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The Perioperative Management of Antithrombotic Therapy*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article discusses the perioperative management of antithrombotic therapy and is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). The primary objectives of this article are the following: (1) to address the perioperative management of patients who are receiving vitamin K antagonists (VKAs) or antiplatelet drugs, such as aspirin and clopidogrel, and require an elective surgical or other invasive procedures; and (2) to address the perioperative use of bridging anticoagulation, typically with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). A secondary objective is to address the perioperative management of such patients who require urgent surgery. The recommendations in this article incorporate the grading system that is discussed in this supplement (Guyatt G et al, *CHEST* 2008; 133:123S–131S). Briefly, Grade 1 recommendations are considered strong and indicate that the benefits do (or do not) outweigh risks, burden, and costs, whereas Grade 2 recommendations are referred to as suggestions and imply that individual patient values may lead to different management choices.

The key recommendations in this article include the following: in patients with a mechanical heart valve or atrial fibrillation or venous thromboembolism (VTE) at high risk for thromboembolism, we recommend bridging anticoagulation with therapeutic-dose subcutaneous (SC) LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 1C); in patients with a mechanical heart valve or atrial fibrillation or VTE at moderate risk for thromboembolism, we suggest bridging anticoagulation with therapeutic-dose SC LMWH, therapeutic-dose IV UFH, or low-dose SC LMWH over no bridging during temporary interruption of VKA therapy (Grade 2C); in patients with a mechanical heart valve or atrial fibrillation or VTE at low risk for thromboembolism, we suggest low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH (Grade 2C).

In patients with a bare metal coronary stent who require surgery within 6 weeks of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C); in patients with a drug-eluting coronary stent who require surgery within 12 months of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C).

In patients who are undergoing minor dental procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure and coadministering an oral prohemostatic agent (Grade 1B); in patients who are undergoing minor dermatologic procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C); in patients who are undergoing cataract removal and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C).

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Key words: arterial thromboembolism; aspirin; bleeding; bridging anticoagulation; clopidogrel; low-molecular-weight heparin; oral anticoagulant; perioperative; stroke; surgery; unfractionated heparin; venous thromboembolism; vitamin K antagonist

Abbreviations: APTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; $CHADS_2$ = Congestive Heart Failure-Hypertension-Age-Diabetes-Stroke; CI = confidence interval; DDAVP = 1-deamino-8-D-arginine vasopressin; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; PCI = percutaneous coronary intervention; SC = subcutaneous; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Summary of Recommendations

2.0 Perioperative Management of Patients Who Are Receiving VKAs

2.1. In patients who require temporary interruption of a VKA before surgery or a procedure and require normalization of the INR for the surgery or procedure, we recommend stopping VKAs approximately 5 days before surgery over stopping VKAs within a shorter time interval before surgery to allow adequate time for the INR to normalize (Grade 1B)**.**

2.2. In patients who have had temporary interruption of a VKA before surgery or a procedure, we recommend resuming VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery and when there is adequate hemostasis over resumption of VKAs closer to surgery (Grade 1C)**.**

2.3. In patients who require temporary interruption of a VKA before surgery or a procedure and whose INR is still elevated (*ie*, ≥ 1.5) 1 to 2 days before surgery, we suggest administering low-dose (*ie*, 1 to 2 mg) oral vitamin K to normalize the INR instead of not administering vitamin K (Grade 2C)**.**

2.4. In patients with a mechanical heart valve or atrial fibrillation or VTE at high risk for thromboembolism, we recommend bridging anticoagulation with therapeutic-dose SC LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 1C)**; we suggest therapeutic-dose SC LMWH over IV UFH** (Grade 2C)**. In patients with a mechanical heart valve or atrial fibrillation or VTE at moderate risk for thromboembolism, we suggest bridging anticoagulation with therapeutic-dose SC LMWH, therapeutic-dose IV UFH, or low-dose SC LMWH over no bridging during temporary interruption of VKA therapy** (Grade 2C)**; we suggest therapeutic-dose SC LMWH over other management options** (Grade 2C)**. In patients with a mechanical heart valve or atrial fibrillation or VTE at low risk for thromboembolism, we suggest low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH** (Grade 2C)**.**

Values and preferences: In patients at high or moderate risk for thromboembolism, the recommendations reflect a relatively high value on preventing thromboembolism and a relatively low value is on preventing bleeding; in patients at low risk for thromboembolism, the recommendations reflect a relatively high value on preventing bleeding and a relatively low value on preventing thromboembolism.

3.0 Perioperative Management of Patients Who Are Receiving Bridging Anticoagulation

3.1. In patients who require temporary interruption of VKAs and are to receive bridging anticoagulation, from a cost-containment perspective we recommend the use of SC LMWH administered in an outpatient setting where feasible instead of inpatient administration of IV UFH (Grade 1C)**.**

Values and preferences: This recommendation reflects a consideration not only of the trade-off between the advantages and disadvantages of SC LMWH and IV UFH as reflected in their effects on clinical outcomes (LMWH at least as good, possibly better), but also the implications in terms of resource use (costs) in a representative group of countries (substantially less resource use with LMWH).

3.2. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we recommend administering the last dose of LMWH 24 h before surgery or a procedure over administering LMWH closer to surgery (Grade 1C)**; for the last preoperative dose of LMWH, we recommend administering approximately half the total daily dose instead of 100% of the total daily dose** (Grade 1C)**. In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we recommend stopping UFH approximately 4 h before surgery over stopping UFH closer to surgery** (Grade 1C)**.**

3.3. In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic-dose LMWH, we recommend resuming this regimen approximately 24 h after (*eg*, the day after) the procedure when there is adequate hemostasis over a shorter (*eg*, < 12 h) time interval (Grade 1C)**. In patients undergoing major surgery or a high bleeding risk**

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surgery/procedure and for whom postoperative therapeutic-dose LMWH/UFH is planned, we recommend either delaying the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured, administering low-dose LMWH/UFH after surgery when hemostasis is secured, or completely avoiding LMWH or UFH after surgery over the administration of therapeutic-dose LMWH/UFH in close proximity to surgery (Grade 1C)**. We recommend considering the anticipated bleeding risk and adequacy of postoperative hemostasis in individual patients to determine the timing of LMWH or UFH resumption after surgery instead of resuming LMWH or UFH at a fixed time after surgery in all patients** (Grade 1C).

3.4. In patients who are receiving bridging anticoagulation with LMWH, we suggest against the routine use of anti-factor Xa levels to monitor the anticoagulant effect of LMWHs (Grade 2C).

4.0 Perioperative Management of Patients Who Are Receiving Antiplatelet Therapy

4.2. In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure, we suggest stopping this treatment 7 to 10 days before the procedure over stopping this treatment closer to surgery (Grade 2C).

4.3. In patients who have had temporary interruption of aspirin therapy because of surgery or a procedure, we suggest resuming aspirin approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming aspirin closer to surgery (Grade 2C)**. In patients who have had temporary interruption of clopidogrel because of surgery or a procedure, we suggest resuming clopidogrel approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming clopidogrel closer to surgery** (Grade 2C).

4.4. In patients who are receiving antiplatelet drugs, we suggest against the routine use of platelet function assays to monitor the antithrombotic effect of aspirin or clopidogrel (Grade 2C).

4.5. For patients who are not at high risk for cardiac events, we recommend interruption of antiplatelet drugs (Grade 1C)**. For patients at high risk of cardiac events (exclusive of coronary stents) scheduled for noncardiac surgery, we suggest continuing aspirin up to and beyond the time of surgery** (Grade 2C)**; if patients are receiving clopidogrel, we suggest interrupting clopidogrel at least 5 days and, preferably, within 10 days prior to surgery** (Grade 2C)**. In patients scheduled for CABG, we recommend continuing aspirin up to and beyond the time of CABG** (Grade 1C)**; if aspirin is interrupted, we recommend it be reinitiated between 6 h and 48 h after CABG** (Grade 1C)**. In patients scheduled for CABG, we recommend interrupting clopidogrel at least 5 days and, preferably, 10 days prior to surgery** (Grade 1C)**. In patients scheduled for PCI, we suggest continuing aspirin up to and beyond the time of the procedure; if clopidogrel is interrupted prior to PCI, we suggest resuming clopidogrel after PCI with a loading dose of 300 to 600 mg** (Grade 2C).

4.6. In patients with a bare metal coronary stent who require surgery within 6 weeks of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C)**. In patients with a drug-eluting coronary stent who require surgery within 12 months of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period** (Grade 1C)**. In patients with a coronary stent who have interruption of antiplatelet therapy before surgery, we suggest against the routine use of bridging therapy with UFH, LMWH, direct thrombin inhibitors, or glycoprotein IIb/IIIa inhibitors** (Grade 2C).

Values and preferences: These recommendations reflect a relatively high value placed on preventing stent-related coronary thrombosis, a consideration of complexity and costs of administering bridging therapy in the absence of efficacy and safety data in this clinical setting, and a relatively low value on avoiding the unknown but potentially large increase in bleeding risk associated with the concomitant administration of aspirin and clopidogrel during surgery.

5.0 Perioperative Management of Antithrombotic Therapy in Patients Who Require Dental, Dermatologic, or Ophthalmologic Procedures

5.1. In patients who are undergoing minor dental procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure and coadministering an oral prohemostatic agent (Grade 1B)**. In patients who are undergoing minor dental procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure** (Grade 1C)**. In patients who are undergoing minor dental procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

5.2. In patients who are undergoing minor dermatologic procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C)**. In patients who are**

undergoing minor dermatologic procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure (Grade 1C)**. In patients who are undergoing minor dermatologic procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

5.3. In patients who are undergoing cataract removal and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C)**. In patients who are undergoing cataract removal and are receiving aspirin, we recommend continuing aspirin around the time of the procedure** (Grade 1C)**. In patients who are undergoing cataract removal and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

6.0 Perioperative Management of Antithrombotic Therapy Patients Who Require Urgent Surgical or Other Invasive Procedures

6.1. In patients who are receiving VKAs and require reversal of the anticoagulant effect for an urgent surgical or other invasive procedure, we recommend treatment with low-dose (2.5 to 5.0 mg) IV or oral vitamin K (Grade 1C)**. For more immediate reversal of the anticoagulant effect, we suggest treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose IV or oral vitamin K** (Grade 2C)**.**

6.2. For patients receiving aspirin, clopidogrel, or both, are undergoing surgery, and have excessive or life-threatening perioperative bleeding, we suggest transfusion of platelets or administration of other prohemostatic agents (Grade 2C)**.**

The perioperative management of patients who require temporary interruption of vitamin K antagonists (VKAs) or antiplatelet drugs because of a surgical or other noninvasive procedure is a common and challenging clinical problem.[1] Approximately 250,000 such patients are being assessed annually in North America alone, which is based on an estimate of the prevalence of patients who are receiving long-term treatment with a VKA, principally due to atrial fibrillation or a mechanical heart valve (~2.5 million),[2,3] and an estimate of the annual proportion of patients who are receiving a VKA and require surgery or an invasive procedure (~10%).[4] The management of these patients is challenging because the risk of a thromboemblic event during interruption of VKA or antiplatelet therapy needs to be balanced against the risk for bleeding when antithrombotic therapy is administered in close proximity to surgery or an invasive procedure. In assessing patients who are receiving antithrombotic therapy and are undergoing a surgical or other procedure, two principal issues should be addressed:

Is interruption of antithrombotic therapy in the perioperative period needed? In patients who are undergoing a major surgical or invasive procedure, interruption of antithrombotic therapy is typically required to minimize the risk for perioperative bleeding. Continuation of VKA or aspirin therapy in the perioperative period confers an increased risk for bleeding.[5–9] On the other hand, in patients who are undergoing minor surgical or invasive procedures, such as dental, skin, or eye procedures, interruption of antithrombotic therapy may not be required.

If antithrombotic therapy is interrupted, is bridging anticoagulation needed? In the context of perioperative anticoagulation, bridging anticoagulation may be defined as the administration of a short-acting anticoagulant, such as subcutaneous (SC) low-molecular-weight heparin (LMWH) or IV unfractionated heparin (UFH), administered typically as a therapeutic-dose regimen for approximately 8 to 10 days during interruption of VKA therapy when the international normalized ratio (INR) is not within a therapeutic range. In patients who are receiving antiplatelet drugs alone, bridging anticoagulation with LMWH or UFH is, typically, not administered. In general, the need for bridging anticoagulation is determined by patient risk for thromboembolism during interruption of antithrombotic therapy. The therapeutic aim of bridging anticoagulation is to minimize the time patients are not receiving anticoagulant therapy, thereby minimizing the risk for thromboembolism, and to do this in a manner that minimizes patients' risk for perioperative bleeding.

The objective of this article is to provide treatment recommendations for patients who are receiving a VKA or antiplatelet drug and may require temporary interruption of treatment because of a surgical or other invasive procedure. Following a discussion of general management principles (Section 1), this review addresses the following patient groups assessed in clinical practice: patients who are receiving VKAs (Section 2); patients who are receiving bridging anticoagulation after interruption of VKAs (Section 3); patients who are receiving antiplatelet drugs (Section 4); patients who are receiving VKAs or antiplatelet drugs and are undergoing minor surgical or invasive procedures (Section 5); and patients who require urgent interruption of antithrombotic therapy (Section 6). The summary recommendations follow the format in Table 1, which frames the questions this article addresses.

At this juncture, some qualifying and explanatory remarks are warranted. First, research in periopera-

Table 1—*Perioperative Antithrombotic Therapy: Question Definition and Eligibility Criteria*

Section	Population	Intervention or Exposure/Comparison*	Outcomes	Available Methodology	Exclusion Criteria
2.0 Perioperative management of patients who are receiving VKAs					
2.1	Any patient receiving VKA and having elective surgery	Timing of interruption of VKA before surgery	Hemostasis at time of surgery (INR)	Observational studies	None
2.2		Timing of resumption of VKA or LMWH after surgery	Hemostasis at time of surgery (bleed time)	Observational studies	None
2.3		INR testing to monitor anticoagulant effect of VKAs before and after surgery vs no testing	Hemostasis at time of surgery (APTT, anti-factor Xa)	Observational studies	None
2.4.1	Patients with a mechanical heart valve having elective surgery	Temporary interruption of VKA and bridging anticoagulation with LMWH/UFH vs no bridging	Stroke, other systemic embolism, major hemorrhage	Observational studies	Not receiving VKA
2.4.2	Patients with chronic atrial fibrillation having elective surgery	Temporary interruption of VKA and bridging anticoagulation with LMWH/UFH vs no bridging	Stroke, other systemic embolism, major hemorrhage	Observational studies	Not receiving VKA
2.4.3	Patients with VTE having elective surgery	Temporary interruption of VKA and bridging anticoagulation with LMWH/UFH vs no bridging	Stroke, other systemic embolism, major hemorrhage	Observational studies	Not receiving VKA
3.0 Perioperative management of patients who are receiving bridging anticoagulation					
3.1	Costs of bridging anticoagulation	Outpatient SC LMWH vs inpatient IV UFH	Health-care system costs	Observational studies	None
3.2	Any patient receiving UFH or LMWH as bridging anticoagulation and having elective surgery	Timing of interruption of LMWH or UFH before surgery	Major postoperative bleeding	Observational studies	None
3.3		Timing of resumption of LMWH or UFH after surgery	Major postoperative bleeding	Observational studies	None
3.4		APTT, and anti-factor Xa testing to monitor anticoagulant effect of LMWH and UFH before and after surgery	Major postoperative bleeding	Observational studies	None
4.0 Perioperative management of patients who are receiving antiplatelet therapy					
4.2	Any patient receiving an antiplatelet drug and having elective surgery	Timing of interruption of antiplatelet drugs before surgery	INR before and after surgery	Observational studies	None
4.3		Timing of resumption of antiplatelet drugs after surgery	Platelet function assay testing before and after surgery	Observational studies	None
4.4		Platelet function assay testing to monitor antiplatelet effect of antiplatelet drugs before and after surgery vs no testing	APTT and anti-factor Xa before and after surgery	Observational studies	None
4.5	Any patient receiving antiplatelet drug and having noncardiac surgery, cardiac surgery, or PCI	Temporary interruption vs continuation of antiplatelet drugs	Myocardial ischemia, major hemorrhage	Randomized controlled trials, observational studies	Receiving VKA
4.6	Any patient with a coronary stent receiving antiplatelet drug and having noncardiac surgery, cardiac surgery, or PCI	Temporary interruption vs continuation of antiplatelet drugs	Myocardial ischemia, major hemorrhage	Randomized controlled trials, observational studies	Receiving VKA
5.0 Perioperative management of antithrombotic therapy in patients who require minor procedures					
5.1	Any patient receiving VKA or antiplatelet drug and having a minor dental procedure	Temporary interruption vs continuation of VKA or antiplatelet therapy	Arterial or VTE, major hemorrhage	Randomized controlled trials, observational studies	None
5.2	Any patient receiving VKA or antiplatelet drug and having a minor skin procedure	Temporary interruption vs continuation of VKA or antiplatelet therapy	Arterial or VTE, major hemorrhage	Randomized controlled trials, observational studies	None
5.3	Any patient receiving VKA or antiplatelet drug and having a minor eye procedure	Temporary interruption vs continuation of VKA or antiplatelet therapy	Arterial or VTE, major hemorrhage	Randomized controlled trials, observational studies	None

Table 1—*Continued*

Section	Population	Intervention or Exposure/Comparison	Outcomes	Available Methodology	Exclusion Criteria
6.0 Perioperative management of antithrombotic therapy patients who require urgent surgical or other invasive procedures					
6.1	Any patient receiving VKA and having urgent surgery	Vitamin K via different routes (IV vs oral/SC) to reverse anticoagulant effect of VKAs; blood products (FFP, PC) to reverse anticoagulant effect of VKAs vs no blood products	(1) Hemostasis at time of surgery (INR) (2) Major bleeding and surrogate	Randomized controlled trials, observational studies	None
6.2	Any patient receiving an antiplatelet drug and having urgent surgery	DDAVP/prohemostatic drugs and platelet transfusion to reverse antiplatelet effect of antiplatelet drugs vs no DDAVP/prohemostatic drugs and platelet transfusions	Myocardial ischemia, major hemorrhage	Observational studies	None

*FFP = fresh frozen plasma; PC = prothrombin concentrate.

tive antithrombotic therapy is an emerging field, with a relative paucity of randomized trials and a preponderance of observational studies assessing perioperative management strategies. Consequently, comparisons of certain management strategies (*eg*, bridging vs no bridging) are lacking whereas comparisons of other strategies (eg, continuation vs interruption of VKAs for minor procedures) are better developed. Second, as many of the pertinent observational studies are based on small patient samples, they may be underpowered to determine if a management approach is efficacious (*ie*, associated with a low risk for thromboembolism) or safe (*ie*, associated with a low risk for bleeding). Such studies should, therefore, be interpreted with caution both because of the observational study design and the small sample size. Third, it should be acknowledged that there is no standardized definition of "bridging anticoagulation." Although it may be defined as the administration of a therapeutic-dose regimen of SC LMWH or IV UFH during interruption of a VKA, bridging anticoagulation may also include a regimen of low-dose SC LMWH. Ultimately, the perioperative anticoagulant regimen used will depend, to a large extent, on patient clinical characteristics and the type of surgery or procedure they are undergoing.

1.0 Perioperative Management of Antithrombotic Therapy: General Principles

1.1 Assessment of Thromboembolic Risk After Interruption of Antithrombotic Therapy

Interruption of antithrombotic therapy exposes patients to an increased risk for thromboembolic events, such as stroke or mechanical valve thrombosis, with the risk varying depending on the indication for antithrombotic therapy and the presence of comorbid conditions.[10] These events can have devastating clinical consequences: embolic stroke, which can result in major disability or death in 70% of patients[11,12]; thrombosis of a mechanical heart valve, which is fatal in 15% of patients[13]; and perioperative myocardial ischemia, which is associated with a two-fold- to fourfold-increased risk for death.[14,15] Similarly, interruption of antiplatelet drugs in patients with a sirolimus or paclitaxel drug-eluting coronary stent, especially within 6 months of stent placement, significantly increases the risk for intracoronary stent thrombosis and myocardial infarction.[16,17]

Stratifying patients according to their risk for perioperative thromboembolism is based on patients' clinical indication for antithrombotic therapy and the presence of comorbidities. Although there is no validated risk stratification of such patients, the approach we have used in these guidelines is to separate patients into a high-risk, moderate-risk, or low-risk group according to their indication for antithrombotic therapy (Table 2).

1.2 Assessment of Bleeding Risk Associated With Surgery or Other Invasive Procedures

The administration of antithrombotic therapy in the perioperative period should be done in a way that considers the risk for bleeding associated with the surgery or procedure. Although bleeding is a treatable perioperative complication, there is emerging evidence that the clinical impact of bleeding is considerable and, perhaps, greater than previously appreciated.[18–20] Furthermore, postoperative bleeding delays the resumption of antithrombotic therapy, with the potential to further expose patients to an increased risk for thromboembolism.[21,22]

Stratifying patients according to their risk for perioperative bleeding can be based on the risk for bleeding associated with the surgery or procedure

Table 2—*Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism*

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	Any mitral valve prosthesis Older (caged-ball or tilting disc) aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack	$CHADS_2$ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack, Rheumatic valvular heart disease	Recent (within 3 mo) VTE Severe thrombophilia (*eg*, deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)
Moderate	Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age $>$ 75 yr	$CHADS_2$ score of 3 or 4	VTE within the past 3 to 12 mo Nonsevere thrombophilic conditions (*eg*, heterozygous factor V Leiden mutation, heterozygous factor II mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0 to 2 (and no prior stroke or transient ischemic attack)	Single VTE occurred $>$ 12 mo ago and no other risk factors

*$CHADS_2$ = Congestive heart failure-Hypertension-Age-Diabetes-Stroke.

and should be coupled with an assessment of postoperative hemostasis.[21–24] Although there is no validated method that quantifies perioperative bleeding risk, special attention is warranted for certain surgical or other invasive procedures associated with a high risk for bleeding. In such patients, postoperative antithrombotic therapy should be administered with caution, especially therapeutic-dose LMWH or UFH when used as bridging anticoagulation. Surgical and other invasive procedures associated with a high bleeding risk include: coronary artery bypass or heart valve replacement surgery[25,26]; intracranial or spinal surgery[27]; aortic aneurysm repair, peripheral artery bypass, and other major vascular surgery; major orthopedic surgery, such as hip or knee replacement[28]; reconstructive plastic surgery[29]; major cancer surgery; and prostate and bladder surgery.[30,31]

In addition, clinicians should note procedures that, on the surface, may appear to be associated with a low risk for bleeding but in which perioperative anticoagulation should be undertaken with caution. Such procedures include: resection of colonic polyps, especially sessile polyps $>$ 2 cm in diameter, in which bleeding may occur at the transected stalk[32]; biopsy of the prostate or kidney, in which the presence of highly vascular tissue and endogenous urokinase may promote post-biopsy bleeding[33]; and cardiac pacemaker or defibrillator implantation, in which separation of the infraclavicular fascial layers and lack of cautery or suturing of unopposed tissues within the pacemaker or defibrillator pocket may predispose to pocket hematoma development.[34]

1.3 Balancing Thromboembolic Risk and Bleeding Risk

Inherent in perioperative antithrombotic management is the need for individualized patient management that balances individual risk for thromboembolism and bleeding. In patients classified as "high risk for stroke or thromboembolism," the need to prevent a thromboembolic event such as embolic stroke or intracoronary stent thrombosis will dominate perioperative antithrombotic management, irrespective of bleeding risk. In such patients, the potential clinical consequences of such events, which may be fatal or may cause permanent disability, will, in most patients, outweigh the potential clinical consequences of bleeding and will justify the need for bridging anticoagulation or perioperative continuation of antithrombotic therapy. This approach, if adopted, should nonetheless consider judicious use of postoperative bridging anticoagulation (*ie*, as outlined in Section 3.0) and optimizing intraoperative hemostasis (*ie*, cautery and other local measures), with the intent of simultaneously minimizing the potential for major surgical bleeding that would have the undesired effect of delaying the resumption of or necessitating interruption of antithrombotic therapy.

In patients classified as "moderate risk for thromboembolism," a single perioperative antithrombotic strategy will not be dominant and management will depend more on an individual patient risk assessment. Thus, in patients at moderate risk for thrombo-

embolism, the need to prevent thromboembolism will have less dominance than in "high-risk" patients and bridging anticoagulation may incorporate a modified, less aggressive, approach postoperatively in patients undergoing surgery or a procedure associated with a high bleeding risk. In patients classified as "low risk for thromboembolism," the need to prevent thromboembolism will have even less dominance and clinicians may avoid bridging anticoagulation altogether; if given, bridging should be curtailed postoperatively in such patients with a high bleeding risk.

1.4 Perioperative Antithrombotic Management: Practical Considerations

In managing antithrombotic therapy before and after surgery or a procedure, clinicians should note the following practical management considerations:

- For patients undergoing a major surgical or invasive procedure, if the intent is to eliminate any effect of antithrombotic therapy, it should be stopped at a time before the procedure (*eg*, approximately 5 days in patients receiving a VKA and 7 to 10 days in patients receiving an antiplatelet drug) that leaves minimal or no residual antithrombotic effect at time of the procedure; doing so will minimize the risk for intraprocedural bleeding.
- The administration of a rapidly acting anticoagulant, such as LMWH or UFH, after surgery or another invasive procedure increases the risk for bleeding. This risk is dependent on the dose of anticoagulant (*eg*, therapeutic-dose more than low-dose) and the proximity to surgery that it is administered (higher bleeding risk when administered closer to surgery). Delaying resumption of a therapeutic-dose LMWH or UFH regimen (for 48 to 72 h after surgery), decreasing the dose of LMWH or UFH (to a low-dose regimen), or avoiding its use altogether in the postoperative period can mitigate the risk for bleeding.
- For perioperative anticoagulant dosing, although there is evidence that low-dose (prophylactic-dose) LMWH or UFH (*eg*, dalteparin 5,000 IU qd or UFH 5,000 IU bid) is effective in preventing venous thromboembolism (VTE), evidence is lacking that such low-dose treatment is effective in preventing arterial thromboembolism.
- In resuming antithrombotic therapy after a surgical or invasive procedure, it takes 2 to 3 days for an anticoagulant effect to begin after the start of warfarin,[35] it takes 3 to 5 h for a peak anticoagulant effect to be reached after the start of LMWH,[36] whereas it takes minutes for an antiplatelet effect to begin after the start of aspirin[37] and 3 to 7 days for peak inhibition of platelet aggregation to be reached after the start of a (75 mg) maintenance dose of clopidogrel.[38]
- The majority of surgical or other invasive procedures are being done without hospitalization or with a short hospital stay; consequently, potential thromboembolic- or bleeding-related complications are likely to occur while the patient is at home, especially during the initial 2 weeks after a procedure.[21,22,39,40] Close follow-up of patients during the early period after a procedure is, therefore, warranted to allow early detection and expedited treatment of potential complications.

2.0 Perioperative Management of Patients Who Are Receiving VKAs

Long-term VKA therapy is widely used for the primary and secondary prevention of arterial thromboembolism and VTE for a wide spectrum of clinical indications that include atrial fibrillation, mechanical heart valve placement, VTE, coronary and peripheral artery disease, dilated cardiomyopathy, and primary pulmonary hypertension. In Section 2.0, we will focus on the perioperative anticoagulant management of patients with the most common clinical indications for long-term VKA therapy: mechanical heart valve, chronic atrial fibrillation, and VTE.

2.1 Interruption of VKAs Before Surgery

In patients undergoing major surgery, interruption of VKAs is generally required to minimize the risk for perioperative bleeding,[5–7] whereas in patients undergoing certain minor surgical or other procedures, some of which are discussed in Section 5.0, interruption of VKAs may not be required. To our knowledge, there are no randomized trials comparing interruption of VKAs vs no interruption or partial interruption of VKAs before major surgery. Three observational studies have assessed continuation[8,41] or partial interruption[42] of VKAs in patients undergoing surgery, with suggestive but not definitive findings that continuation of VKAs increases the risk for perioperative bleeding. In one retrospective cohort study involving 603 VKA-treated patients who underwent surgery, the majority of whom did not have interruption of VKA therapy prior to surgery, the incidence of perioperative major bleeding was 9.5% (95% confidence interval [CI]: 7.1–12.1), which is high; moreover, compared to patients with an INR < 2.0, patients with an INR > 3.0 appeared to be at higher risk for bleeding complications (odds ratio [OR], 1.6; 95% CI: 0.4–4.0).[8] Another retrospective study assessed 100 patients who underwent surgery (58 had major surgery) and who had partial

interruption of VKA, with a mean INR of 1.8 (range: 1.2 to 4.9) on the day of surgery; in this study, only two (2%) patients had major bleeding although 34 (34%) patients required a blood transfusion.[42]

For patients who are receiving VKA therapy with warfarin, which has a half-life of 36 to 42 h, treatment should be interrupted approximately 5 days before surgery (corresponding approximately to 5 half-lives of warfarin) to ensure there is no (or minimal) residual anticoagulant effect remaining by the time of surgery.[43,44] Previous prospective cohort studies assessing standardized perioperative anticoagulation regimens interrupted warfarin 5 to 6 days before surgery.[21,22,39] In one of these studies,[22] in which warfarin was stopped 5 days before surgery and the INR was routinely measured on the day before surgery, only 15 of 224 (7%) patients had an elevated INR (> 1.5) on the day before surgery, which was corrected with low-dose (1 mg) oral vitamin K. A longer (*eg*, > 5 days) duration of VKA interruption to attain a normalized INR by the time of surgery may be required in patients with a mechanical heart valve, who have a higher targeted INR range, which is typically 2.5 to 3.5.[45] In addition, advanced age may be associated with a prolongation in the decay of the anticoagulant effect of warfarin after its interruption. Thus, in a retrospective cohort study of 633 patients who had excessive anticoagulation (INR > 6.0), increasing age, in 10-year increments, conferred an increased likelihood for delayed normalization of the INR after warfarin was stopped (hazard ratio, 1.18; CI: 1.01–1.38).[46]

For a minority of patients who are receiving VKA therapy with phenprocoumon, in whom the VKA-related recommendations in this article would not apply, treatment should be interrupted approximately 10 days before surgery based on the half-life of phenprocoumon of 96 to 140 h.[47] Some investigators have suggested that, in selected patients, warfarin can be interrupted 2 to 3 days before surgery to aim for an INR of 1.5 to 1.9 at the time of surgery; however, the feasibility and safety of this approach remain uncertain.[8,42,48]

Recommendation

2.1. In patients who require temporary interruption of a VKA before surgery or a procedure and require normalization of the INR for the surgery or procedure, we recommend stopping VKAs approximately 5 days before surgery over a shorter time interval to allow adequate time for the INR to normalize (Grade 1B)**.**

2.2 Resumption of VKAs After Surgery

When resuming VKAs after surgery, approximately 48 h is required to attain a partial anticoagulant effect, with an INR > 1.5.[43] Consequently, the potential effect of VKAs to promote postoperative bleeding is likely to be mitigated by the delayed onset of their anticoagulant activity. It is reasonable, therefore, to resume VKA therapy on the evening of the day of surgery or the next day, with an anticipated partial anticoagulant effect to occur 48 h later. In one study of 650 patients who resumed VKA after bridging anticoagulation, with a dose corresponding to patients' usual dose, the mean duration to achieve a therapeutic INR was 5.1 days (SD: 1.1).[21] In another study of 224 patients who resumed VKA after bridging anticoagulation, with doubling of patients' usual dose for the initial 2 days after VKA resumption, the mean duration to achieve a therapeutic INR was 4.6 days (range: 0 to 10).[22] One retrospective cohort study involving 100 patients who received bridging with LMWH found a longer than expected time to attain a therapeutic INR after surgery, which was a median of 7.5 days (interquartile range: 4.3 to 13.0) after warfarin was resumed postoperatively.[49] The delay in attaining therapeutic levels of anticoagulation in this study was possibly related to suboptimal INR monitoring after surgery.

Recommendation

2.2. In patients who have had temporary interruption of a VKA before surgery or a procedure, we recommend resuming VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery and when there is adequate hemostasis over resumption of VKAs closer to surgery (Grade 1C)**.**

2.3 Laboratory Monitoring of VKA Therapy

Perioperative monitoring of the INR in patients who are receiving VKA therapy is predicated on several factors, which include the feasibility of INR monitoring prior to surgery and the time period between interruption of VKAs and surgery. In the preoperative period, it is reasonable to have INR testing done at least once before surgery (preferably 1 to 2 days before surgery) to confirm a normal or near-normal INR and, in patients with an elevated INR (*eg*, INR > 1.5), to administer low-dose vitamin K. Administration of vitamin K at this time will avoid the need to administer plasma or other blood products by ensuring the INR has normalized by the day of surgery. In one retrospective cohort study involving 43 patients who required temporary interruption

of VKA and had an INR between 1.5 and 1.9 (mean: 1.6) on the day before surgery, administering 1 mg oral vitamin K resulted in 91% of patients having a normal or near normal INR (*ie*, ≤ 1.4) on the day of surgery.[50] This study also suggested that preoperative administration of low-dose vitamin K does not appear to confer resistance to re-anticoagulation when a VKA is resumed after surgery. In the postoperative period, INR testing can be done to approximate when therapeutic anticoagulation is (or will be) attained and, therefore, when LMWH or UFH can be stopped for patients who have been receiving bridging anticoagulation.

Recommendation

2.3. In patients who require temporary interruption of a VKA before surgery or a procedure and whose INR is still elevated (*ie*, ≥ 1.5) 1 to 2 days before surgery, we suggest administering low-dose (*ie*, 1 to 2 mg) oral vitamin K to normalize the INR instead of not administering vitamin K (Grade 2C)**.**

2.4 Patient Risk Stratification and Assessing Need for Bridging Anticoagulation

In assessing patients who are receiving VKAs for the three principal indications, a mechanical heart valve, chronic atrial fibrillation, or VTE, perioperative anticoagulant management (and need for bridging) will be driven to a large extent by patients' risk for developing thromboembolism, either arterial or venous, in the perioperative period. In this section, we have attempted to provide a reasonable, though largely empiric, stratification of patients according to their risk for thromboembolism (high, moderate, low) while acknowledging that comparative data on risks for perioperative thromboembolism for the proposed risk strata are limited. This risk stratification scheme may be combined with individual patient factors, which may include prior thromboembolism during VKA interruption or a prior embolic stroke, to determine the overall risk for thromboembolism (and need for bridging).

2.4.1 Patients With a Mechanical Prosthetic Heart Valve

Risk Stratification: Patients with mechanical heart valves are at increased risk for arterial thromboembolism, which includes stroke, systemic embolism, and valvular or intracardiac thrombosis. Risk stratification for patients with a mechanical heart valve is based on studies that have assessed the risk for arterial thromboembolism during anticoagulant therapy and on older studies that assessed thromboembolic risk while patients were receiving either no antithrombotic therapy or treatment that is currently considered suboptimal.[51–53] What is lacking, however, are estimates of the risk for thromboembolism in patients who have modern (bileaflet) prostheses and have not received antithrombotic therapy over an extended time period. As trials that include such patients are lacking and are unlikely to be performed, clinicians can use the risk classification proposed here as a general guide for patient management.

Patients at high risk for arterial thromboembolism (> 10%/yr) may include those with one or more of the following: (1) a mitral valve prosthesis; (2) an older-generation (caged-ball or tilting disk) aortic valve prosthesis; and (3) a recent (within 6 months) stroke or transient ischemic attack. Patients at moderate risk for thromboembolism (4 to 10%/yr) may include those with a bileaflet aortic valve prosthesis and one of the following: (1) atrial fibrillation; (2) prior stroke or transient ischemic attack; and (3) other stroke risk factors (hypertension, diabetes, congestive heart failure, age > 75 years). Patients at low risk for thromboembolism (< 4%/yr) may include those with a bileaflet aortic valve prosthesis without atrial fibrillation and who do not have other risk factors for stroke.

Assessing Need for Bridging Anticoagulation: In 14 prospective cohort studies, bridging anticoagulation was assessed in approximately 1,300 patients with a mechanical heart valve.[7,21,22,40,54–64] As shown in Table 3, investigators studied predominantly therapeutic-dose LMWH regimens, although two studies involving a total of 118 patients also assessed low-dose LMWH regimens.[54,64] The issue of whether a low-dose anticoagulant regimen is efficacious for the prevention of arterial thromboembolism in patients with a mechanical heart valve, as it is for preventing VTE,[65] cannot be definitively addressed based on the limited available evidence. It is probable that a more intense, therapeutic-dose, anticoagulant regimen would be required to prevent valve thrombosis and valve-related systemic embolism during VKA interruption and, until further evidence to the contrary becomes available, is the preferred regimen. The overall crude risk for perioperative arterial thromboembolism was 0.83% (95% CI: 0.43–1.5). There were no reported episodes of mechanical valve thrombosis. The interpretation of this finding is limited because there are no studies, to our knowledge, assessing the risk for arterial thromboembolism in (a comparator group of) patients with a mechanical heart valve who have VKA interruption for surgery but do not receive bridging anticoagulation.

Mathematical modeling can be used to estimate

Table 3—*Nonrandomized Prospective Cohort Studies Assessing Bridging Anticoagulation After Interruption of VKA Therapy: Clinical Description and Results (Section 2.4)*

	Patients					Clinical Outcomes, %			
Study/yr	No.	Indication for VKA Therapy	No. and Type of Procedure	Bridging Anticoagulation Regimen	Follow-up After Procedure	Arterial Thromboembolism in Patients With Mechanical Heart Valve/ Arterial Thromboembolism	Recurrent VTE in Patients With VTE	Death	Major Bleed
Katholi et al[7]/1978	235	Mechanical heart valve (type not specified)	25 surgical 21 nonsurgical	UFH: intermittent or continuous infusion	Not specified	0	Not applicable	0	2
Spandorfer et al[60]/ 1999	20	12 mechanical heart valve (10 aortic, 2 mitral) 4 atrial fibrillation 4 VTE	10 surgical	Enoxaparin: 1 mg/kg bid	1 mo	0 0 0	Not applicable	0	1
Galla and Fuhs[54]/ 2000	88	88 mechanical heart valve (27 aortic, 50 mitral, 9 aortic + mitral, 2 tricuspid)		Enoxaparin: 30 mg bid	1 mo	0	Not applicable	0	3
Nutescu et al[2,37]/ 2001*	23	21 ischemic stroke + hypercoagulable state	18 surgical 7 nonsurgical	Dalteparin: 100 IU/kg bid	3 mo	0	Not applicable	0	0
Tinmouth et al[61]/ 2001	24	12 mechanical heart valve (7 aortic, 5 mitral); 6 atrial fibrillation; 6 VTE	9 surgical 17 nonsurgical	Dalteparin: 200 IU/kg qd	1 mo	1 0 0	0	1 0 0	0
Wilson et al[62]/2001	47	7 mechanical heart valve (type not specified) 11 atrial fibrillation 26 VTE 3 other (cardiomyopathy)	15 surgical 32 nonsurgical	Dalteparin: 200 IU/kg qd or 120 IU/kg bid (5,000 IU qd in 9 patients)	Not specified	0 0 1 0	0	0	0
Ferreira et al[56]/2003	82	82 mechanical heart valve (43 aortic, 39 mitral)	53 surgical 29 nonsurgical	Enoxaparin: 1 mg/kg bid (dose adjusted for renal impairment)	3 mo	0	Not applicable	Not available	1
Baudo et al[72]/2007	411	344 mechanical heart valve or atrial fibrillation 67 VTE	77 surgical 334 nonsurgical	Various therapeutic-dose (22%) or prophylactic-dose (78%) regimens	Not specified	2 (1/1) 0	0	1 0	7
Douketis et al[21]/ 2004†	650	134 mechanical heart valve (52 aortic, 52 mitral, 30 aortic + mitral) 416 atrial fibrillation	251 surgical 399 nonsurgical	Dalteparin: 100 IU/kg bid	0.5 mo	1 3	Not applicable	4	6
Hammerstingl et al[58]/2007	116	Mechanical heart valve (76 aortic valve, 31 mitral valve, 9 aortic and mitral valves)	46 surgical 70 nonsurgical	Enoxaparin: 1 mg/kg qd or bid	1 mo	0	0	0	1

Table 3—*Continued*

Study/yr	Patients: No.	Patients: Indication for VKA Therapy	No. and Type of Procedure	Bridging Anticoagulation Regimen	Follow-up After Procedure	Clinical Outcomes, %: Arterial Thromboembolism in Patients With Mechanical Heart Valve/Arterial Thromboembolism	Clinical Outcomes, %: Recurrent VTE in Patients With VTE	Clinical Outcomes, %: Death	Clinical Outcomes, %: Major Bleed
Kovacs et al[22]/2004‡	224	112 mechanical heart valve (type not specified) 112 atrial fibrillation	67 surgical 157 nonsurgical	Dalteparin: 200 IU/kg qd (5,000 IU postoperative in 35 patients at high risk for bleeding)	3 mo	1 1	Not applicable	0	15
Constans et al[64]/2007	98	30 mechanical heart valve (14 aortic, 16 mitral) 56 atrial fibrillation or arterial disease 12 VTE	98 nonsurgical	Bemiparin: 3,500 IU qd	3 mo	0 0 0	0	0	0
Turpie and Douketis[40]/2004§	220	220 mechanical heart valve (165 aortic, 51 mitral, 5 aortic + mitral)	Not specified	Enoxaparin: 1 mg/kg bid	3 mo	0	Not applicable	3	8
Jaffer et al[57]/2006	69	20 mechanical heart valve 27 atrial fibrillation 18 VTE 4 other arterial indications	18 surgical 47 nonsurgical	Enoxaparin: 1 mg/kg bid (30 mg bid postoperative after surgical procedures)	1 mo	0 0	0	0	2
Spyropoulos et al[55]/2006	901	246 mechanical heart valve 349 atrial fibrillation 230 VTE 76 other arterial indications	394 surgical 507 nonsurgical	Therapeutic-dose (75%) and prophylactic-dose (25%) UFH or LMWH regimens	1 mo	8‖	2‖	6	31
Dunn et al[39]/2006	260	176 atrial fibrillation 81 VTE	105 surgical 145 nonsurgical	Enoxaparin: 1.5 mg/kg qd	1 mo	4	1	2	8
Malato et al[63]/2006	228	53 mechanical heart valve 139 atrial fibrillation 26 VTE 10 other arterial indications	101 surgical 127 nonsurgical	Therapeutic-dose (40%) or prophylactic-dose (60%) LMWH regimens		0 3 0	1	0	6

Table 3—*Continued*

Study/yr	Patients			Bridging Anticoagulation Regimen	Follow-up After Procedure	Clinical Outcomes, %			
	No.	Indication for VKA Therapy	No. and Type of Procedure			Arterial Thromboembolism in Patients With Mechanical Heart Valve/ Arterial Thromboembolism	Recurrent VTE in Patients With VTE	Death	Major Bleed
Halbritter et al[81]/ 2007¶	311	55 mechanical heart valve (29 aortic, 26 mitral) 124 atrial fibrillation 50 LV dysfunction 59 VTE 23 other (not specified)	65 surgical 246 nonsurgical	Therapeutic-dose LMWH or UFH in 62% of mechanical heart valve, 47% of atrial fibrillation, and 55% of left ventricular dysfunction		1	3	4	7

*Bridging episodes in 21 patients.
†110 patients considered high risk for postoperative bleeding did not receive postoperative LMWH.
‡Five patients had intraoperative or postoperative myocardial infarction but were not included in Table 3 to facilitate across-study comparisons, as other studies did not document perioperative myocardial ischemic outcomes.
§Forty patients considered high risk for postoperative bleeding did not receive postoperative LMWH.
‖Patient group (according to indication for VKA) that outcome events occurred in not specified.
¶311 bridging episodes in 268 patients.

the perioperative risk of arterial thromboembolism if bridging anticoagulation is not given based on the prorated fraction of the annual risk of this outcome.[66] Thus, the risk of thromboembolism in a patient with mechanical (mitral or aortic) heart valve who is not treated with a VKA is estimated at 0.046%/d (*ie*, 17% annual risk[67] ÷ 365) or ~0.4% for 8 days when patients are not therapeutically anticoagulated during VKA interruption. The finding of a higher rate of perioperative thromboembolism in studies of bridging anticoagulation compared to that derived from mathematical modeling suggests that the risk for thromboembolism is higher than expected. What remains unclear is whether the administration of bridging anticoagulation decreases this rate further than that which would be observed if bridging had not been administered or whether bridging therapy has no effect on the perioperative risk for arterial thromboembolism. This issue can only be addressed through randomized trials comparing a bridging vs no bridging strategy in patients with a mechanical heart valve, which poses challenges in terms of feasibility. In the meantime, clinicians should consider bridging anticoagulation in patients with a mechanical prosthetic heart valve who are at high or moderate risk for arterial thromboembolism (*ie*, stroke or valve thrombosis).

2.4.2 Patients With Chronic Atrial Fibrillation

Risk Stratification: Risk stratification in patients with chronic atrial fibrillation is based on placebo-controlled randomized trials that assessed different antithrombotic strategies in patients with nonvalvular atrial fibrillation.[68] Patients with rheumatic valvular heart disease were not included in these trials but are considered to be at high risk for stroke. Bridging anticoagulation should be considered in selected patients with chronic atrial fibrillation who are at high or moderate risk for arterial thromboembolism (*ie*, stroke or systemic embolism).[3,69–71] Clinical prediction rules, such as the Congestive Heart Failure-Hypertension-Age-Diabetes-Stroke ($CHADS_2$) score, may help to stratify patients with nonvalvular atrial fibrillation according to their risk for stroke.[70] An administrative linked database study[4] suggested that the $CHADS_2$ score could be applied to the perioperative setting to estimate stroke risk in patients with chronic atrial fibrillation who were undergoing surgery. The score ranges from 0 to 6 and is based on the whether any of five risk factors are present: congestive heart failure, hypertension, diabetes, age > 75 years (1 point each); and prior stroke or transient ischemic attack (2 points). Patients at high risk for arterial thromboembolism (*ie*, > 10% risk per year) may include those with one or more of

the following: (1) $CHADS_2$ score of 5 or 6; (2) a recent (within 3 months) stroke or transient ischemic attack; or (3) rheumatic valvular heart disease. Patients at moderate risk for thromboembolism (*ie*, 5 to 10% risk per year) include those with a $CHADS_2$ score of 3 or 4, whereas patients at low risk for thromboembolism (*ie*, < 5% risk per year) include those with a $CHADS_2$ score of 0 to 2 who have not had a prior stroke or transient ischemic attack.

Assessing Need for Bridging Anticoagulation: In 10 prospective cohort studies, bridging anticoagulation has been assessed in approximately 1,400 patients with chronic atrial fibrillation.[21,22,39,55,57,58,60–64] As outlined in Table 3, investigators studied predominantly therapeutic-dose LMWH regimens, although low-dose LMWH regimens were also assessed in 4 studies involving approximately 300 patients (exact number not discernable from published data).[56,63,64,72] As in patients with a mechanical heart valve, the issue of whether low-dose anticoagulant regimens are efficacious to prevent arterial thromboembolism is also pertinent to patients with atrial fibrillation. Similar to patients with a mechanical heart valve, there is inadequate data to formulate definitive conclusions. It is probable that a more intense, therapeutic-dose, anticoagulation regimen is more efficacious to prevent embolic stroke and systemic embolism than a low-dose regimen and, until evidence to the contrary is available, it is the preferred management. The overall crude risk for perioperative arterial thromboembolism in patients who received bridging anticoagulation was 0.57% (95% CI: 0.26–1.1). In studies that described the clinical characteristics of such patients, most patients had at least one additional risk factor for stroke (*ie*, prior stroke, ventricular dysfunction, hypertension, diabetes, age > 75 years).

There are emerging data assessing the risk for arterial thromboembolism in patients with atrial fibrillation who do not receive bridging anticoagulation. In a community-based prospective cohort study (Anticoagulation Consortium to Improve Outcomes Nationally [ACTION]) involving patients who were receiving a VKA, 726 patients with atrial fibrillation had temporary interruption of a VKA and did not receive bridging.[73] Four (0.6%) patients developed arterial thromboembolism (2 strokes, 1 transient ischemic attack, 1 systemic embolism) during a 1-month follow-up period after surgery. In a retrospective cohort study assessing 690 patients (~90% with atrial fibrillation) who required temporary interruption of VKA therapy prior to GI endoscopy, there were 11 (1.6%) patients who developed a stroke within 1 month of the procedure (A. Jaffer, submitted for publication). Another study examined a linked administrative database of patients discharged from hospital after surgery or an invasive procedure between 1996 and 2001, during a time period when bridging was not routinely given.[4] In this study, the 30-day incidence of postoperative stroke in patients with atrial fibrillation was 1.3%, which was more than fourfold higher than in patients without atrial fibrillation (OR, 4.6; 95% CI: 4.2–5.0). Taken together, these studies suggest that in patients with atrial fibrillation who undergo surgery and do not receive bridging anticoagulation, the risk for perioperative arterial thromboembolism, consisting of stroke and transient ischemic attack, is approximately 1%. Furthermore, based on an average annual risk of stroke of 5% (0.013%/d or ~0.1% during 8 days of VKA interruption), these studies suggest that the risk for arterial thromboembolism in the perioperative period without bridging is higher than that predicted based on mathematical modeling.[74]

2.4.3 Patients With Prior VTE

Risk Stratification: Compared to patients with atrial fibrillation or a mechanical heart valve, there are several distinctions in the assessment of VKA interruption and need for bridging anticoagulation in patients with prior VTE (*ie*, deep vein thrombosis, pulmonary embolism). Whereas the first two groups are at risk for stroke and other arterial thromboembolism, patients with VTE are at risk for recurrent deep vein thrombosis or pulmonary embolism. The consequences of these outcomes differ markedly. Embolic stroke is fatal or associated with significant neurologic deficit in 70% of patients.[11,12] On the other hand, recurrent VTE is fatal in approximately 4 to 9% of patients and is associated with less morbidity.[75,76] In addition, though low-dose anticoagulation has not been proven to decrease the risk of arterial thromboembolic events, it has been shown in nonbridging trials to decrease the risk of postoperative VTE.[65] Thus, although there is a lesser role for low-dose LMWH or UFH for patients with atrial fibrillation or mechanical heart valves, there is a stronger rationale for using these medications as bridging therapy for patients with prior VTE.

Risk stratification in patients with VTE is based on an assessment of the risk for recurrent VTE after the start of treatment,[77] and risk factors for recurrent disease after anticoagulant therapy has been stopped.[78,79] Patients at high risk for recurrent disease may include those with: (1) recent (within 3 months) VTE; or (2) severe thrombophilic conditions (deficiency of protein C, protein

S or antithrombin, antiphospholipid antibodies, or multiple thromobophilic abnormalities). Patients who have had prior VTE after surgery might be considered high risk depending on the type of surgery they are undergoing (and the associated thromboembolic risk) and perioperative antithrombotic management should be individualized. Risk stratification is less precise in other patients and would be predicated on individualized factors. Patients at moderate risk for recurrent disease may include those with prior VTE within the past 3 to 12 months, nonsevere thrombophilic conditions (heterozygous carrier of factor V Leiden mutation or factor II mutation), recurrent VTE, or active cancer (treated within 6 months or palliative). Patients at low risk may include those in whom VTE occurred > 12 months ago and do not have any of the above-mentioned risk factors.

Assessing Need for Bridging Anticoagulation: Prospective cohort studies have evaluated bridging anticoagulation using therapeutic and low-dose regimens of various LMWHs in approximately 500 patients with prior VTE[39,55,57,59–64] (Table 3). The overall crude risk for recurrent symptomatic VTE was 0.60% (95% CI: 0.13–1.7). However, the efficacy of low-dose LMWH or UFH as perioperative anticoagulation is unknown as data are lacking in regard to the risk of recurrent VTE without bridging anticoagulation.

Recommendation

2.4. In patients with a mechanical heart valve or atrial fibrillation or VTE at high risk (Table 2) for thromboembolism, we recommend bridging anticoagulation with therapeutic-dose SC LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 1C)**; we suggest therapeutic-dose SC LMWH over IV UFH** (Grade 2C)**. In patients with a mechanical heart valve or atrial fibrillation or VTE at moderate risk (Table 2) for thromboembolism, we suggest bridging anticoagulation with therapeutic-dose SC LMWH, therapeutic-dose IV UFH, or low-dose SC LMWH over no bridging during temporary interruption of VKA therapy** (Grade 2C)**; we suggest therapeutic-dose SC LMWH over other management options** (Grade 2C)**. In patients with a mechanical heart valve or atrial fibrillation or VTE at low risk (Table 2) for thromboembolism, we suggest low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH** (Grade 2C)**.**

Values and preferences: In patients at high or moderate risk for thromboembolism, the recommendations reflect a relatively high value on preventing thromboembolism and a relatively low value is on preventing bleeding; in patients at low risk for thromboembolism, the recommendations reflect a relatively high value on preventing bleeding and a relatively low value on preventing thromboembolism.

3.0 Perioperative Management of Patients Who Are Receiving Bridging Anticoagulation

In patients who require temporary interruption of VKAs and are to receive bridging anticoagulation, several treatment regimens have been assessed[21,22,39,40,56,57,80,81] and are summarized in Table 3. In total, > 4,000 patients who had temporary interruption of a VKA and received bridging anticoagulation have been studied to date, of whom approximately 72% received therapeutic-dose LMWH, approximately 20% received low-dose LMWH, and approximately 8% received therapeutic-dose UFH.

3.1 Perioperative Anticoagulation Treatment Regimens

3.1.1 Therapeutic-Dose UFH

Therapeutic-dose IV UFH had been the most commonly used bridging regimen[7,82,83] but its use has declined in recent years,[84,85] likely because of the increased inconvenience of IV drug administration and the increase in the number of surgical procedures that are being done without hospitalization.[86] In studies that assessed bridging anticoagulation with therapeutic-dose UFH, a dose-adjusted IV infusion was used, administered to achieve a target activated partial thromboplastin time (APTT) of 1.5 to 2.0 times the control APTT value, with the infusion stopped approximately 4 h before surgery and resumed during the initial 24 h after surgery.[7,83] An emerging alternative to IV UFH is SC UFH, which is administered as a fixed, weight-based dose regimen (250 IU/kg bid) without APTT monitoring and has shown to be efficacious and safe for the treatment of acute VTE.[87] The use of fixed-dose SC UFH may provide a practical alternative to IV UFH for bridging anticoagulation, though it has only been assessed in a small number of patients who required temporary interruption of warfarin for surgery.[55]

3.1.2 Therapeutic-Dose LMWH

Clinicians have, in recent years, increasingly turned to therapeutic-dose SC LMWH in lieu of UFH as bridging anticoagulation,[84,85] likely because

it can be easily administered outside of hospital and without laboratory monitoring.[36] There is no standardized bridging regimen with LMWH, and several therapeutic-dose regimens have been studied: dalteparin 200 IU/kg qd; enoxaparin 1.5 mg/kg qd; tinzaparin 175 IU/kg qd; dalteparin 100 IU/kg bid; and enoxaparin 1 mg/kg bid.[21,22,39,80]

In the postoperative period, the use of therapeutic-dose LMWH administered can vary. The 3 principal management approaches that have been studied are: (1) to administer therapeutic-dose LMWH within a fixed time period after a procedure (within initial 24 h); (2) to administer therapeutic-dose LMWH within a varied time period after a procedure (24 to 72 h), with the initiation depending on the procedure-related bleeding risk and the adequacy of postoperative hemostasis; and (3) to replace therapeutic-dose LMWH with low-dose LMWH in select patients who are undergoing a procedure associated with a high bleeding risk.

3.1.3 Low-Dose LMWH or UFH

Low-dose UFH (*eg*, UFH, 5,000 IU bid) or low-dose LMWH (*eg*, enoxaparin, 30 mg bid, dalteparin, 5,000 IU qd), which is typically used for the prevention of deep vein thrombosis in at-risk surgical and medical patients, provides another bridging anticoagulation treatment option.[65] This approach for perioperative anticoagulation has not been as widely studied as therapeutic-dose regimens and has been assessed mainly in lower-risk patients with atrial fibrillation or those with prior VTE. Though this anticoagulant regimen has been used with the presumed intent of providing some antithrombotic efficacy but at a lower risk for perioperative bleeding, data are very limited in regard to the efficacy of low-dose UFH or LMWH to prevent arterial thromboembolism in patients with a mechanical heart valve or chronic atrial fibrillation.[54,63,64,72] Indirect evidence from nonsurgical clinical settings involving patients with atrial fibrillation who received VKAs indicates that, compared to patients who were therapeutically anticoagulated, patients who had subtherapeutic anticoagulation (INR < 2.0) were more likely to develop a stroke and such strokes were more severe and associated with greater mortality.[88–90] Although, to our knowledge, there have been no studies that have assessed the efficacy of low-dose LWMH or UFH to prevent arterial thromboembolism, a recent trial involving patients with chronic atrial fibrillation found that treatment with idraparinux, a synthetic anti-Xa inhibitor, when administered in a therapeutic-dose regimen was as efficacious as VKA therapy (INR range 2.0 to 3.0) for the prevention of stroke and systemic embolism.[91] This finding supports the premise that administration of a therapeutic-dose regimen of a non-VKA anticoagulant with properties similar to LMWHs is efficacious for the prevention of arterial thromboembolism.

Low-dose LMWH or UFH may be incorporated into a perioperative anticoagulation regimen in two possible clinical scenarios. The first is as a "stand-alone" regimen in patients with prior VTE who are receiving VKA therapy and are at moderate or low risk for recurrent disease in whom a therapeutic-dose anticoagulation regimen may not be considered. In such patients, a low-dose LMWH or UFH regimen could be used during interruption of a VKA with the intent of preventing recurrent venous (but not arterial) thromboembolism. The rationale for this approach is based on the established efficacy of low-dose LMWH or UFH to prevent postoperative VTE.[65] The second scenario is in patients with any clinical indication for VKA therapy who are undergoing surgery that is associated with a high risk for bleeding (*eg*, cardiac, neurosurgical, urologic, major orthopedic). In such patients, administration of therapeutic-dose LMWH or UFH during the initial 48 to 72 h after surgery (or for the entire postoperative period) may confer an unacceptably high risk for bleeding complications and a less intense anticoagulant regimen consisting of low-dose SC LMWH or UFH is likely to confer a lower risk for postoperative bleeding. Thus, in a registry involving 1,077 patients who received bridging anticoagulation, postoperative low-dose LMWH or UFH was associated with a lower risk for minor bleeding compared to bridging anticoagulation with therapeutic-dose LMWH or UFH (OR = 0.46; CI: 0.20–1.01).[80] However, this registry was underpowered to detect potential differences in major bleeding with low-dose or therapeutic-dose anticoagulation.

To our knowledge, no prospective trials have compared low-dose and therapeutic-dose LMWH or UFH as bridging anticoagulation to assess both efficacy, in terms of preventing arterial thromboembolism, and safety, in terms of associated bleeding risk. Although it is plausible that low-dose LMWH or UFH will confer a lower risk for bleeding complications, one cannot exclude the possibility that such treatment will be less effective in preventing arterial thromboembolism than a therapeutic-dose regimen. This issue can only be resolved through well-designed randomized trials assessing different bridging anticoagulation strategies.

3.1.4 Costs of Bridging Anticoagulation Treatment Regimens

Recent studies have compared the costs of bridging anticoagulation before and after surgery with

in-hospital administered IV UFH and out-of-hospital bridging anticoagulation SC LMWH.[92–95] In a prospective cohort study assessing perioperative anticoagulation with patient-administered SC LMWH, nurse-administered SC LWMH, and in-hospital administered IV UFH, the anticoagulant-related costs for patients undergoing an overnight surgical procedure were estimated at $672, $933, and $3,916 (all USD), respectively.[93] 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 underwent elective surgery found a significantly lower mean total health-care cost (by $13,114 USD) in patients who received perioperative LMWH.[94] In a decision analysis study involving patients who required VKA interruption for GI endoscopy, similar findings were found in terms of lower costs associated with out-of-hospital use of LMWH as bridging anticoagulation.[96] Taken together, these findings indicate that, compared to in-patient administration of IV UFH, there is considerable cost savings with the use of SC LMWHs, which can be administered in an outpatient setting, typically by the patient or by another health-care provider.[92–95] Additional studies are needed to assess the feasibility and costs of unmonitored SC UFH as bridging anticoagulation for patients in whom LMWH may be contraindicated, such as those with severe renal insufficiency or in whom LMWHs may be unavailable or too costly.[87]

Recommendation

3.1. In patients who require temporary interruption of VKAs and are to receive bridging anticoagulation, from a cost containment perspective we recommend the use of SC LMWH administered in an outpatient setting where feasible instead of inpatient administration of IV UFH (Grade 1C)**.**

Values and preferences: This recommendation reflects a consideration not only of the trade-off between the advantages and disadvantages of SC LMWH and IV UFH as reflected in their effects on clinical outcomes (LMWH at least as good, possibly better), but also the implications in terms of resource use (costs) in a representative group of countries (substantially less resource use with LMWH).

3.2 Interruption of Bridging Anticoagulation Before Surgery

Bridging anticoagulation with IV UFH, which has a half-life of approximately 45 min, can be interrupted 4 h before planned surgery, a time interval that approximates 5 elimination half-lives of UFH,[36] and is in accordance with the practice used in bridging anticoagulation studies.[7,55] In patients who are receiving bridging anticoagulation with SC LMWHs, which have elimination half-lives of 4 to 5 h,[36] the last dose should be administered 20 to 25 h before surgery (or on the morning of the day before surgery), a time interval that approximates 5 elimination half-lives of LMWHs.[36] There is evidence suggesting that there will be a residual anticoagulant effect if therapeutic-dose LMWH is given too close to the time of the procedure. Thus, in a prospective cohort study involving 73 patients who received therapeutic-dose or low-dose LMWH as bridging anticoagulation, 30% (11 of 37) of patients who received therapeutic-dose LMWH (qd or bid dose regimens) had a residual anticoagulant effect (defined as an anti-factor Xa $\geq$ 0.10 IU/mL) at the time of surgery whereas $<$ 1% (1 of 36) of patients who received low-dose LMWH had a residual anticoagulant effect at surgery.[97] In another prospective cohort study of 98 patients who received bridging anticoagulation with enoxaparin 1 mg/kg bid, with the last dose given on the evening before surgery, a detectable residual anticoagulant effect (anti-factor Xa $\geq$ 0.10 IU/mL) was found in 100% (98 of 98) of patients.[98] Furthermore, 34% of patients had an anticoagulant effect at the time of surgery that is considered within the therapeutic range (anti-factor Xa $\geq$ 0.50 IU/mL). Although there were no major bleeds in the patients from both of these studies, most patients underwent low bleeding risk procedures and the potential for bleeding in patients having major surgical or other higher-risk invasive procedures cannot be excluded. Taken together, these findings suggest that the last preoperative dose of therapeutic-dose LMWH before surgery should be reduced to minimize the risk for a residual anticoagulant effect at the time of surgery. Until prospective trials address this issue further, one management option, especially in patients who are undergoing major surgery or are receiving spinal/epidural anesthesia, is to administer *only* the morning dose of LMWH in patients receiving a twice-daily therapeutic-dose regimen and to reduce by 50% the total dose of LMWH given in patients who are receiving a once-daily therapeutic-dose regimen.

Recommendation

3.2. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we recommend administering the last dose of LMWH 24 h before surgery or a procedure over administering LMWH closer to surgery (Grade 1C); **for the last preoperative dose of**

LMWH, we recommend administering approximately half the total daily dose instead of 100% of the total daily dose (Grade 1C). **In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, we recommend stopping UFH approximately 4 h before surgery over stopping UFH closer to surgery** (Grade 1C).

3.3 Resumption of Bridging Anticoagulation After Surgery

Following parenteral administration, LMWHs induce a rapid anticoagulant effect, with the potential for a detectable anticoagulant effect to occur within 1 h and a peak anticoagulant effect to occur within 3 to 5 h after administration.[36] With UFH, though the time to a peak anticoagulant effect varies, there is the potential for this to also occur within 3 to 5 h following an IV bolus and infusion.[36] Consequently, clinicians should exercise caution when administering these drugs in patients who have recently had surgery or other invasive procedures because of the potential for bleeding at the surgical site, especially when hemostasis is not secured. Three factors appear to affect the risk for surgery-related bleeding: (1) the proximity to surgery that the anticoagulant is administered; (2) the dose of anticoagulant administered; and (3) the type of surgery and its associated bleeding risk. A superimposed consideration is that bleeding can occur after any surgery or procedure, irrespective of the anticipated surgery-related risk for bleeding and postoperative anticoagulant management. Consequently, postoperative administration of UFH and LMWHs should consider *both* the anticipated risk for bleeding, which is determined preoperatively, and the adequacy of surgical hemostasis, which is determined postoperatively.

3.3.1 Proximity to Surgery That Anticoagulants Are Administered

In a pooled analysis of studies involving patients who had major orthopedic surgery and received low-dose fondaparinux (2.5 mg/d) 4 to 8 h postoperatively or low-dose enoxaparin (40 to 60 mg/d) 12 to 24 h postoperatively, the risk for major bleeding was significantly higher in fondaparinux-treated patients (2.7% vs 1.7%; $p < 0.01$).[99] In another pooled analysis that compared bleeding in patients who received low-dose LMWH either within 6 h or 12 to 24 h after major orthopedic surgery, the risk for bleeding was higher in patients who received LMWH closer to surgery (6.3% [95% CI: 5–7] vs 2.5% [95% CI: 1–3]).[100]

In patients who received bridging anticoagulation, three prospective cohort studies suggest that delaying the postoperative initiation of therapeutic-dose LMWH until hemostasis is secured and deferring (or avoiding altogether) postoperative therapeutic-dose LMWH are associated with a low risk for bleeding. In one study assessing 650 patients who underwent a broad spectrum of surgical and nonsurgical procedures and received therapeutic-dose bridging anticoagulation, postoperative management, which included resumption of therapeutic-dose bridging with LMWH, depended on the anticipated bleeding risk and adequacy of postoperative hemostasis.[21] Thus, patients who had procedures associated with a low risk for bleeding (*eg*, GI endoscopy, cardiac catheterization) resumed LMWH approximately 24 h after the procedure (*ie*, day after procedure); patients who had major surgery (*eg*, open abdominal surgery) or in whom there was inadequate postoperative hemostasis resumed LMWH 48 to 72 h after surgery; and patients who had major surgery associated with a high risk for bleeding (*eg*, cardiac, neurosurgical, urologic, major orthopedic) did not receive any postoperative LMWH. With this approach, the incidence of major bleeding was 1.0% during the first week after surgery, with no fatal bleeds. In another study involving 220 patients with a mechanical heart valve that used the same postoperative anticoagulant management approach, the incidence of major bleeding was 2.3% during the first week after surgery, with no fatal bleeds.[40] Another prospective cohort study involved 224 patients, in whom once-daily therapeutic-dose LMWH or low-dose LMWH (in patients having surgery associated with a high bleeding risk) started on the day after surgery and administered only if postoperative hemostasis was secured.[22] The risk for bleeding during the first week after surgery in patients who received therapeutic-dose LMWH was 2.9%, with no fatal bleeds. The risk for arterial thromboembolism with the perioperative management approach used in these studies is low (< 1%) and is discussed further in Section 2.4.

3.3.2 Dose of Anticoagulant Administered

A prospective multicenter registry evaluated 493 patients who required interruption of a VKA and received bridging with LMWH or UFH or no bridging (Jaffer A, submitted for publication). After adjustment for surgical and patient-specific bleeding risk factors, the administration of therapeutic-dose LMWH or UFH after the surgery or procedure conferred a greater than fourfold greater risk for major bleeding (OR, 4.4; 95% CI: 1.5–14.7) compared to the postoperative administration of either a low-dose LMWH or UFH regimen or no bridging.

3.3.3 Type of Surgery and Associated Bleeding Risk

A prospective bridging study[39] of 260 patients in which all patients received therapeutic-dose once-daily LMWH perioperatively, with the first postoperative dose administered 12 to 24 h after surgery, categorized surgeries or procedures as major (expected duration $>$ 1 h) or minor (expected duration $\leq$ 1 h). This study[39] found that major bleeding occurred in 0.7% (1 of 148) of patients who had an invasive procedure, in 0% (0 of 72) of patients who had minor surgery, and in 20.0% (8 of 40) of patients who had major surgery.

Taken together, these findings suggest that in patients who receive bridging anticoagulation with therapeutic-dose LMWH, this regimen should be administered carefully in the postoperative period. It appears that therapeutic-dose LMWH can be safely resumed on the day after surgery in patients who have had a minor surgical or other invasive procedure and in whom there is adequate hemostasis. On the other hand, administering therapeutic-dose LMWH within 24 h after major surgery appears to confer an unacceptably high risk for bleeding complications.

In patients undergoing major surgery or a procedure (surgical or nonsurgical) associated with a high bleeding risk, management options that are preferable over administering therapeutic-dose SC LMWH or IV UFH in close proximity to surgery (*ie*, within 24 h) include: (1) delaying the resumption of therapeutic-dose LMWH or UFH for 48 to 72 h after the surgery/procedure; (2) administering only low-dose LMWH after the surgery/procedure; and (3) avoiding the use of LMWH altogether in the postoperative period. The management option chosen is individualized and will depend on both the bleeding risk associated with the surgical or other invasive procedure and the adequacy of postoperative hemostasis. For example, in patients undergoing major surgery (*eg*, bowel resection), it may be reasonable to delay the resumption of therapeutic-dose LMWH or UFH. In patients undergoing a surgery (*eg*, radical prostatectomy) or procedure (*eg*, kidney biopsy) associated with a high risk for bleeding, it may be reasonable to not administer any LMWH or UFH after surgery and to simply resume VKAs.

Recommendation

3.3. In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic-dose LMWH, we recommend resuming this regimen approximately 24 h after (*eg*, the day after) the procedure when there is adequate hemostasis over a shorter (*eg*, < 12 h) time interval (Grade 1C)**. In patients undergoing major surgery or a high bleeding risk surgery/procedure and for whom postoperative therapeutic-dose LMWH/UFH is planned, we recommend either delaying the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured, administering low-dose LMWH/UFH after surgery when hemostasis is secured, or completely avoiding LMWH or UFH after surgery over the administration of therapeutic-dose LMWH/UFH in close proximity to surgery** (Grade 1C)**. We recommend considering the anticipated bleeding risk and adequacy of postoperative hemostasis in individual patients to determine the timing of LMWH or UFH resumption after surgery instead of resuming LMWH or UFH at a fixed time after surgery in all patients** (Grade 1C)**.**

3.4 Laboratory Monitoring of Bridging Anticoagulation

In patients who are receiving IV UFH as bridging anticoagulation, clinicians can use the APTT to guide preoperative and postoperative anticoagulation. However, use of an UFH dosing nomogram, which was not designed for use in the perioperative setting, may be misleading.[39,101] For example, a dosing nomogram for IV UFH may result in excessive anticoagulation (*ie*, APTT $>$ 150 s) for up to a 24-h period while dose adjustments are being made. Although short periods of excessive anticoagulation with UFH may not increase the risk for bleeding in nonoperative clinical settings,[102,103] such short periods of over-anticoagulation might increase the risk for bleeding in a postoperative setting.

In patients who are receiving bridging anticoagulation with therapeutic-dose LMWH, there is no established role for routine perioperative monitoring of anti-factor Xa levels, as in certain nonoperative clinical settings.[36] In selected patient groups, such as those with severe renal insufficiency (*ie*, calculated creatinine clearance $<$ 30 mL/min or serum creatinine $>$ 178 mmol/L or $>$ 2 g/dL) or at extremes of body weight, anti-factor Xa monitoring may be considered to guide treatment as in nonoperative clinical settings.[36]

Recommendation

3.4. In patients who are receiving bridging anticoagulation with LMWH, we suggest against the routine use of anti-factor Xa levels to monitor the anticoagulant effect of LMWHs (Grade 2C)**.**

4.0 Perioperative Management of Patients Who Are Receiving Antiplatelet Therapy

An increasing number of patients are receiving antiplatelet drugs for the primary and secondary prevention of myocardial infarction or stroke and for the prevention of coronary stent thrombosis after placement of a bare metal or drug eluting stent.[104,105] The perioperative management of these patients is increasing in complexity because the spectrum of risk for a cardiovascular event varies widely. In addition, these patients may be receiving treatment with one of several antiplatelet drug regimens, which include: (1) aspirin alone; (2) clopidogrel alone; (3) aspirin combined with clopidogrel; (4) aspirin combined with dipyridamole; or (5) cilostozol, either alone or combined with either aspirin or clopidogrel. This section will focus on patients who are receiving aspirin and/or clopidogrel.

4.1 Risk Stratification

Patients who are receiving antiplatelet therapy encompass a spectrum of risk for cardiovascular events that depends, to a large extent, on the clinical indication for antiplatelet therapy and whether patients are receiving such treatment for the primary or secondary prevention of cardiovascular disease. Clinicians should incorporate risk stratification in decisions concerning temporary interruption or continuation of antiplatelet therapy in the perioperative period. There are no risk classification schemes, to our knowledge, that encompass the spectrum of benefit from antiplatelet agents. Nonetheless, patients at low risk for perioperative cardiovascular events in whom temporary interruption of antiplatelet drugs would not be expected to confer a substantial increased risk for cardiovascular events include those who are receiving antiplatelet therapy (typically aspirin) for the primary prevention of myocardial infarction or stroke.[106] On the other hand, patients at high risk for cardiovascular events in whom it may be preferable to continue antitplatelet therapy perioperatively include those who have had recent (within 3 to 6 months) placement of a bare metal or drug-eluting coronary stent, and to a lesser extent, who have suffered a myocardial infarction within the past 3 months.[107] The risk for cardiovascular events in these high-risk groups should be weighed against the risk and clinical impact of bleeding with the operation planned when antiplatelet drugs are continued in the perioperative period.

4.2 Interruption of Antiplatelet Therapy Before Surgery

For patients who are receiving aspirin, which irreversibly inhibits platelet function through cyclooxygenase-1 inhibition, clinicians intending no antiplatelet effect at the time of surgery should interrupt therapy 7 to 10 days before surgery.[108] Although aspirin has a half-life of 15 to 20 min, it irreversibly inhibits platelet cyclooxygenase-1 and, therefore, its effect persists for 7 to 10 days, which approximates the platelet lifespan.[109,110] Consequently, 4 to 5 days after stopping aspirin will result in approximately 50% of platelets having normal function, whereas 7 to 10 days after stopping aspirin will result in $>$ 90% of platelets having normal function. In patients who are receiving clopidogrel, a thienopyridine derivative that irreversibly inhibits adenosine diphosphate receptor-mediated platelet activation and aggregation and has a half-life of 8 h, treatment should be interrupted 7 to 10 days before surgery since it takes about that many days to replace the platelet pool.[111] This approach also applies to ticlopidine, another thienopyridine derivative which is used less frequently compared to clopidogrel, in part because of an increased risk for drug-induced adverse effects such as neutropenia.[112,113]

Another antiplatelet agent that is used in combination with aspirin is dipyridamole, a pyrimidopyrimidine derivative with antiplatelet and vasodilator properties that is indicated for secondary stroke prevention in patients with cerebrovascular disease.[114] Dipyridamole has reversible effects on platelet function and has an elimination half-life of approximately 10 h.[115] However, since dipyridamole is combined with aspirin (200 mg dipyridamole + 25 mg aspirin), this drug would need to be interrupted 7 to 10 days before elective surgery to allow elimination of the antiplatelet effects of both drugs.

Cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilatory properties that reversibly affects platelet function through cyclic adenosine monophosphate (cAMP) mediated inhibition of platelet activation and aggregation. Cilostazol may be used in patients with coronary artery disease, typically if they have a coronary stent[116] or peripheral arterial disease.[117] The pharmacokinetics of cilostazol are dose-dependent, with an elimination half-life of approximately 10 h.[118] Consequently, this drug would need to be interrupted 2 to 3 days (corresponding to 5 elimination half-lives of cilostazol) before surgery to ensure elimination of its antiplatelet effect at the time of surgery.

For patients who are receiving a nonselective nonsteroidal antiinflammatory drug (NSAID) or a cyclyooxygenase-2 selective NSAID (*ie*, celecoxib), there is reversible inhibition of platelet-mediated cyclooxygenase activity. To ensure there is no residual antiplatelet effect at the time of surgery, the NSAID should be stopped at a time that corresponds to 5 elimination half-lives for that drug.[119,120] For

NSAIDs with a short, 2 to 6 h, half-life (*eg*, ibuprofen, diclofenac, ketoprofen, indomethacin), these drugs should be stopped on the day before surgery. For NSAIDs with an intermediate, 7 to 15 h, half-life (*eg*, naproxen, sulindac, diflunisal, celecoxib), such treatment should be stopped 2 to 3 days before surgery. Finally, for NSAIDs with a long, > 20 h half-life (*eg*, meloxicam, nabumetone, piroxicam), these drugs should be stopped 10 days before surgery.

Recommendation

4.2. In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure, we suggest stopping this treatment 7 to 10 days before the procedure over stopping this treatment closer to surgery (Grade 2C).

4.3 Resumption of Antiplatelet Therapy After Surgery

In patients who have temporary interruption of antiplatelet drugs before surgery, these agents should, in general, be resumed as soon as there is adequate postoperative hemostasis after surgery. Four studies assessed bridging anticoagulation in patients with a mechanical heart valve, some of whom were receiving both VKAs and aspirin.[21,22,40,55] In these studies, aspirin was resumed on the same day as VKAs, starting with the usual maintenance dose of 81 mg daily. Data are lacking in regard to the resumption of clopidogrel or other antiplatelet drugs after surgery. One issue that warrants consideration is whether resumption of treatment should be with a maintenance dose of clopidogrel (75 mg/d), which achieves maximal platelet function inhibition 5 to 10 days after its administration,[121–123] or with a loading dose (300 to 600 mg/d), which achieves maximal platelet function inhibition within 2 to 15 h after administration.[124–126] The dose of clopidogrel resumption will depend largely on whether a patient has a coronary stent, the type of stent implanted, and how recently the stent was implanted.

Recommendation

4.3. In patients who have had temporary interruption of aspirin therapy because of surgery or a procedure, we suggest resuming aspirin approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming aspirin closer to surgery (Grade 2C)**. In patients who have had temporary interruption of clopidogrel because of surgery or a procedure, we suggest resuming clopidogrel approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming clopidogrel closer to surgery** (Grade 2C)**.**

4.4 Laboratory Monitoring of Antiplatelet Therapy

Platelet function assays are available to measure the antiplatelet activity of aspirin, clopidogrel and, potentially, other antiplatelet drugs, prior to surgery.[127] However, these methods are not well studied outside of a cardiac surgery or percutaneous coronary intervention (PCI) setting.[128] Furthermore, the clinical significance of the assay results is uncertain as they have not been shown to identify patients at increased risk for perioperative bleeding.[127] Additional research is needed to identify the potential clinical utility of platelet function assays.

Recommendation

4.4. In patients who are receiving antiplatelet drugs, we suggest against the routine use of platelet function assays to monitor the antithrombotic effect of aspirin or clopidogrel (Grade 2C)**.**

4.5 Surgery in Patients Receiving Antiplatelet Therapy

4.5.1 Noncardiac Surgery

In patients who are receiving antiplatelet drug therapy and are undergoing noncardiac surgery, there are no randomized trials or prospective cohort studies that compare the clinical benefits and risks of continuing antiplatelet drugs with their temporary interruption. A randomized placebo-controlled trial involving patients undergoing hip fracture repair or joint replacement surgery assessed *de novo* use of aspirin compared to no aspirin use in the perioperative period and reported higher rates of major bleeding in aspirin treated patients (2.9% vs 2.4%, $p = 0.04$).[9]

Studies in patients undergoing abdominal or pelvic surgery are limited. A retrospective cohort study in 52 patients found that perioperative continuation of aspirin increases the risk for bleeding after prostatectomy.[31] A retrospective cohort study involving 200 patients who underwent intraabdominal surgery found that 12 of 55 (22%) patients with aspirin-associated abnormal platelet function had excessive perioperative bleeding, whereas 7 of 97 (7%) with normal platelet function had excessive bleeding.[129] However, another study involving 52 patients who had surgery found that perioperative aspirin use did not confer an increased risk for bleeding.[130]

Retrospective cohort studies have suggested increased rates of bleeding with perioperative continuation of clopidogrel.[131,132] In addition, one prospective cohort study in patients who underwent bronchoscopy found significantly higher incidences of moderate or severe bleeding after biopsy in patients who received clopidogrel (61%) or clopidogrel and aspirin (100%) compared to no antiplatelet drug (2%).[133]

4.5.2 CABG

Elective coronary artery bypass graft (CABG) surgery is frequently done in patients who are receiving antiplatelet therapy with aspirin and/or clopidogrel.[134] In addition, 10 to 15% of patients hospitalized with an acute coronary syndrome will require urgent CABG surgery during their hospitalization and such patients are typically receiving antiplatelet therapy (aspirin alone or aspirin and clopidogrel) and anticoagulant therapy, the later with LMWH or UFH.[135] Minimizing the risk for perioperative bleeding in patients undergoing CABG surgery is important because of an increased risk for death and other adverse outcomes in patients who require a blood transfusion in the perioperative period.[136] In one study involving 11,963 patients who underwent CABG, of whom 49% received transfusion of RBCs, transfusion was associated with significant increases in mortality (OR, 1.77; CI: 1.67–1.87), renal failure (OR, 2.06; CI: 1.87–2.27), and neurologic events (OR, 1.37; CI: 1.30–1.44).[137] The perioperative management of anticoagulant therapy is comparable to that of noncardiac surgery, with interruption of LMWH or UFH at a time prior to CABG surgery that will eliminate the anticoagulant effect by the time of surgery. On the other hand, the perioperative management of antiplatelet therapy is more problematic since 7 to 10 days after stopping treatment is required to eliminate an antiplatelet effect and urgent CABG is often required without advance notice of 7 to 10 days.

In patients who are receiving aspirin and require CABG surgery, observational studies show that continuing aspirin in the perioperative period appears to confer an increased risk for mediastinal bleeding, blood transfusion, and reoperation,[138,139] although this finding was not found in all studies.[140] Against these risks, aspirin use within 5 days prior to CABG was shown in a large cohort study to confer a lower risk of postoperative mortality and without a concomitant increase in reoperation for bleeding or need for blood transfusion.[26] Based on this benefit of continued perioperative aspirin use in patients undergoing CABG, if aspirin therapy has been interrupted before surgery, it should be administered early after surgery, always within 48 h after CABG and, preferably, within 6 h after surgery.[141]

In patients who are receiving clopidogrel and require CABG, there are no data to suggest benefit from the administration of clopidogrel in the perioperative period whereas there are preliminary data suggesting harm with this approach.[142] In the Can Rapid risk stratification of Unstable Angina Patients Supress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) study that included 2,855 patients with a non-ST elevation myocardial infarction, 87% of patients underwent CABG within 5 days of prior clopidogrel exposure.[143] Such patients had a 70% higher likelihood for a transfusion requirement of 4 U or more of RBCs. The most compelling data about the risk of bleeding among patients undergoing CABG who are receiving clopidogrel come from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial.[144] In a postrandomization subgroup analysis of this trial, exposure to clopidogrel within 5 days prior to CABG was associated with an approximately 50% increase in major bleeding. Other retrospective studies have confirmed the increased risk for bleeding with prior clopidogrel exposure in patients undergoing CABG surgery.[145–148] An increased risk of bleeding appears to occur even when CABG is performed in an off-pump manner.[149]

Mitigating the risk for perioperative bleeding and transfusion with antifibrinolytic drugs, such as aprotinin, or platelet transfusion is problematic because both treatments are associated with adverse effects. Although two randomized trials suggested a reduction in the need for transfusion among patients treated with aprotinin undergoing surgery while on clopidogrel without raising concerns of excessive risk of thrombosis, aprotinin appears to be associated with an increased risk for thrombotic and other adverse effects,[150,151] and is no longer available for clinical use in the United States. In one observational study involving 4,374 patients undergoing CABG surgery for ST-segment elevation myocardial infarction, aprotinin use was associated with a 55% increased risk for myocardial infarction or congestive heart failure and a 181% increased risk for stroke or encephalopathy.[152] Similarly, pre-CABG platelet transfusion is associated with longer surgery and, paradoxically, more bleeding and reoperation for bleeding complications.[153] Alternative antifibrinolytic agents that can be used in lieu of aprotonin to reduce perioperative bleeding in patients undergoing cardiac surgery include epsilon-aminocaproic acid and tranexamic acid, which have been shown to reduce transfusion requirements.[154,155] The efficacy of 1-deamino-8-D-arginine

vasopressin (DDAVP) in patients undergoing cardiac surgery who have been exposed to aspirin is less clear.[156]

4.5.3 PCIs

Randomized trials have compared a 325-mg dose of aspirin to placebo among patients undergoing a balloon angioplasty type of PCI. The reduction in risk associated with aspirin administration in these studies has led to the recommendation that aspirin be administered in all patients prior to any PCI procedure.[17]

Clopidogrel has been compared to placebo among patients with acute coronary syndromes and found to reduce the risk of procedure-related events.[157,158] In postrandomization subgroup analyses of patients undergoing PCI in these trials, clopidogrel was particularly beneficial among patients undergoing PCI and the benefit seems to apply not only to patients who received stents but to those undergoing balloon angioplasty and other types of PCI procedures as well. Pretreatment with clopidogrel is recommended before any type of PCI procedure whenever it can be accomplished and such treatment should be continued during the periprocedural period. Among patients on long-term clopidogrel therapy, one study showed that periprocedural administration of a 600-mg loading dose of clopidogrel to such patients resulted in a greater inhibition of platelet aggregation than not receiving a loading dose.[159] Other studies have suggested that clinical outcomes are improved if PCI is performed after a 600-mg loading dose of clopidogrel has been administered; few patients in those studies were receiving long-term clopidogrel and it is not known whether chronically administered clopidogrel achieves the same effect.[160–162]

Recommendation

4.5. For patients who are not at high risk for cardiac events, we recommend interruption of antiplatelet drugs (Grade 1C)**. For patients at high risk of cardiac events (exclusive of coronary stents) scheduled for noncardiac surgery, we suggest continuing aspirin up to and beyond the time of surgery** (Grade 2C)**; if patients are receiving clopidogrel, we suggest interrupting clopidogrel at least 5 days and, preferably, within 10 days prior to surgery** (Grade 2C)**. In patients scheduled for CABG, we recommend continuing aspirin up to and beyond the time of CABG** (Grade 1C)**; if aspirin is interrupted, we recommend it be reinitiated between 6 h and 48 h after CABG** (Grade 1C)**. In patients scheduled for CABG, we recommend interrupting clopidogrel at least 5 days and, preferably, 10 days prior to surgery** (Grade 1C)**. In patients scheduled for PCI, we suggest continuing aspirin up to and beyond the time of the procedure; if clopidogrel is interrupted prior to PCI, we suggest resuming clopidogrel after PCI with a loading dose of 300 to 600 mg** (Grade 2C)**.**

4.6 Surgery in Patients With Coronary Stents

Patients who are receiving antiplatelet therapy because of a bare metal or drug-eluting stent in the coronary arteries deserve special consideration because of the high thrombotic risk if antiplatelet drug therapy is interrupted. In such patients who are undergoing noncardiac surgery, there is a markedly increased risk of coronary stent thrombosis in the postoperative period, especially if surgery is undertaken in close proximity to stent placement.[163–172] Furthermore, the clinical impact of stent thrombosis in this clinical setting is considerable, as it will be fatal or associated with a large myocardial infarction in $>50\%$ of affected patients.[107,163,173–175] A retrospective cohort study assessed 40 consecutive patients who had elective noncardiac surgery <6 weeks after coronary artery stenting.[163] In this study, eight patients (20%) died postoperatively, in whom all but one had perioperative interruption of clopidogrel or aspirin.

To mitigate the risk for perioperative stent thrombosis, elective noncardiac surgery should be avoided during the period after stent placement when stent endothelialization is ongoing as this is the time when coronary stents are most susceptible to thrombosis. In patients with a bare metal stent, the aforementioned study suggested that the risk of thrombosis with surgery was higher in patients who had surgery within 2 weeks of stenting compared to more than 2 weeks after stenting ($p = 0.15$).[163] A larger study suggested that the risk of bare metal stent thrombosis and other adverse events is increased if noncardiac surgery is performed within 6 weeks of stent placement,[164] which is consistent with the approximate time required for endothelialization around the bare metal stents.[176,177]

A relevant, but poorly studied, issue in the management of patients with coronary stents who require surgery is whether bridging therapy is warranted for patients in whom interruption of antiplatelet therapy is required because of a high bleeding risk associated with the planned surgery. In such patients, bridging therapy might consist of administering LMWH or UFH in a manner similar to that in patients who require temporary interruption of VKAs, though this approach has not been formally studied to assess

efficacy and should be weighed against a potential increased risk for postoperative bleeding. An alternative approach might be the use of bridging therapy with short-acting antiplatelet drugs such as the glycoprotein IIb/IIIa antagonists tirofiban or eptifibatide, which have been studied in patients undergoing PCI.[17] These agents have elimination half-lives of approximately 2 h and their interruption 10 h before surgery would allow restoration of platelet function by the time of surgery.[108] Emerging short-acting antiplatelet drugs that target platelet P2 receptors, such as cangrelor, may have clinical utility in the perioperative setting because of rapid reversal of antiplatelet activity after treatment is stopped.[178] Studies are needed to assess the efficacy and safety of bridging therapy in patients who are receiving antiplatelet drugs and, until relevant data are available, clinical judgment and caution are urged in regard to the use of short-acting antithrombotic agents in patients who require temporary interruption of aspirin and/or clopidogrel.

Less is known about the timing of noncardiac surgery in patients with a sirolimus- or paclitaxel-eluting coronary stent, in whom a longer time is required for coronary reendothelialization than patients with a bare metal stent. There have been several reports of thrombosis of such drug-eluting stents during the intraoperative and postoperative period, in some cases even when surgery is performed years after stent placement.[165–170] Though aspirin is recommended indefinitely after placement of a drug-eluting stent and clopidogrel is recommended for at least 3 months after placement of a sirolimus-eluting stent and 6 months after placement of a paclitaxel-eluting stent, most patients are receiving combined aspirin-clopidogrel therapy for at least 12 months after placement of a drug-eluting stent.[179,180] Consequently, elective surgery should be delayed for 12 months after placement of a drug-eluting stent whenever possible.

Recommendation

4.6. In patients with a bare metal coronary stent who require surgery within 6 weeks of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C)**. In patients with a drug-eluting coronary stent who require surgery within 12 months of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period** (Grade 1C)**. In patients with a coronary stent who have interruption of antiplatelet therapy before surgery, we suggest against the routine use of bridging therapy with UFH, LMWH, direct thrombin inhibitors, or glycoprotein IIb/IIIa inhibitors,** (Grade 2C)**.**

Values and preferences: These recommendations reflect a relatively high value placed on preventing stent-related coronary thrombosis, and a consideration of complexity and costs of administering bridging therapy in the absence of efficacy and safety data in this clinical setting, and a relatively low value on avoiding the unknown but potentially large increase in bleeding risk associated with the concomitant administration of aspirin and clopidogrel during surgery.

5.0 Perioperative Management of Antithrombotic Therapy in Patients Who Require Dental, Dermatologic, or Ophthalmologic Procedures

Minor dental, dermatologic, and ophthalmologic procedures can comprise up to 20% of all surgical and nonsurgical procedures performed in patients who are receiving antithrombotic therapy.[21,55] As these procedures are typically associated with relatively little blood loss, a key question relates to the safety of continuing antithrombotic therapy around the time of the procedure and whether continuing treatment confers an increased risk of clinically important bleeding. A practical issue that also relates to the management of such patients is that most, if not all, minor procedures are undertaken in a clinic or other out-of-hospital setting. Consequently, bleeding that may occur after the procedure will occur while the patient is home and may generate concern and anxiety for the patient. Patients should, therefore, be given instructions to deal with potential bleeding, which usually requires prolonged local pressure over the site of a dental or dermatologic procedure. In addition, patients should be advised when bleeding is excessive and warrants medical attention.

In our review of randomized and nonrandomized prospective studies that assessed the risk of bleeding in patients who continue VKAs or antiplatelet drugs during minor procedures, which are summarized in Tables 4–8, we have focused on postprocedural bleeding. To distinguish bleeding that is clinically important and requires medical attention, from bleeding that does not require medical attention and is, typically, self-limiting, we classified bleeding into three categories: (1) major bleeding, which refers to bleeding that requires transfusion of ≥ 2 U packed RBCs[181]; (2) clinically relevant nonmajor bleeding, which refers to bleeding that is not major but requires medical attention (*eg*, application of wound dressing or additional sutures); and (3) minor bleeding, which refers to bleeding that is self-limiting,

Table 4—*Randomized Trials Assessing Continuation of Antithrombotic Therapy in Patients Undergoing Dental Procedures: Clinical Description and Results (Section 5.1)**

	Patients				Periprocedural Intervention			Clinical Outcomes, No./Total			
Study/yr	No.	Type of Treatment	Indication for AT Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Borea et al[182]/ 1993	30	VKA	MHV, n = 30	Dental extractions	15	Treatment: continue VKA + irrigation + tranexamic acid	10 d	0	Treatment: 1/15 (6.67%)	Treatment: 1/15 (6.7%)	Treatment: 0/15
					15	Control: stop VKA			Control: 0/15	Control: 2/15 (13.3%)	Control: 0/15
Evans et al[183]/ 2002	109	VKA	Not reported	Dental extractions	57	Treatment: continue VKA	Not specified	0	Treatment: 13/57 (22.8%)	Treatment: 2/57 (3.5%)	Treatment: 0/57
					52	Control: stop VKA day − 2			Control: 7/52 (13.5%)	Control: 0/52	Control: 0/52
Sacco et al[184]/ 2006	131	VKA	VTE = 16, AF = 39, MHV = 59, valvular heart disease = 13	Oral surgeries (dental extractions, fixture insertions, excision of cystic neoformations)	65	Treatment: VKA (full-dose) + tranexamic acid + sponge	10 d	0	Treatment: not reported	Treatment: 6/65 (9.2%)	Treatment: 0/65
					66	Control: VKA (reduced-dose) day − 3			Control: not reported	Control: 10/66 (15.2%)	Control: 0/66
Ardekian et al[209]/ 2000	39	Aspirin	VTE = 6, AF = 1, coronary artery disease = 20, stroke = 10	Oral surgery (simple and compound dental extractions, and more complex procedures)	19	Treatment: continue aspirin	Not specified	0	Treatment: 0/19	Treatment: 4/19 (21.1%)	Treatment: 0/19
					20	Control: stop aspirin day − 7			Control: 0/20	Control: 2/20 (10%)	Control: 0/20

*MHV = mechanical heart valve; AT = antithrombotic; AF = atrial fibrillation.

Table 5—*Randomized Trials Assessing Prohemostatic Interventions in Patients Undergoing Dental Procedures: Clinical Description and Results (Section 5.1)*

	Patients				Periprocedural Intervention			Clinical Outcomes, No./Total			
Study/yr	No.	Type of Treatment	Indication for AT Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Al-Belasy and Amer[185]/ 2003	30	VKA	VTE = 11, AF = 7, Stroke = 4, MHV = 3, VHD = 5	Dental extractions	15	Treatment: surgical glue	At least 10 d	0	Treatment: 0/15	Treatment: 0/15	Treatment: 0/15
					15	Control: gelatin sponge			Control: 0/15	Control: 5/15 (33.3%)	Control: 0/15
Carter and Goss[186]/ 2003	85	VKA	VTE = 20, AF = 14, CAD = 10, VHD = 33, stroke = 1	Dental extractions	43	Treatment: day − 2 tranexamic acid	Not specified	0	Treatment: 0/43	Treatment: 2/43 (4.6%)	Treatment: 0/43
					52	Control: day − 5 tranexamic acid			Control: 0/52	Control: 1/52 (1.9%)	Control: 0/52
Carter et al[187]/ 2003	49	VKA	VTE = 8, AF = 12, CAD = 5, stroke = 5, VHD = 19	Dental extractions	23	Treatment: surgical glue	10 d	0	Treatment: 0/23	Treatment: 2/23 (8.7%)	Treatment: 0/23
					26	Control: day − 7 tranexamic acid			Control: 0/26	Control: 0/26	Control: 0/26
Halfpenny et al[188]/ 2001	46	VKA	VTE = 16, AF = 12, CAD = 3, stroke = 2, MHV = 9, VHD = 3	Dental extractions	20	Treatment: surgical glue (Beriplast)	Not specified	0	Treatment: 0/20	Treatment: 2/20 (10%)	Treatment: 0/20
					26	Control: surgical glue (Surgicel)			Control: 0/26	Control: 1/26 (3.8%)	Control: 0/26
Ramström et al[189]/ 1993	89	VKA	VTE = 29, AF = 9, CAD = 6, stroke = 15, MHV = 29, VHD = 6	Oral surgeries (dental extractions, endodontic surgery)	44	Treatment: tranexamic acid	Not specified	0	Treatment: 2/44 (4.5%)	Treatment: 0/44	Treatment: 0/44
					45	Control: saline mouthwash			Control: 2/45 (4.4%)	Control: 10/45 (22.2%)	Control: 0/45

*VHD = valvular heart disease; CAD = coronary artery disease; see Table 4 for expansion of abbreviations.

Table 6—*Cohort Studies Assessing Continuation of Antithrombotic Therapy in Patients Undergoing Dental Procedures: Clinical Description and Results (Section 5.1)

	Patients				Periprocedural Intervention			Clinical Outcomes, No./Total			
Study/yr	No.	Type of Treatment	Indication for AT Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Blinder et al[197]/2001	249	VKA	VTE = 23, AF = 53, CAD = 27, VHD = 112	Dental extractions	190 59	Treatment: INR > 2 Control: INR, 1.5–2.0	Not specified	0	Treatment: 0/190 Control: 0/59	Treatment: 27/190 (14.2%) Control: 3/59 (5.1%)	Treatment: 0/190 Control: 0/59
Campbell et al[190]/2000	25	VKA	Not reported	Oral surgeries (dental extractions, soft tissue)	12 13	Treatment: continue VKA Control: stop VKA day − 3 to − 4	1 d	0	Treatment: 1/12 (8.33%) Control: 2/13 (15.4%)	Treatment: 0/12 Control: 0/13	Treatment: 0/12 Control: 0/13
Cannon and Dharmar[191]/2003	70	VKA	VTE = 15, AF = 10, CAD = 12, stroke = 16, MHV = 8, VHD = 9	Dental extractions	35 35	Treatment: continue VKA Control: stop VKA day − 2; sutures + glue	5 d	0	Treatment: 2/35 (5.7)% Control: 3/35 (8.6%)	Treatment: 0/35 Control: 0/35	Treatment: 0/35 Control: 0/35
Della Valle et al[198]/2003	40	VKA	MHV = 40	Dental extractions	40	Treatment: stop VKA; no control	Not specified	0	Treatment: 16/40 (40%)	Treatment: 2/40 (5.0%)	Treatment: 0/40
Devani et al[192]/1998	65	VKA	VTE = 19, AF = 12, CAD = 12, stroke = 8, MHV = 1, VHD = 16	Dental extractions	33 32	Treatment: continue VKA Control: stop VKA day − 2	5 d	0	Treatment: 1/33 (3.0%) Control: 1/32 (3.1%)	Treatment: 0/33 Control: 0/32	Treatment: 0/33 Control: 0/32
Gaspar et al[193]/1997	47	VKA	VTE = 13, AF = 2, MHV = 23, stroke = 4, VHD = 2, CAD = 3	Dental extractions	32 15	Treatment: continue VKA Control: stop VKA day − 3	10 d	0	Treatment: 0/32 Control: 0/15	Treatment: 2/32 (6.2%) Control: 1/15 (6.7%)	Treatment: 0/32 Control: 0/15
Madan et al[210]/2005	51	Aspirin	VTE = 18, CAD = 6, stroke = 4, arterial thromboembolism = 35, PAD = 5	Oral surgeries (not specified)	51	Treatment: continue aspirin; no control	14 d	0	Treatment: 1/51 (2.0%)	Treatment: 0/51	Treatment: 0/51
Martinowitz et al[199]/1990	40	VKA	VTE = 7, MHV = 18, VHD = 18, CAD = 6, stroke = 4	Dental extractions	40	Treatment: continue VKA; no control	Not specified	0	Treatment: 1/40 (2.5%)	Treatment: 0/40	Treatment: 0/40

Table 6—*Continued*

Study/yr	Patients: No.	Patients: Type of Treatment	Patients: Indication for AT Therapy	Type of Procedure	Periprocedural Intervention: No.	Periprocedural Intervention: Group	Follow-up	Clinical Outcomes, No./Total: Thromboembolism Events	Clinical Outcomes, No./Total: Minor Bleeding	Clinical Outcomes, No./Total: Clinically Relevant Nonmajor Bleeding	Clinical Outcomes, No./Total: Major Bleed
Ramli and Abdul Rahman[200]/2005	30	VKA	VTE = 1, AF = 9, VHD = 20	Dental extractions	30	Treatment: continue VKA; no control	10 d	0	Treatment: 3/30 (10%)	Treatment: 1/30 (3.3%)	Treatment: 0/30
Russo et al[201]/2000	104	VKA	MHV = 104, AF = 42	Dental procedures	104	Treatment: stop VKA day − 2; no control	3 mo	0	Treatment: 0/104	Treatment: 2/104 (1.9%)	Treatment: 0/104
Zanon et al[196]/2003	500	VKA	VTE = 33, AF = 59, stroke = 50, MHV = 39, VHD = 12, CAD = 78, other = 4	Dental extractions	250	Treatment: continue VKA	Not specified	0	Treatment: 0/250	Treatment: 4/250 (1.6%)	Treatment: 0/250
					250	Control: stop VKA			Control: 0/250	Control: 3/250 (1.2%)	Control: 0/250
Zusman et al[202]/1992	23	VKA	AF = 5, MHV = 2, VHD = 11, MI = 5	Dental extractions	23	Treatment: continue VKA; no control	Not specified	0	Treatment: 1/23 (4.3%)	Treatment: 3/23 (13%)	Treatment: 0/23
Barrero et al[203]/2002	125	VKA	VTE = 15, AF = 57, stroke = 18, MHV = 10, PAD = 2, VHD = 17, CAD = 2, other = 4	Dental extractions, root leverage, osteotomy	125	Treatment: continue VKA; no control tranexamic acid, pressure, irrigation, surgical	Not specified	0	Treatment: 1/229 (7.9%)	Treatment: 0/229	Treatment: 1/229 (0.4%)
Cieślik-Bielecka et al[204]/2005	40	VKA, aspirin	AF = 3, MHV = 11, CAD = 6, VHD = 3, CAD = 15, other = 5	Dental extractions, other oral surgery	40	Treatment: continue VKA; no control; sutures, sponge	Not specified	0	Treatment: 0/40	Treatment: 2/40 (5.0%)	Treatment: 0/40
Keiani Motlagh et al[205]/2003	40	VKA	AF = 6, MHV = 22, VTE = 12	Dental extractions, other oral surgery	40	Treatment: continue VKA; no control tranexamic acid†	14 d	0	Treatment: 0/40	Treatment: 0/40	Treatment: 0/40
Garcia-Darennes et al[206]/2003	96	VKA	MHV = 56, 40 (VTE, CAD, stroke)	Single and multiple dental extractions	96	Treatment: continue VKA; no control tranexamic acid†, sutures, glue	Not specified	0	Treatment: 0/96	Treatment: 3/96 (3.1%)	Treatment: 0/96
Saour et al[194]/1994	396	VKA	AF = 39, MHV = 396	Dental extractions	156	Treatment: continued VKA	Not specified	0	Treatment: 0/156	Treatment: 0/156	Treatment: 0/156
					240	Control: discontinue VKA day − 2			Control: 0/240	Control: 2/240 (0.8%)	Control: 0/240
Street and Leung[195]/1990	14	VKA		Dental extractions	12	Treatment: continue VKA	Not specified	0	Treatment: 0/12	Treatment: 1/12 (8.3%)	Treatment: 0/12
					2	Control: stop VKA + tranexamic acid + sutures			Control: 0/2	Control: 0/2	Control: 0/2

*See Tables 4, 5 for expansion of abbreviations. MI = myocardial infarction; PAD = peripheral artery disease.
†Mouthwash.

Table 7—*Cohort Studies Assessing Prohemostatic Interventions in Patients Undergoing Dental Procedures: Clinical Description and Results (Section 5.1)**

Patients				Periprocedural Intervention			Clinical Outcomes, No./Total			
Study	No.	Type of Treatment	Indication for AT Therapy	Type of Procedure	No.	Group	Follow-up, d	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Blinder et al[207]/ 1999	150	VKA	VTE = 5, AF = 26, CAD = 29, VHD = 70	Dental extractions	50	Treatment 1: tranexamic acid	10	0	Treatment 1: 4/50 (8%)	Treatment 1: 2/50 (4%)	Treatment 1: 0/50
					50	Treatment 2: 50 control: surgical glue			Treatment 2: 2/50 (4%)	Treatment 2: 2/50 (4%)	Treatment 2: 0/50
									-ve control 0/50	Control: 3/50 (6%)	Control: 0/50
Bodner et al[208]/ 1998	69	VKA	VTE = 14, AF = 23, MHV = 32	Dental extractions	69	Treatment: continue VKA; no control	10	0	Treatment: 3/69 (4%)	Treatment: 0/69	Treatment: 0/69

*PAD = peripheral artery disease; Treatment = treatment group; VHD = valvular heart disease; -ve control = patients not receiving antithrombotic therapy. See Tables 4, 5 for expansion of abbreviations..

usually with pressure at the bleeding site, and does not require medical attention.

5.1 Dental Procedures

Minor dental procedures assessed consist of single or multiple tooth extractions and endodontic (root canal) procedures. The studies assessing periprocedural antithrombotic therapy in patients having dental procedures are summarized in Tables 4–7.

5.1.1 Patients Who Are Receiving VKAs

Three randomized trials, summarized in Table 4, involving a total of 270 patients compared continuing VKA therapy with interrupting treatment prior to a dental procedure.[182–184] In these studies, there were no episodes of thromboembolism or major bleeding with either perioperative management strategy. In one trial that compared continuing VKA vs stopping treatment 2 days before the procedure, there were more clinically relevant nonmajor bleeds in patients who continued VKA therapy (26.3% vs 13.5%).[183] In another trial that compared continuing VKA therapy in conjunction with coadministered tranexamic acid mouthwash vs stopping VKA therapy 3 days before the procedure, there were fewer clinically relevant nonmajor bleeds in patients who continued VKA therapy (9.2% vs 15.2%).[184]

Five randomized trials, summarized in Table 5, compared different prohemostatic drugs in a total of 299 patients who continued VKA therapy around the time of a dental procedure.[185–189] In these studies, there were no episodes of thromboembolism or major bleeding. In one trial which compared tranexamic acid mouthwash to saline mouthwash in patients who continued VKA therapy, there were fewer clinically relevant nonmajor bleeds in patients who received tranexamic acid (0% vs 22.2%).[189] Another trial compared treatment with 2 or 5 days of tranexamic acid mouthwash before the procedure.[186] In this study, there was a lower incidence of clinically relevant nonmajor bleeding in patients who received 5 days of tranexamic acid (1.9% vs 4.6%). In the other trials, continuing VKA therapy while coadministering a prohemostatic agent was associated with no episodes of major bleeding although the incidence of clinically relevant nonmajor bleeding varied across studies.[185,187,188]

Seven prospective cohort studies, summarized in Table 6, assessed bleeding in patients who continued VKA therapy during dental extraction and in a control group of patients who interrupted VKA therapy before the procedure.[190–196] In one study involving 396 patients, of whom 156 continued VKA therapy and 240 discontinued this treatment, there were no major bleeds and the incidence of clinically

Table 8—*Cohort Studies Assessing Continuation of Antithrombotic Therapy in Patients Undergoing Dermatologic Procedures: Clinical Description and Results (Section 5.2)

	Patients				Periprocedural Intervention			Clinical Outcomes, No./Total			
Study	No.	Type of Treatment	Indication for Antithrombotic Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events, %	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Alcalay[212]/ 2001	93	VKA	AF = 10, CAD = 1, MHV = 3, other = 2	Cutaneous surgeries	16	Treatment: continue VKA	Not specified	0	Treatment: 0/16	Treatment: 0/16	Treatment: 0/16
					77	-ve control	Control: 0/77		Control: 0/77	Control: 0/77	
Bartlett[216]/ 1999	171	Aspirin	Not reported	Cutaneous surgeries	52	Treatment: continue aspirin	5–10 d	0	Treatment: 1/52 (2%)	Treatment: 2/52 (3.8%)	Treatment: 0/52
					119	-ve control			Control: 5/119 (4.2%)	Control: 4/119 (3.4%)	Control: 0/119
Billingsley and Maloney[213]/ 1997	306		Not reported	Cutaneous surgeries	81	Treatment 1: continue aspirin	1 d	0	Treatment 1: 17/81 (21%)	Treatment 1: 1/81 (1%)	Treatment 1: 0/81
		VKA, aspirin			12	Treatment 2: continue VKA			Treatment 2: 6/12 (50%)	Treatment 2: 1/12 (8%)	Treatment 2: 0/12
					213	-ve control			Control: 28/213 (13.1%)	Control: 1/213 (0.5%)	Control: 0/213
Kargi et al[214]/ 2002	102		Not reported	Cutaneous surgeries	37	Treatment 1: continue aspirin	6–10 d	0	Treatment 1: 8/37 (21.6%)	Treatment 1: 0/37	Treatment 1: 0/37
		VKA, aspirin			21	Treatment 2: continue VKA			Treatment 2: 7/21 (33.3%)	Treatment 2: 5/21 (23.8%)	Treatment 2: 0/21
					44	-ve control			Control: 6/44 (13.6%)	Control: 0/44	Control: 0/44
Shalom and Wong[217]/ 2003	253	Aspirin	Not reported	Cutaneous surgeries	41	Treatment = continued aspirin	3–6 mo	0	Treatment- 0/41	Treatment: 0/41	Treatment: 0/41
					212	-ve control			Control: 3/212 (1.4%)	Control: 0/212	Control: 0/212
Syed et al[215]/ 2004	96	VKA	Not reported	Cutaneous surgeries	47	Treatment = continued VKA	Not specified	0	Treatment: 0/47	Treatment: 12/47 (25.5%)	Treatment: 0/47
					49	-ve control			Control: 0/49	Control: 3/49 (6.1%)	Control: 0/49

*See Tables 4–7 for expansion of abbreviations.

relevant nonmajor or minor bleeding was low in patients who continued and interrupted VKA therapy, at 0% and 0.8%, respectively.[194] In another study that assessed bleeding in 250 patients who underwent dental extractions during VKA therapy and a control group of 250 patients who had dental extractions but were not receiving a VKA, there were no major bleeds reported, and the incidence of clinically relevant nonmajor bleeding was similar in the VKA and no VKA groups, of 1.6% and 1.2%, respectively.[196] Five additional smaller studies involving between 14 and 249 patients provided similar results, with no major bleeds reported. However, these studies reported incidences of minor bleeding of 0 to 8.3%. In 11 prospective cohort studies, summarized in Table 6, that assessed continuation of VKA therapy but without a control group, there were no major bleeds reported.[196–206] Two other cohort studies with a total of 211 patients, summarized in Table 7, assessed different prohemostatic agents in patients undergoing dental extraction and receiving a VKA.[207,208] There were no major bleeds reported, and the incidence of clinically relevant nonmajor and minor bleeding was 0 to 8%.

Taken together, these studies indicate that continuing VKA therapy around the time of a minor dental procedure does not confer an increase in clinically important major bleeding. However, these studies were not adequately powered to exclude the possibility that undertaking dental procedures during VKA therapy confers an increased risk for clinically relevant nonmajor or minor bleeding. Until such studies are undertaken, it is reasonable to consider coadministration of a local prohemostatic agent, which appears to decrease the risk for clinically relevant nonmajor and minor bleeding.

5.1.2 Patients Who Are Receiving Antiplatelet Drugs

In one small randomized trial of 39 patients that compared continuing or interrupting aspirin before a dental procedure, there were no major bleeds in both treatment arms but the incidence of clinically relevant nonmajor bleeding was higher in patients who continued aspirin therapy (21% vs 10%).[209] In a cohort study involving 51 patients who continued aspirin therapy around the time of a dental procedure, there were no major bleeds and clinically relevant nonmajor bleeding occurred in one patient.[210]

Studies are lacking in regard to patients who are receiving clopidogrel and require a dental procedure, although it is probable that the continuation of clopidogrel and aspirin in patients undergoing dental procedures will increase the risk of bleeding above that seen with aspirin alone.[211] In high-risk patients with a coronary stent implanted within the past year, or perhaps at any time in the past in the case of a drug-eluting stent, the risk of stent thrombosis with clopidogrel interruption probably outweighs the risk of procedure-related bleeding associated with continuation of treatment. In lower-risk patients without a coronary stent, periprocedural management is uncertain, although it is probably reasonable to interrupt clopidogrel therapy and to continue aspirin given that combined antiplatelet treatment will increase bleeding risk above that of the risk with either drug alone.

Recommendation

5.1. In patients who are undergoing minor dental procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure and coadministering an oral prohemostatic agent (Grade 1B)**. In patients who are undergoing minor dental procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure** (Grade 1C)**. In patients who are undergoing minor dental procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

5.2 Dermatologic Procedures

Minor dermatologic procedures assessed include excisions of basal and squamous cell carcinomas, actinic keratoses, and malignant or premalignant nevi. Studies of periprocedural antithrombotic management are summarized in Table 8.

5.2.1 Patients Who Are Receiving VKAs

Four cohort studies assessed continuing VKA therapy around the time of a dermatologic procedure in a total of 96 patients.[212–215] In one study that assessed 47 patients who continued VKA therapy (and 49 control patients who were not receiving VKA therapy at the time of procedure), there were no major bleeds but the incidence of clinically relevant nonmajor bleeding was higher in patients who continued VKA therapy (25.5% vs 6.1%).[215] There were similar findings in two other cohort studies,[213,214] whereas no bleeds were reported in a third study involving 16 patients who continued VKA therapy.[212]

5.2.2 Patients Who Are Receiving Antiplatelet Drugs

Four cohort studies assessed continuing aspirin therapy around the time of a dermatologic procedure

in a total of 211 patients.[213,214,216,217] There were no major bleeds associated with continuing aspirin. In two studies, minor bleeding was more frequent in patients who continued aspirin around the time of the procedure compared to patients who were not receiving aspirin (21% vs 13%, respectively; 21.6% vs 13.6%, respectively).[213,214] However, in two other cohort studies the incidence of minor bleeding appeared comparable in patients who received or who did not receive aspirin around the time of the procedure (1.9% vs 4.2%, respectively; 0% vs 1.4%, respectively).[216,217]

Data for patients who are receiving clopidogrel and require dermatologic procedures are limited to case reports of patients who developed thromboembolic events during antiplatelet therapy interruption.[218] Periprocedural management in such patients can follow that in patients undergoing dental or other minor procedures.

Recommendation

5.2. In patients who are undergoing minor dermatologic procedures and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C)**. In patients who are undergoing minor dermatologic procedures and are receiving aspirin, we recommend continuing aspirin around the time of the procedure** (Grade 1C)**. In patients who are undergoing minor dermatologic procedures and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

5.3 Ophthalmologic Procedures

Minor ophthalmologic procedures assessed are dominated by cataract extraction, which was undertaken in > 90% of patients studied. A small minority of patients studied had vitreoretinal or other ophthalmologic procedures. Our recommendations, therefore, pertain to patients undergoing cataract extraction. These studies are summarized in Table 9.

5.3.1 Patients Who Are Receiving VKAs

Six prospective cohort studies assessed bleeding in patients who continued VKA therapy during ophthalmologic surgery and in a control group of patients who were either not receiving VKA therapy or who interrupted VKA therapy before surgery.[219–224] Two other prospective cohort studies assessed bleeding in patients who continued VKA therapy during ophthalmologic surgery but did not have a control group.[225,226] In one prospective cohort study assessing patients who had cataract surgery, there was no apparent increase in arterial thromboembolic events in 208 patients who discontinued VKAs compared to 526 patients who continued VKAs and the incidence of such events appeared higher in patients who continued VKAs (1.14% vs 0.48%).[221] In these patients, there were no major or clinically relevant nonmajor bleeds. In another cohort study involving 639 patients who continued VKAs and 1,203 controls who were not taking VKAs around the time of cataract surgery, there were no arterial thromboembolic events.[219] There appeared to be a higher incidence of clinically relevant nonmajor bleeding (0.16% vs 0.08%) and minor bleeding (1.41% vs 0.67%) in patients who continued VKAs although there were no major bleeds reported. While other smaller cohort studies demonstrated similar results,[225,226] one cohort study involving 125 patients who had cataract surgery reported a high rate of major bleeding (8.7%).[224]

5.3.2 Patients Who Are Receiving Antiplatelet Drugs

A prospective cohort study assessing patients who underwent cataract surgery found no important increase in arterial thromboembolic events in 977 patients who interrupted aspirin compared to 3,363 patients who continued aspirin (0.20% vs 0.65%).[221] In these patients, there were no major or clinically relevant nonmajor bleeds and marginally higher clinically relevant nonmajor bleeds in patients who continued aspirin (0.06% vs 0%). Other studies reported similar results in patients undergoing cataract or vitreoretinal surgery.[222,223]

There are few data in regard to the safety of continuing clopidogrel in patients undergoing ophthalmologic surgery. One study of patients undergoing cataract surgery found that although subconjunctival hemorrhage was more common in patients who were receiving either clopidogrel or warfarin than aspirin or no antithrombotic drugs, there were no sight-threatening bleeding complications.[227] One study described a patient who was receiving aspirin and clopidogrel and underwent an intracapsular extraction and anterior vitrectomy in whom the postoperative course was complicated by extensive hyphema and vitreous hemorrhage that cleared within 3 months.[228] As with other minor procedures, perioperative management will be driven by thromboembolic risk.

Recommendation

5.3. In patients who are undergoing cataract removal and are receiving VKAs, we recommend continuing VKAs around the time of the procedure (Grade 1C)**. In patients who are un-**

Table 9—*Cohort Studies Assessing Continuation of Antithrombotic Therapy in Patients Undergoing Ophthalmologic Surgery: Clinical Description and Results (Section 5.3)***

	Patients				Periprocedural Intervention			Clinical Outcomes, No./Total (%)			
Study	No.	Type of Treatment	Indication for Antithrombotic Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Hirschman and Morby[219]/2006	1,842	VKA	Not reported	Cataract surgery	639	Treatment: continue VKA	10 d	0	Treatment-9/639 = 1.4%	Treatment: 1/63 (0.16%)	Treatment: 0/639
					1,203	-ve control			Control: 8/1203 (0.7%)	Control: 1/1203 (0.08%)	Control: 0/1203
Kallio et al[220]/2000	1,167	VKA, aspirin	Not reported	Cataract surgery (> 80%)	482	Treatment 1: stop aspirin day − 3l treatment 2: stop VKA day − 2	Not specified	0	Treatment 1: 18/482 (3.7%); treatment 2: 3/76 (3.9%)	Treatment 1: 0/482; treatment 2: 0/76	Treatment 1: 0/482; treatment 2: 0/76
					76	-ve control			Control: 25/609 (4.1%)	Control: 0/609	Control: 0/609
Katz et al[221]/2003	37,611	VKA, aspirin	VTE = 206, CAD = 793, stroke = 738, VHD = 248, CAD = 2,040, other = 169	Cataract surgery	3,363	Treatment 1: continue aspirin	10 d	Treatment 1: 22/3,363 (0.65%)	Treatment 1: 0/3,363	Treatment 1: 2/3,363 (0.06%)	Treatment 1: 0/3,363
					977	Treatment 2: stop aspirin		Treatment 2: 2/977 (0.20%)	Treatment 2: 0/977	Treatment 2: 0/977	Treatment 2: 0/977
					14,322	-ve control aspirin		Control aspirin: 33/14,322 (0.23%)	Control aspirin: 3/14,322 (0.02%)	Control aspirin: 5/14,322 (0.03%)	Control aspirin: 0/14,322
					526	Treatment 3: continue VKA		Treatment 4: 6/526 (1.14%)	Treatment 4: 0/526	Treatment 4: 0/526	Treatment 4: 0/526
					208	Treatment 4: stop VKA		Treatment 5: 1/208 (0.48%)	Treatment 5: 0/208	Treatment 5: 0/208	Treatment 5: 0/208
					18,215	-ve control VKA		Control VKA: 52/18,215 (0.29%)	Control VKA: 3/18,215 (0.02%)	Control VKA: 7/18,215 (0.04%)	Control VKA: 0/18,215
Lumme and Laatikainen[222]/1994	351	VKA, aspirin	Not reported	Cataract surgery	54	Treatment 1: continue aspirin	At least 3 d	0	Treatment 1: 6/54 (11.1%)	Treatment 1: 0/54	Treatment 1- 0/54
					17	Treatment 2: stop VKA			Treatment 2: 0/17	Treatment 2: 3/17 (17.6%)	Treatment 2- 0/17
					208	-ve control			Control: 21/208 (10.1%)	Control: 0/208	Control- 0/208
Narendran and Williamson[223]/2003	541	VKA, aspirin	VTE = 1,	Vitreoretinal surgery	60	Treatment 1: continue aspirin	Not specified	0	Treatment 1: 0/60	Treatment 1: 2/60 (3.3%)	Treatment 1- 0/60
			AF = 2,		7	Treatment 2: stop VKA	Treatment 2: 1/7 (14.3%)		Treatment 2: 1/7 (14.3%)	Treatment 2- 1/7 = 14.3%	
			MHV = 3, Other = 1		474	-ve control	Control: 10/474 (2.1%)		Control: 0/474	Control: 0/474	
Roberts et al[225]/1991	31	VKA, aspirin, dipyridamole, sulfinpyrazone	Not reported	Cataract surgery	31	Treatment: continue VKA; no control	2 mo	0	Treatment: 0/31	Treatment: 1/31 (3.2%)	Treatment- 0/31
Rotenstreich et al[226]/2001	35	VKA	VTE = 4, AF = 27, VHD = 4	Cataract surgery	35	Treatment: continue VKA; no control	30 d	0	Treatment: 2/35 (5.7%)	Treatment: 0/35	Treatment: 0/35

Table 9—*Continued*

Study	Patients			Periprocedural Intervention			Clinical Outcomes, No./Total (%)			
	No.	Type of Treatment	Indication for Antithrombotic Therapy	Type of Procedure	No.	Group	Follow-up	Thromboembolism Events	Minor Bleeding	Clinically Relevant Nonmajor Bleeding	Major Bleed
Wirbelauer et al[224]/2004	128	VKA	VTE = 9, AF = 11, MHV = 14, CAD = 17, VHD = 15, other = 26	Cataract surgery	103	Treatment: continue VKA	Not specified	0	Treatment: 0/103	Treatment: 0/103	Treatment: 9/103 = 8.7%
					19	Control: stop VKA 16 d prior			Control: 0/19	Control: 0/19	Control: 0/19

*See Tables 4–7 for expansion of abbreviations.

dergoing cataract removal and are receiving aspirin, we recommend continuing aspirin around the time of the procedure (Grade 1C)**. In patients who are undergoing cataract removal and are receiving clopidogrel, please refer to the recommendations outlined in Section 4.5 and Section 4.6.**

6.0 Perioperative Management of Antithrombotic Therapy Patients Who Require Urgent Surgical or Other Invasive Procedures

6.1 Patients Who Are Receiving VKAs

In the nonbleeding patient who requires rapid (within 12 h) reversal of the anticoagulant effect of VKAs because of an urgent surgical or other invasive procedure, treatment options that have been assessed in observational studies include fresh-frozen plasma, prothrombin concentrates, and recombinant factor VIIa.[229] No randomized trials, to date and to our knowledge, have compared these treatments in patients who require urgent reversal of anticoagulation.[230] In addition to these treatment options, all patients should receive vitamin K, at a dose of 2.5 to 5.0 mg po or by slow IV infusion.[231] Administering fresh-frozen plasma, prothrombin concentrates, or recombinant factor VIIa alone will temporarily override but will not eliminate the anticoagulant effect of VKAs, which persist until VKAs are endogenously metabolized or neutralized by vitamin K. For example, as fresh-frozen plasma has an elimination half-life of 4 to 6 h, not administering vitamin K will lead to reemergence of a VKA-associated anticoagulant effect within 12 to 24 h. If surgery is urgent but can be delayed for 18 to 24 h, the anticoagulant effect of VKAs is likely to be neutralized by IV vitamin K, at a dose of 2.5 to 5.0 mg without the need for blood product or recombinant factor VII administration.[230,232]

Recommendation

6.1. In patients who are receiving VKAs and require reversal of the anticoagulant effect for an urgent surgical or other invasive procedure, we suggest treatment with low-dose (2.5 to 5.0 mg) IV or oral vitamin K (Grade 1C)**. For more immediate reversal of the anticoagulant effect, we suggest treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose IV or oral vitamin K** (Grade 2C)**.**

6.2 Patients Who Are Receiving Antiplatelet Drugs

There is no pharmacologic agent that can reverse the antithrombotic effect of aspirin, clopidogrel, or

ticlopidine, which irreversibly inhibit platelet function. Consequently, patients who require an urgent surgical or other invasive procedure that requires normalized platelet function may receive transfused platelets, which would not be affected by prior administration of antiplatelet drugs.[233] However, the efficacy and safety of platelet transfusion in patients who are not thrombocytopenic and who require an urgent surgical or other invasive procedure are not known. One randomized trial in 11 healthy volunteers who received aspirin (325 mg loading dose, 81 mg maintenance dose) and clopidogrel (300-mg or 600-mg loading dose, 75-mg maintenance dose) found that subsequent transfusion of 12.5 U platelets led to normalized platelet function as determined by platelet function assays.[234] However, studies to assess the efficacy and safety of a platelet transfusion to neutralize the antiplatelet effects of aspirin or clopidogrel in the perioperative setting are lacking. Until such studies are done, it is reasonable to limit platelet transfusion to those patients who have excessive or life-threatening bleeding in the perioperative period.

Potential alternatives to platelet transfusion in patients who have been exposed to antiplatelet drugs are prohemostatic agents. These include ε-aminocaproic acid and tranexamic acid, which are antifibrinolytic agents, and 1-deamino-8-D-arginine vasopressin, which increases plasma levels of von Willebrand factor and associated coagulation factor VIII. These agents may improve platelet function in patients who have been exposed to antiplatelet drugs.[235] However, outside of the setting of cardiac surgery, these drugs have not been widely studied[113,236] and should be limited to patients who have excessive or life-threatening perioperative bleeding because of potential prothrombotic effects.

Recommendation

6.2. For patients receiving aspirin, clopidogrel, or both, are undergoing surgery and have excessive or life-threatening perioperative bleeding, we suggest transfusion of platelets or administration of other prohemostatic agents (Grade 2C)**.**

Conflict of Interest Disclosures

Dr. Ansell discloses that he has received consultant fees from Bristol-Myers Squibb, Roche Diagnostics, and International Technidyne Corporation. He is also on the speakers bureau for Roche Diagnostic Corporation and Sanofi-Aventis, and is the past president of the Anticoagulation Forum.

Dr. Douketis reveals no real or potential conflicts of interest or commitment.

Dr. Dunn discloses that he received grant monies from and is on the speakers bureau for Sanofi-Aventis. He has also served on advisory committees for Sanofi-Aventis, Eisai, and Roche Diagnostics.

Dr. Jaffer discloses that he has received consultant fees from Sanofi-Aventis and AstraZeneca, and that he is on the speakers bureau for Sanofi-Aventis.

Dr. Becker reveals no real or potential conflicts of interest or commitment.

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