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## **Perioperative Management of Antithrombotic Therapy : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**

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A M E R I C A N C O L L E G E O F  
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## Perioperative Management of Antithrombotic Therapy

### Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

James D. Douketis, MD, FCCP; Alex C. Spyropoulos, MD, FCCP; Frederick A. Spencer, MD; Michael Mayr, MD; Amir K. Jaffer, MD, FHM; Mark H. Eckman, MD; Andrew S. Dunn, MD; and Regina Kunz, MD, MSc (Epi)

**Background:** This guideline addresses the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure.

**Methods:** The methods herein follow those discussed in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines article of this supplement.

**Results:** In patients requiring vitamin K antagonist (VKA) interruption before surgery, we recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, we suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, we suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C). In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require non-cardiac surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, we recommend deferring surgery > 6 weeks after bare-metal stent placement and > 6 months after drug-eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, we suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).

**Conclusions:** Perioperative antithrombotic management is based on risk assessment for thromboembolism and bleeding, and recommended approaches aim to simplify patient management and minimize adverse clinical outcomes. *CHEST 2012; 141(2)(Suppl):e326S–e350S*

**Abbreviations:** aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; ATE = arterial thromboembolism; CABG = coronary artery bypass graft; CHADS<sub>2</sub> = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PICO = population, intervention, comparator, and outcome; SC = subcutaneous; UFH = unfractionated heparin; VKA = vitamin K antagonist

#### SUMMARY OF RECOMMENDATIONS

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are

newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

**2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery *instead of* stopping VKAs a shorter time before surgery (Grade 1C).**

**2.2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs (Grade 2C).**

**2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation *instead of* no bridging during interruption of VKA therapy (Grade 2C).**

*Remarks:* Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

**In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no bridging *instead of* bridging anticoagulation during interruption of VKA therapy (Grade 2C).**

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**In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.**

**2.5. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure *instead of* alternative strategies (Grade 2C). In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis *instead of* other strategies (Grade 2C). In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery *instead of* other strategies (Grade 2C).**

**3.4. In patients who are receiving ASA for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure *instead of* stopping ASA 7 to 10 days before the procedure (Grade 2C).**

**3.5. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C). In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery *instead of* continuation of ASA (Grade 2C).**

**3.6. In patients who are receiving ASA and require CABG surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C). In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery *instead of* continuing dual antiplatelet therapy around the time of surgery (Grade 2C).**

**3.7. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement**

of a drug-eluting stent *instead of* undertaking surgery within these time periods (Grade 1C). In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery *instead of* stopping dual antiplatelet therapy 7 to 10 days before surgery (Grade 2C).

**4.2. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we suggest stopping UFH 4 to 6 h before surgery *instead of* closer to surgery (Grade 2C).**

*Remarks:* Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.

**4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of* 12 h before surgery (Grade 2C).**

**4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery *instead of* resuming LMWH within 24 h after surgery (Grade 2C).**

The perioperative management of patients who are receiving vitamin K antagonists (VKAs) or antiplatelet drugs and require a surgical or invasive procedure presents a dilemma for practicing clinicians. This clinical problem affects an estimated 250,000 patients annually in North America alone and is of interest to a wide spectrum of clinicians, including internists, surgeons, anesthesiologists, family physicians, and dentists.<sup>1-3</sup> However, there is a relative paucity of well-designed clinical trials to inform best practices and a disproportionately large number of methodologically weak observational studies.<sup>4-8</sup> The aims of this article are to (1) provide guidelines for perioperative antithrombotic management that reflect the quality of the available evidence and (2) provide guidance for clinicians as to the practical aspects of antithrombotic management in the perioperative setting.

The current iteration of this article differs from that of Douketis et al<sup>6</sup> in the Antithrombotic and Thrombolytic Therapy: American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (AT8), in the following ways:

- There is a downgrading of several recommendations. This reflects the emergence of additional evidence and, in general, a higher threshold for conferring strong (level 1) recommendations, which has been adopted across the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9).
- There are fewer recommendations in AT9. We aimed to make evidence-based recommendations on areas where studies exist that are directly pertinent to the clinical questions we developed, which were based on the population, intervention, comparator, and outcome (PICO) format. Whenever possible, we relied less on indirect evidence from studies in the nonperioperative setting.
- For areas in which a PICO question was not developed but are, nonetheless, considered relevant for everyday practice, we have provided narrative comments in the text without specific recommendations.
- The antithrombotic management of patients requiring urgent surgery is now addressed in the article by Falck-Ytter et al<sup>9</sup> in this guideline.

The following definitions and qualifying remarks are aimed to facilitate an understanding of this article and its accompanying recommendations:

- *Bridging anticoagulation.* In the absence of a universally accepted definition,<sup>6,10,11</sup> we define bridging anticoagulation as the administration of a short-acting anticoagulant, consisting of subcutaneous (SC) low-molecular-weight heparin (LMWH) or IV unfractionated heparin (UFH), for an ~10- to 12-day period during interruption of VKA therapy when the international normalized ratio (INR) is not within a therapeutic range.
- *Therapeutic intent of heparin bridging and dose regimens.* Bridging anticoagulation aims to minimize the risk for arterial thromboembolism (ATE), such as stroke and systemic embolism, in patients with a mechanical heart valve or atrial fibrillation and to minimize the risk for recurrent thrombosis in patients with prior VTE. The argument for using a high-dose (or therapeutic-dose) heparin regimen to prevent ATE is based on two considerations. First, this dose regimen with LMWH or UFH is comparable to a therapeutic-dose VKA regimen when used for the prevention of ATE in patients with a mechanical heart valve and the treatment of acute

VTE.<sup>12,13</sup> Second, a therapeutic-dose regimen of idraparinux, a factor Xa antagonist with LMWH-like anticoagulant properties, is as efficacious as a VKA to prevent ATE in patients with atrial fibrillation.<sup>14</sup> However, its efficacy to prevent perioperative ATE is not established. A low-dose (or prophylactic-dose) heparin regimen is known to prevent postoperative VTE, but its efficacy to prevent ATE is also not established, and the biological plausibility to support its efficacy for this therapeutic aim may be questioned.<sup>15</sup> Finally, the use of LMWH or UFH as perioperative bridging is considered an off-label use of these drugs because their use is not approved by regulatory authorities or drug manufacturers in this clinical setting as a bridging agent.

- *Bridging dose regimens.* Three dose regimens have been studied:

1. A high-dose (therapeutic-dose) heparin bridging regimen involves administering an anticoagulant dose that is similar to that used for the treatment of acute VTE or an acute coronary syndrome (eg, enoxaparin 1 mg/kg bid or 1.5 mg/kg daily, dalteparin 100 International Units/kg bid or 200 International Units/kg daily, tinzaparin 175 International Units/kg daily, IV UFH to attain an activated partial thromboplastin time [aPTT] 1.5 to 2 times the control aPTT).
2. A low-dose (prophylactic-dose) heparin regimen involves administering a dose that is used, typically, to prevent postoperative VTE (eg, enoxaparin 30 mg bid or 40 mg daily, dalteparin 5,000 International Units daily, UFH 5,000-7,500 International Units bid).
3. An intermediate-dose regimen has recently been studied for bridging and is intermediate in anticoagulant intensity between high- and low-dose regimens (eg, enoxaparin 40 mg bid).

- Our recommendations relating to the need for bridging anticoagulation (section 2.4) will not refer to a specific bridging dose regimen and will deal with the issue of whether bridging is needed in a more generic sense.
- Our recommendations relating to the perioperative management of patients who are receiving bridging (section 4.0) will refer to a therapeutic-dose bridging regimen because it is the most widely studied and most widely used in clinical practice. It is also the dose regimen that we consider most important for practice guidelines because it has the potential to confer the great-

est therapeutic benefit and the greatest harm. (We acknowledge that different bridging regimens may be used and that such regimens may have potential advantages or drawbacks compared with a therapeutic-dose regimen.)

- *VKAs.* Although several VKAs are available for clinical use, including warfarin, acenocoumarol, phenprocoumon, and anisindione,<sup>16</sup> our recommendations will refer to warfarin because pertinent studies are dominated by warfarin use, with little or no study of other VKAs.

### *Practical Aspects of Perioperative Antithrombotic Therapy Management*

The perioperative management of patients who are receiving antithrombotic therapy is based on (1) an assessment of patient risk for thromboembolism and (2) an assessment of risk for perioperative bleeding. Addressing these issues will determine whether antithrombotic therapy is interrupted around the time of the surgery or procedure and, if so, whether bridging anticoagulation is considered. This article focuses on the three dominant clinical indications for VKA therapy: mechanical heart valves, chronic atrial fibrillation, and VTE.

To date, there are no validated risk stratification schemes to reliably separate VKA-treated patients into risk strata for thromboembolism and bleeding. Of necessity, our recommendations are based largely on indirect evidence and clinical experience.<sup>17-20</sup> These risk stratification schemes are meant to provide general guidance; however, patient management may vary depending on individual patient characteristics, the surgery or procedure type, and patient values and preferences.

### *Assessing Risk for Thromboembolism*

Assessing patient risk for thromboembolism during the perioperative interruption of antithrombotic therapy is distinguished from assessing patient risk for postoperative VTE. In the former setting, patients are already receiving antithrombotic therapy, and the aim is mainly to prevent ATE, in some instances, with heparin bridging, whereas in the latter setting, the focus is on preventing postoperative VTE with de novo use of antithrombotic drugs.

The suggested thromboembolic risk stratification shown in Table 1 is based largely on indirect evidence from studies outside of the perioperative setting involving patients with a mechanical heart valve,<sup>21-23</sup> chronic atrial fibrillation,<sup>2,24-27</sup> or VTE<sup>28-30</sup> who either were not receiving anticoagulation (ie, placebo instead of a VKA in patients with chronic atrial fibrillation) or were receiving less-effective treatment (eg, ASA instead

**Table 1—[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism**

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High <sup>a</sup>	<ul style="list-style-type: none"> <li>Any mitral valve prosthesis</li> <li>Any caged-ball or tilting disc aortic valve prosthesis</li> <li>Recent (within 6 mo) stroke or transient ischemic attack</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 5 or 6</li> <li>Recent (within 3 mo) stroke or transient ischemic attack</li> <li>Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>Recent (within 3 mo) VTE</li> <li>Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age &gt; 75 y</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 3 or 4</li> </ul>	<ul style="list-style-type: none"> <li>VTE within the past 3-12 mo</li> <li>Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation)</li> <li>Recurrent VTE</li> <li>Active cancer (treated within 6 mo or palliative)</li> </ul>
Low	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 0 to 2 (assuming no prior stroke or transient ischemic attack)</li> </ul>	<ul style="list-style-type: none"> <li>VTE &gt; 12 mo previous and no other risk factors</li> </ul>

CHADS<sub>2</sub> = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.

<sup>a</sup>High-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a CHADS<sub>2</sub> score < 5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

of a VKA in patients with a mechanical heart valve). In this suggested risk classification, patients classified as high risk have a > 10% annual risk for thromboembolism, patients classified as moderate risk have a 5% to 10% annual risk for thromboembolism, and patients classified as low risk have a < 5% annual risk for thromboembolism. Estimates as to the perioperative risk for thromboembolism in specific patient groups that do not receive heparin bridging during VKA therapy interruption are limited and pertain mainly to patients with chronic atrial fibrillation or VTE.<sup>3,31</sup>

One limitation of the suggested risk stratification is that individual patient factors may trump this classification. For example, a perceived high-risk patient group may also include those with atrial fibrillation and prior stroke and one additional stroke risk factor (ie, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack [CHADS<sub>2</sub>] score of 3), even though such patients would be classified as being in the moderate-risk group in the classification shown in Table 1. In addition, patients with remote (> 1 year ago), but severe VTE associated with pulmonary hypertension may be perceived as high risk, even though they would be classified as low risk.

Another general consideration in estimating perioperative risk for thromboembolism is the surgery type. Although it is established that patients having coronary artery bypass, heart valve replacement, or carotid endarterectomy are at increased risk for stroke compared with patients having other types of surgery, emerging evidence also suggests that among patients undergoing noncardiovascular surgery, the risk for stroke may vary depending on the type of surgery.<sup>3</sup> Taken together, an estimate of individual patient risk for perioperative thromboembolism is subjective but should consider both the estimated baseline risk and the individual factors related to the patient and the surgery or procedure type.

### Assessing Risk for Bleeding

The assessment of perioperative bleeding risk should consider two broad issues. First, for this article, we consider perioperative bleeding risk in the context of perioperative anticoagulant and antiplatelet drug administration and, in particular, when such drugs are administered in proximity to surgery. This distinction is important because whereas certain procedures may not typically result in postoperative bleeding, the administration of antithrombotic drugs may induce bleeding complications. For example, seemingly minor procedures, such as bowel polypectomy or pacemaker insertion, are not, in isolation, associated with increased bleeding but may be if anticoagulants are administered in proximity to the procedure.

Second, a distinction should be made as to bleeding risk when anticoagulants are used as heparin bridging and when these agents are used to prevent postoperative venous thrombosis. In the former clinical setting, high-dose (or therapeutic-dose) bridging anticoagulation is administered, whereas in the latter setting, low-dose anticoagulants are used. The importance of surgical bleeding risk, therefore, is heightened in the setting of heparin bridging because of the potential to induce bleeding complications.

Providing an evidence-based scheme that stratifies surgeries and procedures according to the risk for bleeding in the context of perioperative antithrombotic drug use and, in particular, perioperative heparin bridging administration is problematic because the available evidence on such bleeding risk is based mainly on case series involving selected types of surgery. Furthermore, although there are schemes that stratify patients according to the expected intraoperative blood loss, these classifications have not been prospectively validated and do not account for the effects of perioperative use of antithrombotic drugs. Consequently, rather than propose a multi-tiered scheme that encompasses most surgery or procedure types that would be entirely subjective, we have identified a group of surgeries and procedures that appear to be associated with a high risk for bleeding in the context of perioperative anticoagulant and antiplatelet drug use.

Surgeries and procedures associated with an increased bleeding risk during perioperative antithrombotic drug administration include the following:

- Urologic surgery and procedures consisting of transurethral prostate resection, bladder resection, or tumor ablation; nephrectomy; or kidney biopsy in part due to untreated tissue damage (after prostatectomy) and endogenous urokinase release<sup>32-34</sup>
- Pacemaker or implantable cardioverter-defibrillator device implantation in which separation of infraclavicular fascial layers and lack of suturing of unopposed tissues within the device pocket may predispose to hematoma development<sup>35-38</sup>
- Colonic polyp resection, typically of large (ie, >1-2 cm long) sessile polyps, in which bleeding may occur at the transected stalk following hemostatic plug release<sup>39</sup>
- Surgery and procedures in highly vascular organs, such as the kidney, liver, and spleen
- Bowel resection in which bleeding may occur at the bowel anastomosis site
- Major surgery with extensive tissue injury (eg, cancer surgery, joint arthroplasty, reconstructive plastic surgery)<sup>40,41</sup>

- Cardiac, intracranial, or spinal surgery, especially as small pericardial, intracerebral, or epidural bleeds can have serious clinical consequences<sup>42-44</sup>

### *Standardized Perioperative Anticoagulant Therapy Protocols*

Patients who are receiving warfarin and other antithrombotic drugs and require elective surgery or procedures may benefit from management according to standardized, institution-specific protocols. Although there are no randomized trials showing that a standard management approach improves clinical outcomes and minimizes health-care resource use, observational studies that incorporated standardized perioperative anticoagulant therapy protocols and heparin bridging regimens had low rates of thromboembolic and bleeding outcomes and appeared to allow efficient use of health-care resources.<sup>31,45-51</sup> Institutions and practitioners may consider incorporating the following components into a standardized perioperative management protocol:

- Assessing patients at least 7 days before surgery to allow planning of perioperative anticoagulant management, especially before major surgery
- Providing patients and providers with a calendar outlining the perioperative timing of warfarin and antiplatelet drug discontinuation and resumption, dose and timing of LMWH bridging, and INR measurement schedule
- Ensuring that the perioperative management strategy (including timing of VKA and antiplatelet drug interruption and initiation and resumption of LMWH bridging) accounts for the drugs' pharmacokinetic profile and patients' thromboembolic and bleeding risks
- Ensuring patient and caregiver education on injection technique when outpatient LMWH bridging is administered
- INR testing on the day before surgery, where appropriate and feasible, to identify patients with elevated INRs and permit timely use of corrective oral vitamin K (1.0-2.5 mg), thereby avoiding blood product administration or surgery deferral<sup>52</sup>
- Assessing postoperative hemostasis, preferably on the day of surgery and on the first postoperative day, to facilitate safe resumption of anticoagulant drugs

### *Cost-effectiveness of Perioperative Management Strategies*

The cost-effectiveness of bridging anticoagulation has been assessed using various decision analysis models.<sup>53-55</sup> These studies suggest that for patients

other than those at highest risk for stroke and ATE, bridging anticoagulation is unnecessary. In patients undergoing minor dental procedures, decision analyses have suggested that continuation of VKA therapy is less expensive than VKA interruption with bridging therapy.<sup>56</sup> Studies of GI endoscopy have been consistent with American Society of Gastroenterology Guidelines, suggesting that continuing VKA therapy in patients having procedures associated with a low bleeding risk (eg, diagnostic endoscopy without biopsy) is less expensive than bridging, whereas discontinuation of VKA therapy without bridging is more cost-effective in patients at low thromboembolic risk who are undergoing high-bleeding-risk procedures.<sup>57</sup> Prospective cohort studies have compared the costs of bridging anticoagulation with either in-hospital IV UFH or out-of-hospital SC LMWH.<sup>58-61</sup> In one study comparing patient-administered SC LMWH, nurse-administered SC LMWH, and in-hospital IV UFH, the anticoagulant-related costs for patients having surgery with an overnight hospital stay were estimated at US \$672, \$933, and \$3,916, respectively.<sup>59</sup> Another cohort study comparing costs in 26 patients who received in-hospital IV UFH and 40 patients who received out-of-hospital SC LMWH and had elective surgery found a significantly lower mean total health-care cost (by \$13,114) in patients who received perioperative LMWH.<sup>60</sup> Taken together, these findings lead to questions about the need for bridging therapy in patients not considered at high risk for ATE. Furthermore, these studies confirm considerable cost savings with the use of SC LMWHs instead of IV UFH, which can be given in an outpatient setting by the patient or a family member in > 90% of cases.<sup>45,46</sup>

## 1.0 METHODS

### 1.1 Data Sources

The Medline English-language database was searched from January 1970 to January 2010 using multiple keywords and standardized terminology, where applicable, as outlined in Appendix S1. This search was done in two parts. The first was a systematic review of the literature from 1970 to January 2007, which was used in AT8.<sup>6</sup> The second search updated this search strategy to include studies up until January 2010. We supplemented these literature searches by conducting Internet-based searches of ClinicalTrials.gov, meeting abstracts, and conference proceedings. In addition, reference lists of studies that satisfied inclusion criteria were manually reviewed. Finally, content experts were contacted to identify additional studies that were not identified by these search strategies.

### 1.2 Development of Chapter Recommendations and Narrative

The development of recommendations followed a prespecified process based on the following four steps: (1) developing PICO questions for clinical topics deemed important, which are summarized in Table 2; (2) identifying pertinent studies from

AT8 supplemented by additional searches of more recent studies; (3) developing provisional recommendations and parallel development of a draft manuscript and revision of original PICO questions; and (4) developing final recommendations by nonconflicted panelists. The development of article recommendations was guided by the topic editor (R. K.), whereas the development of the article narrative was overseen by the deputy editor (J. D.).

### 1.3 Development of Evidence Profiles, Summary of Findings Tables, and Recommendations

The recommendations in this article were developed in accordance with the methodologic changes in AT9 based on evidence profiles and summary of findings tables that followed the Grades of Recommendations, Assessment, Development, and Evaluation system format.<sup>62,63</sup>

For the section on the perioperative management of VKA therapy, we developed evidence profiles to formulate recommendations for the prespecified PICO questions. These evidence profiles include studies directly pertinent to our PICO questions. Our recommendations were based on studies in the evidence profile that provided data specific to the perioperative clinical setting. In cases where there also were relevant studies from the nonperioperative setting, which were not part of the evidence profile because they provided indirect data, these studies also had a bearing on the recommendations.

For the section on the perioperative management of antiplatelet therapy, evidence profiles were not produced in part because there were insufficient studies to develop profiles specific to the prespecified PICO questions. We produced summary of findings tables of all pertinent (but often indirect) data. The recommendations provided were based on the studies in these summary of findings tables, which are available in the online data supplement. As with the perioperative VKA management sections, additional studies may have been referenced in the narrative, but the recommendations were based entirely on studies in the summary of findings tables.

## 2.0 PERIOPERATIVE MANAGEMENT OF PATIENTS WHO ARE RECEIVING VKA THERAPY

### 2.1 Interruption of VKAs Before Surgery

In patients undergoing major surgery or procedures, interruption of VKAs, in general, is required to minimize perioperative bleeding,<sup>64-68</sup> whereas VKA interruption may not be required in minor procedures as discussed in subsequent sections of this article. Interruption of VKAs before surgery with the intent of achieving normal or near-normal hemostasis at the time of surgery is based on the residual pharmacodynamic effects of VKAs and the associated time required for the regeneration of vitamin K-dependent coagulation factors. This can be estimated by the elimination half-life of a VKA<sup>69-72</sup>: 8 to 11 h for acenocoumarol, 36 to 42 h for warfarin, and 96 to 104 h for phenprocoumon. Assuming first-order pharmacokinetics, each half-life elapsed corresponds to an ~50% reduction in residual anticoagulant effect: 50% after one half-life, 25% after two half-lives, 12.5% after three half-lives, 6.25% after four half-lives, and 3.125% after five half-lives. For patients in whom the intent is to normalize the



**Table 2—[Section 1.2] Structured Clinical Questions**

Section	Population	Intervention and Comparator	Outcomes	Available Methodology
		Patients receiving warfarin therapy		
2.1	Patients receiving warfarin therapy who require an elective surgery or invasive procedure	In patients who require warfarin interruption before surgery to attain normal or near-normal INR at surgery, stopping warfarin 5-6 d before surgery vs stopping warfarin <5 d before surgery	Hemostasis at time of surgery (INR)	Observational studies
2.2		In patients with warfarin interruption before surgery, resuming warfarin 12-24 h after surgery (evening of or next day) and when there is hemostasis vs resuming warfarin > 24 h from surgery	Hemostasis at time of surgery	Observational studies
2.3		INR testing to monitor anticoagulant effect of warfarin before and after surgery vs no testing	Hemostasis at time of surgery (aPTT, antifactor Xa)	Observational studies
2.4	Need for bridging anticoagulation during perioperative warfarin interruption Patients considered at high risk for perioperative thromboembolism Patients considered at moderate risk for perioperative thromboembolism Patients considered at low risk for perioperative thromboembolism Patients having minor dental, skin, or eye procedures Patients receiving warfarin therapy and having a minor dental procedure	Bridging anticoagulation with heparin/LMWH vs no bridging Bridging anticoagulation with heparin/LMWH vs no bridging Bridging anticoagulation with heparin/LMWH vs no bridging	Stroke, other systemic embolism, major hemorrhage Stroke, other systemic embolism, major hemorrhage Stroke, other systemic embolism, major hemorrhage	Observational studies Observational studies Observational studies
2.5		Continuing warfarin and coadministering an oral prohemostatic drug vs stopping warfarin 5-6 d before the procedure without administering a prohemostatic drug	ATE or VTE, major hemorrhage	RCTs, observational studies
	Patients receiving warfarin therapy and having a minor skin procedure Patients receiving warfarin therapy and having cataract procedure	Continuing warfarin around the time of the procedure vs stopping warfarin 5-6 d before the procedure Continuing warfarin around the time of the procedure vs stopping warfarin 5-6 d before the procedure	ATE or VTE, major hemorrhage ATE or VTE, postoperative bleeding	RCTs, observational studies RCTs, observational studies
3.4	Patients receiving antiplatelet therapy and having minor dental, skin, or eye procedure	Patients receiving antiplatelet therapy Continuing antiplatelet drugs around the time of the procedure vs stopping antiplatelet drugs 7-10 d before procedure	Myocardial ischemia, postoperative bleeding	Observational
3.5	Patients receiving antiplatelet therapy and having elective noncardiac surgery	Continuing antiplatelet drugs around the time of the procedure vs stopping antiplatelet drugs 7-10 d before noncardiac surgery	Myocardial ischemia, postoperative bleeding	RCTs, observational studies
3.6	Patients receiving antiplatelet therapy and having elective CABG surgery	Continue antiplatelet drugs around the time of surgery vs stopping antiplatelet drugs 7-10 d before CABG	Myocardial ischemia, postoperative bleeding	Observational studies

(Continued)

**Table 2—Continued**

Section	Population	Intervention and Comparator	Outcomes	Available Methodology
3.7	Patients with a coronary stent receiving antiplatelet therapy and having elective surgery	<p>Patients receiving warfarin therapy</p> <p>In patients with a bare-metal coronary stent who require surgery within 6 wk of stent placement or patients with a drug-eluting coronary stent who require surgery within 6 mo of stent placement, continuing antiplatelet drugs around the time surgery vs stopping antiplatelet drugs 7-10 d before surgery</p>	Myocardial ischemia, postoperative bleeding	Observational studies
4.2	Patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH	<p>Patients receiving heparin bridging anticoagulation</p> <p>Stopping UFH 4-6 h before surgery vs stopping UFH closer to surgery</p>	Postoperative bleeding	Observational studies
4.3	Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH	Administering the last preoperative dose of LMWH ~24 h before surgery vs administering the last preoperative dose of LMWH ~12 h before surgery	Postoperative bleeding	Observational studies
4.4	<p>Patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH</p> <p>Having surgery associated with high bleeding risk</p> <p>Having surgery associated with low to moderate bleeding risk</p>	<p>Resuming therapeutic-dose LMWH <math>\leq 24</math> h after surgery vs resuming LMWH <math>&gt; 24</math> h after surgery</p> <p>Resuming therapeutic-dose LMWH <math>\leq 24</math> h after surgery vs resuming LMWH <math>&gt; 24</math> h after surgery</p>	<p>Postoperative bleeding</p> <p>Postoperative bleeding</p>	<p>Observational studies</p> <p>Observational studies</p>

aPPT = activated partial thromboplastin time; ATE = arterial thromboembolism; CABG = coronary artery bypass graft; INR = international normalized ratio; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; SC = subcutaneous; UFH = unfractionated heparin.

INR after interruption of warfarin (half-life, 36-42 h), one would anticipate requiring at least 5 days for most anticoagulant effect to be eliminated after stopping warfarin. However, the decay of the anticoagulant effect of warfarin after interruption may not follow this pattern; for example, there may be delayed decay in elderly patients.<sup>73</sup> For patients having minor procedures, where the anticipated bleeding is less, a shorter interval for VKA interruption may be sufficient whereby the aim is to attain an INR of 1.5 to 1.8 at the time of the procedure.<sup>74</sup>

No randomized trials have directly compared the effects of early (5-6 days before surgery) vs delayed (<5 days before surgery) interruption of warfarin on perioperative bleeding outcomes (Table S1). (Tables that contain an "S" before the number and Appendices denote supplementary information not contained in the body of the article and available instead in an online data supplement; see the "Acknowledgments" for more information.) The only nonrandomized study addressing this issue is a retrospective case series of 21 patients who stopped warfarin 36 h prior to polypectomy and had a mean INR of 2.3 (range, 1.4-4.9) on the day of endoscopy.<sup>75</sup> Although no patients developed major bleeding despite being given anticoagulants, all patients had endoscopic clips applied to the polyp stalks, which likely minimized any bleeding.

Most studies have assessed an early and delayed interruption of warfarin on a surrogate outcome of bleeding, namely the INR at the time of surgery. In the nonperioperative setting, a prospective cohort provides indirect evidence that a 5-day period of warfarin interruption is sufficient to allow decay of the anticoagulant effect and a normalization or near-normalization of the INR.<sup>76</sup> In the perioperative setting, a prospective cohort study assessed 224 patients in whom warfarin was stopped 5 days before surgery and had INR testing on the day before surgery.<sup>46</sup> This study found that only 15 patients (7%) had an INR > 1.5 on the day of surgery, thereby supporting a 5-day interruption period before surgery to allow normalization of the INR.<sup>46</sup> A retrospective case series that assessed delayed (2-3 days before procedure) interruption of warfarin did not allow sufficient time for normalization of the INR (mean INR at time of procedure, 1.8).<sup>68</sup> Finally, in a randomized trial in which patients interrupted warfarin either 5 days or 1 day before surgery (with the latter group also receiving 1 mg vitamin K the day before surgery), the mean (95% CI) INR at the time of surgery was 1.24 (1.19-1.29) in the 5-day interruption group and 1.61 (1.50-1.71) in the 1-day interruption plus vitamin K group.<sup>77</sup> Our recommendation, therefore, is based on the assumption that at the time of surgery, an elevated INR (ie,  $\geq 2.0$ ) will increase bleeding and a normal or near-normal INR

(ie, < 1.5) will not increase bleeding, with the caveat that there may be selected (usually minor) procedures that can be safely performed in patients managed with anticoagulant therapy. Additional study in this area is needed to better inform risks for bleeding in patients who continue or interrupt warfarin therapy.

## Recommendation

**2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery *instead of* stopping VKAs a shorter time before surgery (Grade 1C).**

### 2.2 Resumption of VKAs After Surgery

For most types of surgery, resumption of VKAs is feasible on the evening of or the day following surgery, when oral intake is permitted. One prospective cohort study of 650 patients who required VKA interruption before surgery and routinely resumed warfarin within 24 h after surgery (at the patients' usual dose), the mean  $\pm$  SD time to attaining an INR  $\geq 2.0$  was  $5.1 \pm 1.1$  days.<sup>45</sup> Bleeding outcomes with this regimen were infrequent, irrespective of the use of LMWH bridging. Other prospective cohort studies support the feasibility and safety of early initiation of postoperative warfarin,<sup>19,45,47</sup> and one study supports resuming warfarin at a dose that is double the patients' usual dose for the first 2 postoperative days, with a mean duration to attain an INR  $\geq 2.0$  of 4.6 days.<sup>46</sup>

## Recommendation

**2.2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs (Grade 2C).**

### 2.3 Perioperative Laboratory Monitoring of VKA Therapy

Laboratory monitoring of VKA therapy with INR testing before surgery is intended to ensure normalization of the INR at surgery, which is important for patients who are receiving spinal/epidural anesthesia. No studies have assessed the effect of routine perioperative INR monitoring on health-care resource utilization, such as the need for blood products to reverse an excessive residual anticoagulant effect or deferral of surgery. Indirect evidence suggests that INR testing on the day before surgery will allow correction of elevated INRs with the potential to minimize blood product use or deferral of surgery.<sup>46</sup> In a cohort

study in which INR was routinely measured the day before surgery, 7% of patients had an INR > 1.5, which were all corrected with low-dose (1 mg) oral vitamin K. The use of vitamin K in this setting is also supported by a cohort study of 43 patients who had an INR of 1.5 to 1.9 on the day before surgery; administering 1 mg po vitamin K resulted in 39 patients (91%) having a normal or near-normal INR ( $\leq 1.4$ ) on the day of surgery, with no surgeries cancelled.<sup>52</sup>

#### 2.4 Need for Bridging Anticoagulation During Interruption of VKA Therapy

In patients with chronic atrial fibrillation, risk stratification for thrombotic events is based on the CHADS<sub>2</sub> score because it is validated in a nonoperative setting, is widely used, and may be applicable in the perioperative setting<sup>2,25-27</sup> (Table 1). In patients with a mechanical heart valve, the risk stratification is based on the position and type of valve. A high, moderate, or low risk for ATE and valve thrombosis refers to > 10%/y, 5% to 10%/y, and < 5%/y risks, respectively, in the absence of anticoagulation<sup>21,22</sup> (Table 1). Finally, in patients with VTE, the risk stratification primarily depends on the time interval from the index VTE event to the surgery, and the distinction among high-, intermediate-, and low-risk groups is largely arbitrary<sup>28-30,78</sup> (Table 1). This classification scheme has not been prospectively validated because data are lacking on risks for thromboembolism in the perioperative period when patients have interruption of VKA therapy and do not receive heparin bridging. Until such data are available, clinicians should consider this classification as an initial guide for decision-making that should be adapted to individual patient circumstances.

In observational studies, patients at high risk for thromboembolism have typically received bridging with therapeutic-dose SC LMWH (Table S2). This bridging regimen was associated with a low (1%-2%) incidence of ATE.<sup>31,45-47,51,79-85</sup> Fewer, typically older, studies assessed bridging therapy with IV UFH in high-risk patients.<sup>47,66,86</sup> The incidence of thromboembolic events with IV UFH bridging was more varied, between 0% and 5%, in these studies. In one cohort study involving patients with a mechanical heart valve, there was no significant difference in thromboembolic and major bleeding between patients bridged with LMWH and those bridged with UFH.<sup>86</sup> In one cohort study that included 79 patients with a mechanical heart valve who received intermediate-dose bridging (ie, enoxaparin 40 mg bid), there were no perioperative ATE events.<sup>49</sup> As shown in the evidence profile (Table S3), there were no studies assessing thromboembolic risk in high-risk patients who had VKA interruption and did not receive any heparin bridging.

Prospective cohort studies with standardized bridging regimens,<sup>19,31,45,46,48,49,51,84</sup> prospective registries,<sup>47,80,87</sup> or retrospective case series<sup>81,82,88</sup> have assessed moderate-risk patients who require VKA interruption. In some studies, particularly more recent ones, some patients within this risk stratum received no bridging, although it appears that many of these patients were at the lower end of the thromboembolic risk spectrum.<sup>31,87</sup> Irrespective of the management strategy used, whether therapeutic-dose bridging, intermediate-dose bridging, or no bridging, the incidence of ATE events was low ( $\sim 1\%$ ).

The ideal strategy for patients at moderate risk for thromboembolism is unclear, and individual patient and surgery-related criteria need to be taken into consideration. Such uncertainty and variability in presumed thromboembolic risk precludes developing a specific management recommendation for this patient group. Patients groups within the moderate-risk stratum undergoing surgeries or procedures associated with a low risk for bleeding in whom bridging may be considered include the following:

- Patients with a mechanical bileaflet aortic valve and additional stroke risk factors comprising prior stroke or systemic embolism or transient ischemic attack, hypertension, diabetes, congestive heart failure, or age > 75 years
- Patients with atrial fibrillation and a CHADS<sub>2</sub> score of 3 or 4 or prior thromboembolism during interruption of warfarin
- Patients with VTE within the past 3 to 12 months, nonsevere thrombophilia, active cancer, and recurrent VTE

Patient groups within the moderate-risk stratum undergoing the following high-bleeding-risk procedures in whom no bridging therapy may be considered include the following:

- Major cardiac surgery
- Carotid endarterectomy surgery

In addition, clinicians may consider using low-dose LMWH or UFH for VKA-treated patients with prior VTE because low-dose anticoagulation reduces the incidence of postoperative VTE in nonbridging clinical settings.<sup>89</sup> For many patients whose indication for VKA therapy is prior VTE, low-dose LMWH or UFH is likely to achieve much of the benefit of therapeutic-dose anticoagulation while minimizing the risk of postoperative major bleeding, especially for patients undergoing major surgery. However, resumption of VKA therapy alone also may be considered as a method of prophylaxis against postoperative VTE.<sup>89</sup>

*Evidence profile:* There were no studies to match the associated PICO question, namely, studies limited

to or specific for patients at moderate risk for thromboembolism (Table S3).

Several studies assessed thromboembolic and bleeding outcomes of LMWH bridging with either a therapeutic-dose<sup>19,45-47,80</sup> or a low-dose<sup>48,49</sup> regimen in patients with atrial fibrillation, a mechanical heart valve, or VTE. However, there are other prospective and retrospective cohort studies in which patients with atrial fibrillation or VTE did not receive bridging.<sup>31,87,88</sup> One prospective study assessed a no-bridging approach in low-risk patients with bileaflet aortic mechanical heart valves and no other major cardiovascular risks.<sup>85</sup> The rate of ATE in low-risk patients who did not receive bridging appeared very low (<1%), thereby suggesting that bridging therapy may be unnecessary.

## Recommendations

**2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation *instead of* no bridging during interruption of VKA therapy (Grade 2C).**

*Remarks:* Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

**In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no-bridging instead of bridging anticoagulation during interruption of VKA therapy (Grade 2C).**

**In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.**

## 2.5 Perioperative Management of VKA-Treated Patients Who Require Minor Procedures

Approximately 15% to 20% of all VKA-treated patients who are assessed for perioperative anticoagulant management require minor dental, dermatologic, or ophthalmologic procedures.<sup>45,47</sup> Because these procedures, in general, are associated with relatively little blood loss or self-limiting blood loss that is controlled with local hemostatic measures, this section focuses on whether VKA therapy can be safely continued in the periprocedural period. Although we indicate that these procedures are minor and bleeding that occurs may not result in serious

bleeding, such occurrences, nevertheless, may be important to patients if it engenders anxiety and distress. For patients having dental, skin, or eye procedures that are associated with a higher risk for bleeding, such as reconstructive dental or plastic surgery or vitreoretinal surgery, in which interruption of VKA therapy is required, bridging anticoagulation can be considered (as with other major surgeries and procedures) but is addressed in section 4.0 of this article.

Minor dental procedures assessed include tooth extractions and endodontic (root canal) procedures (Table S4). Many randomized trials<sup>90-99</sup> and prospective cohort studies<sup>100-118</sup> have assessed periprocedural anticoagulant management in VKA-treated patients undergoing minor dental procedures (Table S5). Despite the extent of study in this area, one problem in identifying a single optimal practice is that several different management strategies have been assessed, including continued VKA in the peridental period with or without coadministered prohemostatic interventions (eg, antifibrinolytic drugs, sutures), partial (2-3 days before procedure) VKA interruption, and complete (5-6 days before procedure) VKA interruption.

Among these management approaches, perhaps the most relevant question is whether VKAs can be safely continued in the peridental period, especially if an oral antifibrinolytic drug (tranexamic acid mouthwash) is coadministered. One randomized trial compared continuing VKA therapy with or without tranexamic acid;<sup>97</sup> other trials compared continuing VKAs with tranexamic acid against other strategies, such as interruption of VKAs 3 or 5 days before the procedure.<sup>90,92,95</sup> Prospective cohort studies<sup>114,115,118</sup> have assessed continuing VKAs with tranexamic acid. Taken together, these studies suggest that continuing VKAs with a prohemostatic agent is associated with a low (<5%) risk for clinically relevant nonmajor bleeding. If tranexamic acid is used, it is given as a 5-mL oral dose, 5 to 10 min before the dental procedure and 3 to 4 times daily for 1 to 2 days after the procedure. Another approach associated with a low risk for bleeding, based on findings from prospective cohort studies<sup>100,102,103,107</sup> is partial interruption of VKA therapy for 2 to 3 days before a dental procedure, which would result in an INR of 1.6 to 1.9 on the day of the procedure.<sup>76</sup>

Overall, the available studies suggest that two approaches—VKA continuation with a prohemostatic agent or partial (2-3 days) VKA interruption—confer a low risk for bleeding. Nonetheless, minor bleeding (or oozing from gingival mucosa) may be more common with these approaches than complete VKA interruption. Patients should be informed of this outcome and of the need to continue tranexamic acid use and to apply local pressure to stop such bleeding. Thromboembolic outcomes are rare (<0.1%), although

prior studies were underpowered to detect relative and absolute differences in thromboembolic events occurring in association with different interventions.

Minor dermatologic procedures assessed include excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi.<sup>119</sup> No randomized trials have assessed perioperative management. Prospective, controlled cohort studies noted a more than threefold higher incidence of nonmajor and minor bleeding in patients who continued VKA therapy compared with patients who had VKA interruption (Table S6).<sup>120-123</sup> Most of these bleeding episodes reported were self-limiting. The incidence of major bleeding with periprocedural continuation of VKAs appears to be low (<5%), although these studies may have been underpowered to detect an increase in major bleeding.

Cataract extraction is largely an avascular procedure, and prospective cohort studies<sup>124-135</sup> have reported an incidence of clinically important bleeding of <3% (Table S7). In a meta-analysis of observational studies of VKA-treated patients undergoing cataract surgery, patients who continued VKA had an increased risk for bleeding (OR, 3.26; 95% CI, 1.73-6.16) with an overall incidence of bleeding of 10% (95% CI, 5-19).<sup>35</sup> Almost all bleeds were self-limiting, consisting of dot hyphemas or subconjunctival bleeds, and no patient had compromised visual acuity related to bleeding.

An important consideration is the safety of retrobulbar anesthesia in patients who are given anticoagulants and are also undergoing cataract surgery given the potential that without prompt orbital decompression, retrobulbar hematoma may lead to vision loss. The available data suggest that such bleeds are uncommon, occurring in fewer than one per 100 procedures,<sup>126</sup> irrespective of whether a patient is receiving a VKA. An alternative approach that also appears safe during VKA therapy is a phacoemulsification technique under topical anesthesia.<sup>135</sup>

## Recommendation

**2.5. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure *instead of* alternative strategies (Grade 2C). In patients who require minor dermatologic procedures and are receiving VKA therapy, we suggest continuing VKAs around the time of the procedure and optimizing local hemostasis *instead of* other strategies (Grade 2C). In patients who require cataract surgery and are receiving VKA therapy, we suggest continuing VKAs around the time of the surgery *instead of* other strategies (Grade 2C).**

## 3.0 PERIOPERATIVE MANAGEMENT OF PATIENTS WHO ARE RECEIVING ANTIPLATELET DRUGS

### 3.1 Interruption of Antiplatelet Drugs Before Surgery

Antiplatelet drugs that irreversibly inhibit platelet function—making their short half-lives clinically irrelevant—include ASA, clopidogrel, ticlopidine, and prasugrel.<sup>136</sup> For each day after interruption of any of these agents, ~10% to 14% of normal platelet function is restored; later, it takes 7 to 10 days for an entire platelet pool to be replenished.<sup>137,138</sup>

Antiplatelet drugs that reversibly inhibit platelet function, with self-limiting effects depending on their elimination half-lives, include dipyridamole, cilostazol, and nonsteroidal antiinflammatory drugs. Dipyridamole, a pyridopyrimidine derivative with antiplatelet and vasodilator properties, has a half-life of 10 h, but because it is typically combined with ASA, this nullifies its reversible antiplatelet effect.<sup>139</sup> Cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilator properties, has a half-life of 10 h.<sup>140</sup> Nonsteroidal antiinflammatory drugs have half-lives that vary from 2 to 6 h (ibuprofen, ketoprofen, indomethacin), to 7 to 15 h (celecoxib, naproxen, diflunisal), to > 20 h (meloxicam, nabumetone, piroxicam).<sup>141</sup>

No randomized trials have assessed the optimal timing of antiplatelet drug interruption before surgery, in particular, whether stopping 7 to 10 days before surgery (to allow complete elimination of the antiplatelet effect) or closer to surgery affects bleeding and thromboembolic outcomes. Cohort studies involving patients who were receiving a VKA combined with ASA typically stopped ASA 7 to 10 days before surgery, although many of these patients also received LMWH bridging during VKA interruption.<sup>45-47</sup>

### 3.2 Resumption of Antiplatelet Drugs After Surgery

When resuming ASA, the maximal antiplatelet effect occurs within minutes, whereas with resumption of clopidogrel at a maintenance dose (75 mg/d), it takes 5 to 10 days to attain maximal platelet function inhibition.<sup>142</sup> With a clopidogrel loading dose (300-600 mg/d), maximal platelet function inhibition is attained within 12 to 15 h after administration.<sup>143,144</sup> Cohort studies involving patients who were receiving a VKA and ASA typically resumed ASA at the same time as the VKA, which was within 24 h after surgery in most patients.<sup>45-47</sup>

### 3.3 Laboratory Monitoring of Antiplatelet Therapy

Several platelet function assays are available to measure the antiplatelet effect of ASA and clopidogrel and have been assessed primarily in patients

having cardiac surgery or percutaneous coronary interventions.<sup>145,146</sup> However, the clinical significance of assay findings is uncertain, and the assay results have not been shown to predict clinical outcomes.<sup>147,148</sup> Additional study is needed, especially in patients having noncardiac surgery, before these assays can be considered for use in clinical practice.

### 3.4 Patients Having a Minor Dental, Dermatologic, or Ophthalmologic Procedure

In patients having dental procedures, several small studies (<100 patients) comprising randomized trials<sup>149-151</sup> and cohort studies<sup>118,152,153</sup> suggested no increase in major bleeding with ASA continuation. Only one 43-patient retrospective cohort study assessed the safety of dental procedures in 29 patients receiving combined ASA and clopidogrel and found no bleeding episodes with continuation of dual antiplatelet therapy.<sup>151</sup>

In patients having minor skin procedures, several prospective cohort studies, including ~200 patients, suggested a very-low (<1%) risk for major bleeding with continuation of ASA.<sup>121,122,154,155</sup> These studies also suggested an increase in minor bleeding with ASA continuation compared with controls who were not receiving antithrombotic therapy, but the incidence rates varied widely (2%-51%), likely reflecting different thresholds for defining minor bleeding. Nonetheless, these findings are consistent with those in patients who continued VKAs around minor skin procedures and indicate the need for adequate attention to postprocedure hemostasis.

Among patients undergoing cataract surgery, prospective cohort studies have suggested a low (<1%) incidence of major bleeding with perioperative continuation of ASA.<sup>126,127,156</sup> The incidence of cardiovascular events in one cohort study was similar in patients who continued or interrupted ASA (0.20% vs 0.65%), although a distinction was not made according to patient clinical indication for ASA therapy.<sup>126</sup> No studies assessed the management of patients who receive clopidogrel alone and require minor dental, skin, or eye procedures.

#### Recommendation

**3.4. In patients who are receiving ASA for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure (Grade 2C).**

### 3.5 Patients Having Noncardiac Surgery

Several studies assessed the effects of ASA continuation or interruption before surgery (Table S8).

Indirect evidence is available from a 19,000-patient placebo-controlled trial (Pulmonary Embolism Prevention trial) that compared de novo low-dose ASA use started before hip fracture repair or joint replacement surgery and continued for 35 days after surgery.<sup>157</sup> ASA use was associated with a possible increase in clinically recognized myocardial infarction (risk ratio, 1.57; 95% CI, 0.93-2.65) but failed to demonstrate a reduction or increase in stroke (risk ratio, 1.13; 95% CI, 0.69-1.85). Although this study was done in the pretrypsin era, effects of ASA therapy on clinically silent myocardial ischemia or stroke cannot be excluded. Furthermore, patients were not limited to those at risk for acute coronary events because the trial was intended to determine the effect of ASA on postoperative prevention of VTE. Perioperative ASA use conferred a small increase in the risk for major bleeding (2.9% vs 2.4%,  $P = .04$ ) and, indeed, decreased the risk for postoperative VTE (risk ratio, 0.71; 95% CI, 0.54-0.94).

A small randomized trial is unique in that it involved patients at high risk for cardiovascular events who were undergoing noncardiac surgery and who started ASA (75 mg once daily) or placebo 7 days before surgery and continued it for 30 days after surgery.<sup>158</sup> This study found that perioperative ASA use conferred a significant reduction in myocardial infarction and other major cardiovascular events (1.8% vs 9.0%,  $P = .02$ ), but the study was underpowered to detect differences in bleeding outcomes.<sup>158</sup> A meta-analysis of >49,000 patients who had noncardiac surgery, of whom 15,000 were receiving long-term ASA prior to surgery, found that perioperative continuation of ASA increased the overall risk for bleeding (risk ratio, 1.5; interquartile range, 1.0-2.5) but did not increase bleeding requiring a medical intervention.<sup>159</sup> However, patients requiring intracranial or prostate surgery did have an increase in bleeding with perioperative ASA continuation, and in such patients (and others deemed at high risk for bleeding), perioperative continuation of ASA should be considered with caution. This meta-analysis did not report on cardiovascular outcomes. Taken together, these data suggest that patients with coronary artery or other cardiovascular disease, who may be considered at moderate to high risk for perioperative adverse cardiovascular events,<sup>160,161</sup> may benefit from perioperative continuation of ASA. Such moderate-to-high-risk patients include those with ischemic heart disease, compensated or prior congestive heart failure, diabetes mellitus, renal insufficiency, or cerebrovascular disease. In addition, patients undergoing selected types of surgery associated with an increased risk for perioperative cardiovascular events, such as carotid endarterectomy and peripheral artery

bypass surgery, may also benefit from perioperative continuation of ASA.<sup>162-164</sup> In patients considered at low risk for cardiovascular events in whom there is likely to be fewer potential benefits of perioperative continuation of ASA, interruption of ASA may be reasonable.

Few studies assessed perioperative continuation of clopidogrel. These studies, all of which were retrospective cohort analyses, suggested increased rates of bleeding with perioperative or periprocedural clopidogrel continuation.<sup>165-167</sup> Indirect data from a linked database involving patients in the nonoperative setting indicate that clopidogrel-only users are at 33% higher risk for bleeding than ASA-only users (risk ratio, 1.33; 95% CI, 1.11-1.59),<sup>168</sup> thereby implying that the antiplatelet potency of clopidogrel is greater than that of ASA. This finding appears to support anecdotal observations of clinicians (including the article panelists) involved in perioperative antithrombotic management because there appears to be a higher bleeding tendency in patients continuing clopidogrel than in those continuing ASA perioperatively. Although clopidogrel appears to confer less GI bleeding than ASA in the nonoperative setting,<sup>169</sup> this decreased tendency for bleeding may be related to less GI irritation with clopidogrel and may not be applicable to the perioperative setting.

#### Recommendation

**3.5. In patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery, we suggest continuing ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C). In patients at low risk for cardiovascular events who are receiving ASA therapy, we suggest stopping ASA 7 to 10 days before surgery *instead of* continuation of ASA (Grade 2C).**

#### 3.6 Patients Having Coronary Artery Bypass Graft Surgery

Most patients who require a coronary artery bypass graft (CABG) are receiving long-term ASA therapy. In addition, 10% to 15% of patients who have had an acute coronary syndrome will require urgent CABG surgery and are, typically, receiving both ASA and clopidogrel/prasugrel.<sup>170</sup> The issue of whether antiplatelet drugs should be continued or stopped is important because of the need to minimize perioperative bleeding, especially mediastinal bleeding that can cause pericardial tamponade. In a >11,000-subject cohort study of patients undergoing CABG, packed red cell transfusion (which occurred in 49% of patients) conferred an increased risk for mortality (risk ratio, 1.77; 95% CI, 1.67-1.87) as well as renal

failure and neurological events.<sup>171</sup> Other observational studies have shown an increased risk for bleeding with perioperative ASA use in patients having CABG.<sup>172,173</sup> A meta-analysis of studies assessing perioperative continuation of ASA confirmed an increase in postoperative bleeding (as measured by chest tube drainage) but no increase in the need for reoperation.<sup>174</sup> Against these potential bleeding risks, ASA use within 5 days prior to CABG surgery was associated in a >8,000-patient cohort study to reduce overall mortality without a concomitant increased risk for reoperation for pericardial bleeding or need for blood transfusion.<sup>43</sup> Other smaller observational studies have also found a reduction in cardiovascular events and overall mortality in patients who continue ASA prior to CABG surgery.<sup>175,176</sup> Taken together, it appears that although ASA increases the risk for postoperative bleeding, there is no increased risk for reoperation, which is coupled with the potential for decreased cardiovascular events and overall mortality. However, given the uncertainty in the relative risks and benefits of perioperative ASA continuation, clinicians may individualize patient management; for example, it may be reasonable to stop ASA in patients with stable coronary artery disease who require CABG.

With the common use of thienopyridine derivatives, such as clopidogrel, in patients who require CABG, the issue of how to manage ASA and clopidogrel around the time of CABG surgery is clinically relevant. Subgroup analyses of large trials involving patients with an acute coronary syndrome who were receiving dual antiplatelet therapy (ASA and clopidogrel) and who subsequently needed CABG found a 50% higher incidence in major bleeding and a 70% higher incidence of transfusion requirements in those who received clopidogrel within the 5-day period before CABG, but this risk appears to be minimized if clopidogrel is stopped at least 5 days before CABG surgery.<sup>177,178</sup> Observational studies also found increased bleeding in patients exposed to clopidogrel within 5 days of CABG surgery.<sup>179-181</sup>

For patients who are receiving dual ASA-clopidogrel therapy in whom urgent CABG surgery is required and a 5-day or longer delay after clopidogrel interruption is not feasible, a probable increase in bleeding risk should be anticipated. Options to reduce bleeding transfusion requirements include preoperative platelet transfusion and administering antifibrinolytic drugs such as tranexamic acid or  $\epsilon$ -aminocaproic acid<sup>182,183</sup> but not aprotinin,<sup>184</sup> which confers an increased risk for thrombotic and other adverse events.

#### Recommendation

**3.6. In patients who are receiving ASA and require CABG surgery, we suggest continuing**



**ASA around the time of surgery *instead of* stopping ASA 7 to 10 days before surgery (Grade 2C). In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 days before surgery *instead of* continuing dual antiplatelet therapy around the time of surgery (Grade 2C).**

### 3.7 Patients With Coronary Stents Having Surgery

The management of patients with coronary stents who require surgery is a common and challenging clinical problem. One retrospective-linked database study of 17,797 stented patients found that 11% of patients required surgery during a 2-year period after stent placement and that 4% required surgery within 1 year of stent placement.<sup>185</sup>

Patient management is problematic because of concerns about the incidence and clinical consequences of stent-related coronary thrombosis if antiplatelet therapy is interrupted. In the nonoperative setting, observational studies and case reports of suboptimal methodological quality have suggested a markedly increased risk for stent thrombosis after premature antiplatelet drug interruption and after temporary interruption of treatment because of surgery.<sup>186-191</sup> In several retrospective studies totaling >2,200 patients who had surgery within 2 years of stent placement, the incidence of postoperative stent thrombosis was, on average, between 2% and 5%.<sup>192-197</sup> Moreover, these studies suggested that the clinical impact of stent thrombosis and associated coronary events is considerable, with case-fatality rates of  $\geq 50\%$ .

Despite concerns about the extent and severity of perioperative thrombotic events in patients with coronary stents, there are no randomized trials comparing different perioperative management strategies. Furthermore, in observational studies of stented patients who had surgery, outcome events generally were not reported according to a prespecified intervention, such as whether patients had perioperative interruption of dual antiplatelet therapy (ASA and clopidogrel/prasugrel), interruption of a single agent, or continuation of dual antiplatelet therapy. Consequently, conclusions are limited about optimal perioperative management.

Indirect evidence from the nonoperative clinical setting indicates that premature discontinuation of dual antiplatelet therapy, within 6 weeks of bare-metal stent placement or within 3 to 6 months of drug-eluting stent placement, increases the risk for stent thrombosis and appears to be the strongest predictor of stent thrombosis.<sup>198</sup> On the other hand,

in patients who require CABG, perioperative continuation of dual antiplatelet therapy confers an increased risk for bleeding, which includes life-threatening pericardial tamponade. What is unclear is whether there is a similarly increased risk for serious bleeding with perioperative continuation of dual antiplatelet therapy in patients having noncardiac surgery and procedures. Overall, there is substantial uncertainty about whether the potential benefits of continuing dual antiplatelet therapy outweigh the likely increased risk for bleeding.

The role of bridging therapy in patients with coronary stents who require elective surgery is uncertain. Only a few case reports assessed the use of short-acting antithrombotic drugs such as UFH, LMWHs, or glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatid) in the perioperative setting.<sup>199-201</sup> Reversible platelet P2-receptor inhibitors, such as ticagrelor, may play a role as bridging therapy in this clinical setting. Studies are needed to assess the role of bridging therapy, if any, in patients who are receiving antiplatelet drugs. Until such data are available, the use of short-acting antithrombotic agents in patients who require temporary interruption of antiplatelet therapy is inadvisable.

#### Recommendation

**3.7. In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, we recommend deferring surgery for at least 6 weeks after placement of a bare-metal stent and for at least 6 months after placement of a drug-eluting stent *instead of* undertaking surgery within these time periods (Grade 1C). In patients who require surgery within 6 weeks of placement of a bare-metal stent or within 6 months of placement of a drug-eluting stent, we suggest continuing dual antiplatelet therapy around the time of surgery *instead of* stopping dual antiplatelet therapy 7 to 10 days before surgery (Grade 2C).**

*Remarks:* Patients who are more concerned about avoiding the unknown, but potentially large increase in bleeding risk associated with the perioperative continuation of dual antiplatelet therapy than avoiding the risk for coronary stent thrombosis are unlikely to choose continuation of dual antiplatelet therapy.

## 4.0 PERIOPERATIVE MANAGEMENT OF PATIENTS WHO ARE RECEIVING HEPARIN BRIDGING ANTICOAGULATION

### 4.1 Anticoagulants and Anticoagulant Dose Regimens Considered for Bridging

There is no established single heparin bridging regimen. Variability exists in the type of anticoagulant

(LMWH or UFH), intensity of anticoagulation (therapeutic dose, low dose, or intermediate dose), and timing of perioperative administration. In considering which regimen and administration approach to use, there are several points to consider:

- *Anticoagulant intensity to prevent thromboembolism.* In the absence of randomized trials assessing the efficacy of different intensities of bridging regimens to prevent ATE, including stroke, we have used indirect data. First, although evidence is lacking that LMWHs prevent recurrent stroke, indirect data from a large trial investigating idraparinux (a synthetic factor Xa inhibitor with similar anticoagulant properties as LMWHs) found it to be as effective as warfarin for stroke prevention in patients with atrial fibrillation, thereby supporting the use of therapeutic-dose LMWH for perioperative stroke prevention.<sup>14</sup> Second, although low-dose LMWH or UFH is effective to prevent VTE after surgery,<sup>15,89</sup> evidence is lacking about whether such low-dose heparin regimens are effective in preventing ATE, including stroke. Lower-dose VKA regimens (target INR < 2.0), which might be considered comparable to low-dose heparin regimens, are less effective for stroke prevention.<sup>202</sup>
- *Proximity to surgery of anticoagulant administration and risk for bleeding.* From randomized trials assessing different anticoagulant regimens for postoperative VTE prophylaxis, there is consistent evidence that the closer to surgery an anticoagulant is given, the higher the risk for bleeding.<sup>203,204</sup> Thus, bleeding is greater when a first dose is given early (4-8 h postoperatively), lower when given at an intermediate interval (12-24 h postoperatively), and lowest when administration is delayed for > 24 h postoperatively. Clinicians should assess postoperative hemostasis and determine whether wound-site hemostasis has occurred and the surgical bed is dry. Although subjective, this can be aided by assessing the amount, type (serous, serosanguinous, bloody), and progress (continuing, increasing, decreasing) of drainage and blood collection in wound bandages or surgical drains. Heparin bridging, especially a therapeutic-dose regimen, should be delayed after surgery until there is adequate hemostasis.
- *Dose of anticoagulant administration and risk for bleeding.* One observational study suggested that use of a higher-intensity therapeutic-dose bridging regimen may be associated with a more than fourfold risk (OR, 4.4; 95% CI, 1.5-14.7) for postoperative major bleeding com-

pared with a low-dose regimen.<sup>51</sup> This finding is consistent with studies assessing the intensity of anticoagulant therapy for the secondary prevention of VTE and stroke.<sup>205-207</sup> Other observational studies suggested that a once-daily therapeutic-dose bridging regimen may be associated with a higher risk for bleeding than a bid (split-dose) therapeutic-dose regimen, but direct comparisons of once-daily vs bid heparin bridging regimens have precluded definitive conclusions.<sup>19,45-47</sup> Taken together, these findings suggest caution in using higher-intensity therapeutic-dose heparin bridging after surgery, especially in patients undergoing high-bleeding-risk surgery and procedures.

Based on these considerations, we suggest the following two guides for postoperative management of bridging anticoagulation:

1. LMWH or UFH should not be resumed at a fixed time after a surgery or procedure without consideration of the anticipated bleeding risk or adequacy of postoperative hemostasis.
2. If therapeutic-dose bridging is used in patients at high risk for postoperative bleeding, its initiation should be delayed for 48 to 72 h after surgery when adequate surgical hemostasis has been achieved. If bleeding continues beyond 72 h, options include a low-dose heparin bridging regimen or VKA resumption alone without postoperative bridging.

#### 4.2 Perioperative Use of IV UFH

IV UFH administered to achieve an aPTT of 1.5 to 2.0 times the control aPTT is an option for perioperative bridging. UFH may be of particular use in, for example, patients with severe renal insufficiency or dependency on dialysis in whom LMWHs should be avoided. No studies have assessed the timing of interruption of IV UFH. However, the dose-dependent elimination half-life of 90 min (range, 30-120 min) suggests that an infusion can be stopped 4 to 6 h before surgery.<sup>208</sup> Resumption of IV UFH after surgery should follow the approach used for SC LMWH, with IV UFH resumed without a bolus dose at the same infusion rate as that used preoperatively.<sup>66,209</sup> Bridging anticoagulation with UFH may be considered for out-of-hospital administration using a fixed-dose, weight-based, SC regimen (250 International Units/kg bid) that does not require aPTT monitoring.<sup>210</sup>

#### Recommendation

#### 4.2. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we

**suggest stopping UFH 4 to 6 h before surgery *instead of closer to surgery*** (Grade 2C).

#### 4.3 Preoperative Interruption of Therapeutic-Dose Bridging LMWH

In observational studies assessing LMWH bridging, there were no apparent higher bleeding rates (compared with nonbridged controls from other studies) if the last dose of LMWH was given ~12 h (ie, the evening) before surgery or ~24 h before surgery.<sup>45,46</sup> However, in studies assessing a surrogate marker for bleeding (antifactor Xa levels), >90% of patients who received their last LMWH dose ~12 h before surgery had a detectable anticoagulant effect at surgery, with 34% of patients having a therapeutic level of anticoagulation (ie, antifactor Xa  $\geq 0.50$  International Units/mL) at surgery.<sup>211,212</sup> Although these studies could not assess the effect of residual anticoagulation on bleeding outcomes, clinicians should consider withholding the last LMWH dose before surgery when a bid regimen is used and giving half the total dose the morning before surgery when a once-daily regimen is used to minimize the residual anticoagulant effect at the time of surgery.

#### Recommendation

**4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery *instead of 12 h before surgery*** (Grade 2C).

#### 4.4 Postoperative Resumption of Therapeutic-Dose Bridging LMWH

An observational study in which all patients received LMWH (1.5 mg/kg) started 12 to 24 h after all types of surgery, patients who had major (>1 h duration) surgery had a 20% (8/40) incidence of major bleeding, whereas major bleeding occurred in 0.7% (1/148) in patients who had a minor (<1 h duration) surgery or procedure.<sup>19</sup> In other observational studies assessing therapeutic-dose LMWH bridging, an indirect, across-study comparison yielded an apparent lower risk for nonmajor bleeding with delayed resumption of LMWH. Other observational studies that allowed a flexible postoperative bridging regimen in high-bleeding-risk patients with either delayed resumption of therapeutic-dose LMWH or substitution of a low-dose regimen found a low incidence of major bleeding (<5%).<sup>31,47-49,51,55,213,214</sup> Taken together, these studies suggest that the resumption of LMWH should be delayed for at least 24 h and probably longer (48-72 h) in patients undergoing major surgery, with resumption contingent on clinical evi-

dence of surgical-site hemostasis. In studies that assessed moderate- or low-bleeding-risk patients who received therapeutic-dose LMWH started approximately 24 h after surgery (on the morning of the day after surgery), the incidence of major and nonmajor bleeding was low (<3%).<sup>45-47</sup>

#### Recommendation

**4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery *instead of resuming LMWH within 24 h after surgery*** (Grade 2C). **In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing non-high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH approximately 24 h after surgery *instead of resuming LMWH more than 24 h after surgery*.**

## 5.0 RESEARCH RECOMMENDATIONS

Additional research is necessary to establish best practices for patients who are receiving antithrombotic therapy and require surgery. Efforts to bridge these gaps in knowledge are ongoing. The randomized placebo-controlled trials PERIOP-2 (A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin),<sup>215</sup> BRIDGE (Effectiveness of Bridging Anticoagulation for Surgery),<sup>216</sup> PACEBRIDGE (Preoperative Low Molecular Weight Heparin vs Tapered Warfarin as Bridging Therapy for patients with Implantation of Pacemaker or Defibrillator), and BRUISECONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial)<sup>217</sup> are assessing the need for LMWH bridging in VKA-treated patients. POISE-2 (PeriOperative Ischemic Evaluation-2 Trial)<sup>218</sup> is a placebo-controlled trial assessing the perioperative continuation or interruption of ASA in patients undergoing noncardiac surgery, and ATACAS (Aspirin and Tranexamic Acid for Coronary Artery Surgery Trial) (ACTR [Australian Clinical Trials Registry] No. 12605000557639) is assessing perioperative use of ASA in patients undergoing CABG surgery.<sup>219</sup> Large observational studies are planned to assess best perioperative practices in patients who are receiving new oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, and new antiplatelet drugs, such as prasugrel and ticagrelor. Additional research is needed to inform best perioperative practices in special populations (obese, renal insufficiency) and, especially, in patients with coronary stents.

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### Perioperative Management of Antithrombotic Therapy

#### Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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#### APPENDIX S1—MEDLINE LITERATURE SEARCH STRATEGY

1. Anticoagulants/ or perioperative anticoagulation.mp.
2. warfarin.mp. or exp Warfarin/
3. exp Heparin/ or exp Heparin, Low-Molecular-Weight/ or heparin.mp.
4. exp Perioperative Care/ or perioperative.mp.
5. atrial fibrillation.mp. or exp Atrial Fibrillation/
6. exp Heart Valve Prosthesis/ or mechanical heart valve.mp.
7. exp Thrombosis/ or thrombosis.mp. or exp Venous Thrombosis/
8. 4 or 1
9. 8 and 7 and 2
10. 3 and 9
11. 9 and 5
12. 8 and 6
13. aspirin.mp. or exp Aspirin/
14. antiplatelet agent.mp. or exp Platelet Aggregation Inhibitors/
15. 13 or 14
16. 4 and 15

**Table S1—[Section 2.1] Evidence Profile: PICO in Patients Who Require Warfarin Interruption Before Surgery to Attain Normal or Near-Normal INR At Surgery, Stopping Warfarin 5 to 6 Days Before Surgery vs Stopping Warfarin <5 d Before Surgery**

No. of Studies	Quality Assessment					Summary of Findings				
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients	Effect	Relative (95% CI)	Absolute Quality Importance
C:0						Thromboembolic event	Not reported	Not relevant	Not relevant	Low Critical
C:1	Case series	Very serious <sup>a</sup>	Not relevant	No serious indirectness	Very serious <sup>b</sup>	No publication bias <sup>c</sup>	0 Events in 21 patients	Not relevant	Not relevant	Low Critical
0						Death	Not reported	Not relevant	Not relevant	Low Critical

Bibliography: Friedland S, Soetikno R, Friedland S, et al. Colonoscopy with polypectomy in anticoagulated patients. *Gastrointest Endosc.* 2006;64(1):98-100. C = comparator; INR = international normalized ratio; PICO = population, intervention, comparator, outcome; VKA = vitamin K antagonist.

<sup>a</sup>Single-arm case series without comparison and no information on adjustment, blinding of outcome assessment, or patients lost to follow-up.

<sup>b</sup>Only 21 patients.

<sup>c</sup>Only one publication identified.

**Table S2—[Section 2.4] PICO: In Patients Considered at High Risk for Perioperative Thromboembolism, Bridging Anticoagulation With Heparin/LMWH vs No Bridging**

No. of Studies	Quality Assessment							Summary of Findings				
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect			
							Bridging Anticoagulation With a Heparin	No Bridging	Relative (95% CI)	Absolute	Quality	Importance
I: 1, C: 0	Observational study	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious <sup>b</sup>	Thromboembolic event (follow-up 4 wk): Pengo et al, 2009 No publication bias	5 events in 295 patients, pIR0.02 [CI: 0.01-0.04]	Not reported	Not relevant	Not relevant	Low	Critical
I: 1, C: 0	Observational study	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious <sup>b</sup>	Major bleeding (follow-up 4 wk): Pengo et al, 2009 No publication bias	8 events in 295 patients, pIR 0.03 [CI: 0.01-0.05]	Not reported	Not relevant	Not relevant	Low	Critical
I: 1, C: 0	Observational study	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious <sup>b</sup>	Death (follow-up 4 wk): Pengo et al, 2009 No publication bias	1 event in 295 patients, pIR 0.0 [CI: 0.00-0.02]				Low	Critical

Bibliography: Pengo V, Cucchini U, Denas G, et al; Italian Federation of Centers for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA). Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. *Circulation*. 2009;119(22):2920-2927. I = intervention; LMWH = low-molecular-weight heparin; pIR = pooled incidence rate. See Table S1 legend for expansion of other abbreviation.

<sup>a</sup>No information on adjustment, and blinding of outcome assessment.

<sup>b</sup>Sparse events.

**Table S3—[Section 2.4] PICO: In Patients Considered at Low Risk for Perioperative Thromboembolism, Bridging Anticoagulation With Heparin/LMWH vs No Bridging**

No. of Studies	Quality Assessment							Summary of Findings				
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect		Importance	
							Bridging Anticoagulation With a Heparin	No Bridging	Relative (95% CI)	Absolute	Quality	
I: 1, C: 0	Observational study	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious <sup>b</sup>	No publication bias	0 events in 967 patients	Not reported	Not relevant	Not relevant	Low	Critical
I: 1, C: 0	Observational study	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious <sup>b</sup>	Major bleeding bias	7 events in 967 patients, pIR 0.01 [CI: 0.00-0.02]	Not reported	Not relevant	Not relevant	Low	Critical
0						Death						Critical

Bibliography: Pengo V, Cucchini U, Denas G, et al; Italian Federation of Centers for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA). Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. *Circulation*. 2009;119(22):2920-2927. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>No specific information on adjustment, and blinding of outcome assessment.

<sup>b</sup>Sparse events.

**Table S4—[Section 2.5] PICO: In Patients Receiving Warfarin Therapy and Having a Minor Dental Procedure, Continuing Warfarin and Coadministering an Oral Prohemostatic Drug vs Stopping Warfarin 5 to 6 Days Before Procedure Without Administering a Prohemostatic Drug (Observational Studies)**

No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Considerations	Summary of Findings						
							Quality	Importance	Effect				
						Other	Continue VKA + Prohemostatic Intervention	Stopping VKA 2-3 d Before Procedure With Target INR 1.5-1.8	Relative (95% CI)	Absolute	Quality	Importance	
I: 0; C: 2	Prospective cohort, case series	Serious <sup>a</sup>	No serious inconsistency	Serious indirectness to any comparison <sup>b</sup>	No serious imprecision	No serious publication bias	No studies	0 in 260 patients				Critical	
Thromboembolic event (follow-up 3 mo) C: Russo et al, 2000; Saour et al, 1994													
Major bleeding (follow-up 1-8 d): I: Blinder et al, 1999; Bodner et al, 1998; Cieslik-Bielewska et al, 2005; Della Valle et al, 2003; Ferrieri et al, 2007; Keiani Motlagh et al, 2003; Martinowitz et al, 1990; Ramli et al, 2005; Street et al, 1990; Zusman et al, 1992; C: Blinder et al, 2001; Campbell et al, 2000; Russo et al, 2000; Saour et al, 1994													
I: 10; C: 4	Prospective cohort, case series	Serious <sup>a</sup>	No serious inconsistency	Serious indirectness to any comparison <sup>b</sup>	No serious imprecision	No serious publication bias	1 event in 699 patients, pIR 0.001	0 in 332 patients	Not relevant	Not relevant	Not relevant	Low	Critical
Moderate bleeding (follow-up 1-8 d): I: Binder et al, 1999; Bodner et al, 1998; Cieslik-Bielewska et al, 2005; Della Valle et al, 2003; Ferrieri et al, 2007; Keiani Motlagh et al, 2003; Martinowitz et al, 1990; Morimato et al, 2008; Ramli et al, 2005; Street et al, 1990; Zusman et al, 1992; C: Blinder et al, 1992; C: Blinder et al, 2001; Campbell et al, 2000; Russo et al, 2000; Saour et al, 1994													
I: 11; C: 4	Prospective cohort, case series	Serious <sup>a</sup>	No serious inconsistency	Serious indirectness to any comparison <sup>b</sup>	No serious imprecision	No serious publication bias	33 events in 833 patients, pIR 0.06 [CI: 0.04-0.09]	5 events in 332 patients, pIR 0.03 [CI: 0.01-0.09]	Not relevant	Not relevant	Not relevant	Low	Important
Minor bleeding (follow-up 1-8 d): I: Binder et al, 1999; Bodner et al, 1998; Cieslik-Bielewska et al, 2005; Della Valle et al, 2003; Ferrieri et al, 2007; Keiani Motlagh et al, 2003; Martinowitz et al, 1990; Morimato et al, 2008; Ramli et al, 2005; Street et al, 1990; Zusman et al, 1992; C: Binder et al, 1992; C: Binder et al, 2001; Campbell et al, 2000; Russo et al, 2000; Saour et al, 1994													
I: 11; C: 4	Prospective cohort, case series	Serious <sup>a</sup>	No serious inconsistency	Serious indirectness to any comparison <sup>b</sup>	No serious imprecision	No serious publication bias	24 events in 444 patients, pIR 0.08 [CI: 0.02-0.29]	2 events in 332 patients, pIR 0.15 [CI: 0.04-0.55]	Not relevant	Not relevant	Not relevant	Low	Important
Death: not reported													

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<sup>a</sup>No information on adjustment, and blinding of outcome assessment.

<sup>b</sup>No direct comparator.

<sup>c</sup>No serious imprecision: judgment might change when frequencies are recalculated with the inverse variance method; however, no impact on overall judgment.

**Table S5—[Section 2.5] PICO: In Patients Receiving Warfarin Therapy and Having a Minor Dental Procedure, Continuing Warfarin and Coadministering an Oral Prohemostatic Drug vs Stopping Warfarin 5-6 Days Before Procedure Without Administering a Prohemostatic Drug (Randomized Trials)**

No. of Studies	Design	Quality Assessment					Summary of Findings					
		Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect			
							Continue VKA Combined With Prohemostatic Intervention	Stopping VKA 2-3 d Before Procedure With Target INR of 1.5-1.8	Relative (95% CI)	Absolute	Quality	Importance
3	RCT	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious imprecision <sup>b</sup>	No serious publication bias	0 events in 138 patients	0 events in 132 patients	0	Low	Critical	
						Thromboembolic event: Borea et al, 1993; Evans et al, 2002; Sacco et al, 2006						
3	RCT	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious imprecision <sup>b</sup>	No serious publication bias	0 events in 138 patients	0 events in 132 patients	0	Low	Critical	
						Major bleeding (follow-up 1-8 d): Borea et al, 1993; Evans et al, 2002; Sacco et al, 2006						
3	RCT	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious imprecision <sup>b</sup>	No serious publication bias	9 events in 138 patients	12 events in 132 patients	0.68 (0.29-1.53)	Low	Important	
						Moderate bleeding (follow-up 1-8 d): Borea et al, 1993; Evans et al, 2002; Sacco et al, 2006						
2	RCT	Serious <sup>a</sup>	Not relevant	No serious indirectness	Serious imprecision <sup>b</sup>	No serious publication bias	14 events in 72 patients	7 events in 67 patients	1.76 (0.78-3.96)	Low	Important	
						Minor bleeding (follow-up 1-8 d): Borea et al, 1993; Evans et al, 2002						

Death: not reported

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<sup>a</sup>No blinding of the patients, probably no blinding of the other research team members.

<sup>b</sup>Few patients, few events, broad CIs include benefit as well as harm.



**Table S6—[Section 2.5] PICO: In Patients Receiving Warfarin Therapy and Having a Minor Skin Procedure, Continuing Warfarin Around the Time of the Procedure vs Stopping Warfarin 5-6 Days Before the Procedure**

No. of Studies	Design	Quality Assessment				Summary of Findings						
		Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect			
						Continue VKA Around the Time of the Procedure	Stopping VKA Approximately 5 d Before the Procedure	Relative (95% CI)	Absolute	Quality	Importance	
I: 0; C: 0						Thromboembolic event: not reported					Critical	
I: 4; C: 4	Prospective cohort	Serious <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	No serious publication bias	0 events in 96 patients	0 events in 383 patients	Not reported	Not reported	Not reported	Critical
I: 4; C: 4	Prospective cohort	Serious <sup>a</sup>	No serious inconsistency <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	No serious publication bias	6 events in 96 patients pIR 0.20 [0.10-0.42]	5 events in 383 patients pIR 0.34 [0.01-0.06]	Not reported	Not reported	Not reported	Low
I: 4; C: 4	Prospective cohort	Serious <sup>a</sup>	No serious inconsistency <sup>b</sup>	No serious indirectness	Serious <sup>c</sup>	No serious publication bias	25 events in 96 patients pIR 0.34 [0.23-0.51]	33 events in 383 patients pIR 0.34 [0.08-0.15]	Not reported	Not reported	Not reported	Low

Death: not reported

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<sup>a</sup>No information on adjustment, and blinding of outcome assessment.

<sup>b</sup>Risk increase among studies varied between factor 0 and 10 (moderate bleeding event) and between factor 0 and 4.4 (minor bleeding event).

<sup>c</sup>Small event rates in both groups.

**Table S7—[Section 2.5] PICO: In Patients Receiving Warfarin Therapy and Having Cataract Removal, Continuing Warfarin Around the Time of the Procedure vs Stopping Warfarin 5 to 6 Days Before the Procedure**

No. of studies	Quality Assessment					Summary of Findings			
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients	Effect	Importance
I; 2; C; 2	Prospective cohort, case series <sup>a</sup>	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	No publication bias	Continue VKA Around the Time of the Procedure 1,165 patients <sup>c</sup> Stopping VKAs Approximately 5 d Before the Procedure 19,626 patients <sup>c</sup>	Relative (95% CI) Not relevant	Low Critical
Thromboembolic event: (follow-up 1 wk) I; Hirschman 2006; Katz et al, 2003; C; Hirschman et al, 2006; Katz et al, 2003 (2 arms)									
Major bleeding (follow-up median, 1 wk; range, 1/2 wk to 144 wk) I; Fu 2007; Hirschman 2006; Katz et al, 2003; Narendran and Williamson, 2003; Rotenstreich et al, 2001; Wirbelauer et al, 2004; C; Hirschman 2006; Kallio et al, 2004 (2 arms); Katz et al, 2003 (2 arms); Lumme et al, 1994; Narendran and Williamson, 2003; Wirbelauer et al, 2004									
I; 6; C; 6	Prospective cohort, case series <sup>a</sup>	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	No publication bias	0 events in 1,335 patients <sup>c</sup> 25 events in 21,084 patients <sup>c</sup>	0 0	Low Critical
Moderate bleeding (follow-up median, 1 wk; range, 1/2 wk to 144 wk) I; Fu 2007; Hirschman 2006; Katz et al, 2003; Narendran and Williamson, 2003; Rotenstreich et al, 2001; Wirbelauer et al, 2004; C; Hirschman 2006; Kallio et al, 2004 (2 arms); Katz et al, 2003 (2 arms); Lumme et al, 1994; Narendran and Williamson, 2003; Wirbelauer et al, 2004									
I; 6; C; 6	Prospective cohort, case series <sup>a</sup>	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	No publication bias	4 events in 1,335 patients <sup>c</sup> 42 events in 21,084 patients <sup>c</sup>	Not relevant relevant	Low Important
Minor bleeding (follow-up median, 1 wk; range, 1/2 wk to 144 wk) I; Fu 2007; Hirschman 2006; Katz et al, 2003; Narendran and Williamson, 2003; Rotenstreich et al, 2001; Wirbelauer et al, 2004; C; Hirschman 2006; Kallio et al, 2004 (2 arms); Katz et al, 2003 (2 arms); Lumme et al, 1994; Narendran and Williamson, 2003; Wirbelauer et al, 2004									
I; 6; C; 6	Prospective cohort, case series <sup>a</sup>	Serious <sup>b</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	No publication bias	20 events in 1,335 patients <sup>c</sup> 61 events in 21,084 patients <sup>c</sup>	Not relevant relevant	Low Important

Death: not reported

**Bibliography:** Katz J, Feldman MA, Bass EB, et al; Study of Medical Testing for Cataract Surgery Team. Risks and benefits of anticoagulant and antiplatelet medication use before cataract surgery. *Ophthalmology*. 2003;110(9):1784-1788. Narendran N, Williamson TH. The effects of aspirin and warfarin therapy on haemorrhage in vitreoretinal surgery. *Acta Ophthalmol Scand*. 2003;81(1):38-40. Rotenstreich Y, Rubowitz A, Segev F, Jaeger-Roshu S, Assia EI. Effect of warfarin therapy on bleeding during cataract surgery. *J Cataract Refract Surg*. 2001;27(9):1344-1346. Wirbelauer C, Weller A, Häberle H, Pham DT. [Cataract surgery under topical anesthesia with oral anticoagulants]. *Klin Monatsbl Augenheilkd*. 2004;221(9):749-752. Kallio H, Paloheimo M, Maunukela EL. Haemorrhage and risk factors associated with retrobulbar/peribulbar block: a prospective study in 1383 patients. *Br J Anaesth*. 2000;85(5):708-711. Lumme P, Laatikainen LT. Risk factors for intraoperative and early postoperative complications in extracapsular cataract surgery. *Eur J Ophthalmol*. 1994;4(3):151-158. Hirschman DR, Morby LJ. A study of the safety of continued anticoagulation for cataract surgery patients. *Nursing Forum*. 2006;41(1):30-37. Fu AD, McDonald HR, Williams DF, et al. Anticoagulation with warfarin in vitreoretinal surgery. *Retina*. 2007;27:290-295. See Table S1 and S2 legends for expansion of abbreviations.

<sup>a</sup>In the presence of no events in many studies no pooling performed.

<sup>b</sup>Two of eight studies are cohort studies, six of eight studies are single-arm studies; no information on adjustment, and blinding of outcome assessment.

<sup>c</sup>Six of eight studies were cohort studies by design but four of six cohort studies contributed only one study arm to the profile (the alternative study arm did not match our PICO question). Those studies were treated like case series.

**Table S8—[Section 3.5] PICO: Patient Receiving Antiplatelet Therapy and Having Elective Noncardiac Surgery, Continuing Antiplatelet Drugs Around the Time of the Procedure vs Stopping Antiplatelet Drugs 7 to 10 Days Before Noncardiac Surgery**

No. of Studies	Design	Quality Assessment						Summary of Findings			Importance	
		Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Relative (95% CI)	Absolute		Quality
							Antiplatelet Drugs Continued	Stopping Antiplatelet Drugs				
1	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>a</sup>	None	235 of 6,679 (3.5%)	252 of 6,677 (3.8%)	RR, 0.93 (0.78-1.11)	3 fewer per 1,000 (from 8 fewer to 4 more)	Moderate	Critical
Vascular mortality in low-risk patients/surgery (follow-up 1 mo): PEP-Trial 2000												
1	RCTs	No serious limitations	No serious inconsistency	Serious indirectness	Serious <sup>b</sup>	None	235 of 6,679 (3.5%)	252 of 6,677 (3.8%)	RR, 0.93 (0.78-1.11)	3 fewer per 1,000 (from 8 fewer to 4 more)	Low	Critical
Vascular mortality in moderate/high-risk patients/surgery (follow-up 1 mo): PEP-Trial 2000												
2	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious	None	106 of 6,705 (1.6%)	80 of 6,704 (1.2%)	RR, 1.33 (0.99-1.77)	4 more per 1,000 (from 0 fewer to 9 more)	Moderate	Important
Nonfatal MI in low-risk patients/surgery (follow-up 1 mo): Nielson 2000; PEP-Trial 2000												
2	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>c</sup>	None	21 of 395 (5.3%)	44 of 374 (11.8%)	RR, 0.45 (0.27-0.74)	65 fewer per 1,000 (from 31 fewer to 86 fewer)	Moderate	Important
Nonfatal MI in moderate/high-risk patients/surgery (follow-up 1-36 mo <sup>b</sup> ): McCollum 1991; Oscarsson 2010												
1	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>d</sup>	None	54 of 6,679 (0.8%)	49 of 6,677 (0.7%)	RR, 1.1 (0.75-1.62)	1 more per 1,000 (from 2 fewer to 5 more)	Moderate	Critical
Stroke/TIA in low-risk patients/surgery (follow-up 1 mo): PEP-Trial 2000												
4	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>e</sup>	None	30 of 560 (5.4%)	37 of 538 (6.9%)	RR, 0.77 (0.49-1.23)	16 fewer per 1,000 (from 35 fewer to 16 more)	Moderate	Critical
Stroke/TIA in moderate/high-risk patients/surgery (follow-up 1-36 mo): Lindblad 1993; McCollum 1991; Oscarsson 2010; Tytgat 2004												
1	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>f</sup>	None	28 of 6,679 (0.4%)	38 of 6,677 (0.6%)	RR, 0.74 (0.45-1.21)	1 fewer per 1,000 (from 3 fewer to 1 more)	Moderate	Important
Nonfatal pulmonary embolism (follow-up 1 mo): PEP-Trial 2000												

(Continued)

**Table S8—Continued**

No. of Studies	Quality Assessment					Summary of Findings					
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Relative (95% CI)	Quality	Importance
1	RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Serious <sup>a</sup>	None	197 of 6,679 (2.9%)	157 of 6,677 (2.4%)	RR, 1.24 (1.01-1.53)	Moderate	Important
Bleeding requiring transfusion (follow-up 1 mo): PEP-Trial 2000											
							Stopping Antiplatelet Drugs	Absolute			
							6 more per 1,000 (from 0 more to 12 more)				

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<sup>a</sup>CI includes four additional vascular deaths in 1,000 patients.

<sup>b</sup>McCollum et al: follow-up 3 y; Oscarsson: follow-up 1 mo.

<sup>c</sup>Event rate low (65 events in total).

<sup>d</sup>Rating down for imprecision: CI includes five additional strokes/TIA per 1,000 patients.

<sup>e</sup>CI includes 16 additional strokes/TIA in 1,000 patients.

<sup>f</sup>CI includes one additional PE in 1,000 patients.

<sup>g</sup>CI includes one additional bleeding event in 1,000 patients.

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