the presence of prosthetic heart valves and/or coronary stents, and venous thromboembolism. Patients can be stratified into low or high risk of thromboembolism (Table 1), and in patients with atrial fibrillation, this can be formalized through scoring systems. Objectively stratifying the bleeding risk associated with specific otolaryngologic procedures is challenging, as the supporting literature is sparse with wide ranges in reported hemorrhage rates. Otolaryngologic surgery has been generally classified as “moderate risk” for bleeding, although the implications of this classification are not well defined. We sought to better delineate low- and high-risk otolaryngologic procedures based on published data (Table 2).

On the basis of the first 2 considerations—the patient’s thromboembolic risk and the procedural risk and potential consequences of hemorrhage—the clinician can formulate a decision on whether to interrupt antithrombotic therapy (Table 3). Patients undergoing procedures with low bleeding risk (≤1.5%) and with an inherently low risk of major hemorrhage-associated complications can safely continue antithrombotic therapy, especially if they are at high risk for thromboembolic events (>5%). However, patients who are at low thromboembolic risk (≤5%) and who are undergoing a procedure with a high risk of bleeding (>1.5%) or a...
procedure in which bleeding could cause a life- or organ-threatening complication should temporarily discontinue antithrombotic therapy without the use of bridging therapy. Patients who are at high risk of a thromboembolic event (≥5%) and who are undergoing a procedure with a high risk of bleeding (≥1.5%) or with the potential of major sequelae in the event of bleeding should temporarily discontinue antithrombotic therapy. In these patients, bridging therapy is generally recommended. In patients with recent valve surgery or recent venous thromboembolism, surgery should be delayed whenever possible for at least 3 months. Similarly, after coronary stent placement, patients should not be subject to elective surgical procedures for 1 year after stent placement. If surgery must be performed within the first year, then the patient-specific risk of thromboembolism must be balanced against the risk of surgical bleeding and the risk of not performing the operation.

The last factor to consider when interrupting antithrombotic therapy is the time at which the specific agent should be discontinued. Warfarin requires the longest duration of interruption, 5 to 7 days, often with monitored bridging therapy. Newer oral anticoagulants have begun to replace warfarin and have a much faster therapeutic onset. However, these drugs are highly dependent on renal clearance and are without reliable reversal agents, which can be concerning in an emergency. Aspirin is the classic antiplatelet agent and, at low

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration Route</th>
<th>Mechanism of Action</th>
<th>Recommended Duration of Interruption</th>
<th>Recommended Resumption of Therapy Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Oral</td>
<td>Prevents synthesis of vitamin K–dependent factors II, VII, IX, and X and proteins C and S</td>
<td>5 d with a preoperative international normalized ratio &lt;1.5</td>
<td>12-24 h</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Oral</td>
<td>Direct thrombin inhibitor that reversibly blocks the function of thrombin (factor II) in converting fibrinogen to fibrinogen</td>
<td>2 d (if creatinine clearance ≥ 50 mL/min) or 4 d (if creatinine clearance &lt; 50 mL/min)</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Desirudin (Iprivask)</td>
<td>Subcutaneous</td>
<td>Direct thrombin inhibitor</td>
<td>10 h</td>
<td>2-3 d</td>
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<tr>
<td>Argatroban</td>
<td>Intravenous</td>
<td>Direct thrombin inhibitor</td>
<td>4 h</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Oral</td>
<td>Direct factor Xa inhibitor; reversibly blocks the function of factor Xa in converting prothrombin to thrombin</td>
<td>2 d with a creatinine clearance ≥ 60 mL/min and 4-5 d with a creatinine clearance &lt; 60 mL/min</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Oral</td>
<td>Direct factor Xa inhibitor</td>
<td>2 d with a creatinine clearance ≥ 60 mL/min and 4-5 d with a creatinine clearance &lt; 60 mL/min</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>Subcutaneous</td>
<td>Direct factor Xa inhibitor</td>
<td>2 d</td>
<td>2-3 d</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Intravenous or Subcutaneous</td>
<td>Activates antithrombin, which inhibits factors IIa, IXa, Xa, Xla, and XIIa</td>
<td>Intravenous 4-6 h; subcutaneous 12 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Low molecular weight heparins, such as enoxaparin (Lovenox) and dalteparin (Fragmin)</td>
<td>Subcutaneous</td>
<td>Antithrombin activation with more targeted antifactor Xa activity</td>
<td>24 h at 50% of the daily dose</td>
<td>48 h</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Oral</td>
<td>Irreversible inhibition of cyclooxygenase resulting in suppression thromboxane A2</td>
<td>No need to discontinue</td>
<td>24 h</td>
</tr>
<tr>
<td>Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta)</td>
<td>Oral</td>
<td>Inhibit adenosine diphosphate receptor P2Y12</td>
<td>5-7 d</td>
<td>24 h</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Oral</td>
<td>Inhibits adenosine diphosphate receptor P2Y12</td>
<td>10-14 d</td>
<td>24 h</td>
</tr>
</tbody>
</table>
doses (81 mg), can be safely continued perioperatively. Guidelines for timing interruption of therapy are discussed in detail above.

The management of perioperative antithrombotic agents in patients on long-term therapy must be individualized. The paucity of prospective data on the bleeding risk in otolaryngologic procedures has necessitated the use of nonspecialty specific bleeding risk thresholds, such as the 1.5% cutoff cited in this study. Although we present several recommendations related to the management of perioperative antithrombotic therapy in otolaryngology patients, these are not intended to act as clinical guidelines, and their use must be coupled with sound clinical judgment. In particular, the otolaryngologist must consider the potential consequences of a perioperative hemorrhage—even if such hemorrhage is deemed unlikely—and balance this against the risk of thrombosis in the individual patient. Because definitive guidelines cannot be established on the basis of presently available data, it is critical to involve patients in the decision-making process after discussing the risk-benefit balance.119

Overall, the recommendations above cannot substitute for appropriate patient-centered clinical judgment about perioperative antithrombotic management but should instead be used to facilitate a critical discussion between surgical and medical care providers regarding the management of a patient’s antithrombotic regimen. In the future, the publication of prospective studies quantifying bleeding risks and complications in specific otolaryngologic procedures may allow for the establishment of definitive clinical guidelines.

Author Contributions
Wayne D. Hsueh, review concept and design, drafting of manuscript; Peter H. Hwang, review concept and design, critical revision; Waleed M. Abuzeid, review concept and design, drafting of manuscript, critical revision.

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