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).

(CHEST 2008; 133:299–339S)

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

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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Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0675

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: No.	Patients: Indication for VKA Therapy	Patients: 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
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 ≤ 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*

	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
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)**

Study	Patients: No.	Patients: Type of Treatment	Patients: Indication for AT Therapy	Periprocedural Intervention: Type of Procedure	Periprocedural Intervention: No.	Periprocedural Intervention: Group	Follow-up, d	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
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.

Dr. Spyropoulos discloses that he has received consultant fees from Boehringer Ingelheim, and has served on the speakers bureau for Sanofi-Aventis and Eisai.

Dr. Berger discloses that he has spoken at Council on Medical Education-approved scientific symposia supported by Bristol-Myers Squibb, Sanofi-Aventis, the Medicines Company, AstraZeneca, Medtronic, Schering-Plough, Lilly, and Daiichi Sankyo. He has served as a consultant for PlaCor, Lilly, Daiichi Sankyo, Molecular Insight Pharmaceuticals, and CV Therapeutics. Dr. Berger also owns equity in Lumen, Inc (a company that is developing an embolic protection device).

References

1 Ansell JE. The perioperative management of warfarin therapy. Arch Intern Med 2003; 163:881–883
2 American Heart Association. Heart Disease and Stroke Statistics Update. Dallas, TX: American Heart Association, 2001
3 Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med 1999; 131:927–934
4 White RH, Kaatz S, Douketis J, et al. Comparison of the 30-day incidence of ischemic stroke and bleeding after major surgery in patients with or without atrial fibrillation (AF). J Thromb Haemost 2007; 5(suppl 1):O-M-035
5 McKenna R. Abnormal coagulation in the postoperative period contributing to excessive bleeding. Med Clin North Am 2001; 85:1277–1310
6 Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses: observations in 180 operations. JAMA 1978; 239:738–739
7 Katholi RE, Nolan SP, McGuire LB. The management of anticoagulation during noncardiac operations in patients with prosthetic heart valves: a prospective study. Am Heart J 1978; 96:163–165
8 Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. Br J Haematol 2003; 123:676–682
9 Anonymous. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295–1302
10 Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med 2003; 163:901–908
11 Kaplan RC, Tirschwell DL, Longstreth WT Jr, et al. Vascular events, mortality, and preventive therapy following ischemic stroke in the elderly. Neurology 2005; 65:835–842
12 Longstreth WT Jr, Bernick C, Fitzpatrick A, et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. Neurology 2001; 56: 368–375
13 Martinelli J, Jiminez A, Rabago G, et al. Mechanical cardiac valve thrombosis: is thrombectomy justified? Circulation 1991; 84(suppl):70S–75S
14 Kini AS, Lee P, Marmur JD, et al. Correlation of postper-

cutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004; 93:18–23
15 Landesberg G, Einav S, Christopherson R, et al. Perioperative ischemia and cardiac complications in major vascular surgery: importance of the preoperative twelve-lead electrocardiogram. J Vasc Surg 1997; 26:570–578
16 Stone GW, Aronow HD. Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy. Mayo Clin Proc 2006; 81:641–652
17 Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):576S–599S
18 Yang X, Alexander KP, Chen AY, et al. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 2005; 46:1490–1495
19 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for VTE: a meta-analysis. Ann Intern Med 2003; 139:893–900
20 Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004; 292:1555–1562
21 Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med 2004; 164:1319–1326
22 Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation 2004; 110:1658–1663
23 Dagi TF. The management of postoperative bleeding. Surg Clin North Am 2005; 85:1191–1213
24 Litaker D. Preoperative screening. Med Clin North Am 1999; 83:1565–1581
25 Jones HU, Muhlestein JB, Jones KW, et al. Preoperative use of enoxaparin compared with unfractionated heparin increases the incidence of re-exploration for postoperative bleeding after open-heart surgery in patients who present with an acute coronary syndrome: clinical investigation and reports. Circulation 2002; 106:I19–I22
26 Mangano DT. Multicenter Study of Perioperative Ischemia Research: aspirin and mortality from coronary bypass surgery. N Engl J Med 2002; 347:1309–1317
27 Lazio BE, Sumard JM. Anticoagulation in neurosurgical patients. Neurosurgery 1999; 45:838–847
28 Patterson BM, Marchand R, Ranawat C. Complications of heparin therapy after total joint arthroplasty. J Bone Joint Surg Am 1989; 71:1130–1134
29 Hoy E, Granick M, Benevenia J, et al. Reconstruction of musculoskeletal defects following oncologic resection in 76 patients. Ann Plast Surg 2006; 57:190–194
30 Nielson JD, Gram J, Holm-Nielsen A, et al. Postoperative blood loss after transurethral prostatectomy is dependent on in-situ fibrinolysis. Br J Urol 1997; 889–893
31 Watson CJ, Deane AM, Doyle PT, et al. Identifiable factors in post-prostatectomy haemorrhage: the role of aspirin. Br J Urol 1990; 66:85–87
32 Sorbi D, Norton I, Conio M, et al. Postpolypectomy lower GI bleeding: descriptive analysis. Gastrointest Endosc 2000; 51:690–696
33 Ihezue CU, Smart J, Dewbury KC, et al. Biopsy of the prostate guided by transrectal ultrasound: relation between warfarin use and incidence of bleeding complications. Clin Radiol 2005; 60:459–463
34 Wiegand UK, LeJeune D, Boguschewski F, et al. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. Chest 2004; 126:1177–1186
35 Wessler S, Gitel SN. Pharmacology of heparin and warfarin. J Am Coll Cardiol 1986; 8:10B–20B
36 Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):188S–203S
37 Pedersen AK, FitzGerald GA. Dose-related kinetics of aspirin: presystemic acetylation of platelet cyclooxygenase. N Engl J Med 1984; 311:1206–1211
38 Savcic M, Hauert J, Bachmann F, et al. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Haemost 1999; 25(suppl 2):15–19
39 Dunn AS, Spyropoulos A, Turpie AG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007; 5:2211–2218
40 Turpie AG, Douketis JD. Enoxaparin is effective and safe as bridging anticoagulation in patients with a mechanical prosthetic heart valve who reqire temporary interruption of warfarin because of surgery or an invasive procedure [abstract]. Blood 2004; 104:202A
41 Carrel TP, Klingenmann W, Mohacsi PJ, et al. Perioperative bleeding and thromboembolic risk during non-cardiac surgery in patients with mechanical prosthetic heart valves: an institutional review. J Heart Valve Dis 1999; 8:392–398
42 Larson BJ, Zumberg MS, Kitchens CS. A feasibility study of continuing dose-reduced warfarin for invasive procedures in patients with high thromboembolic risk. Chest 2005; 127: 922–927
43 White RH, McKittrick T, Hutchinson R, et al. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995; 122:40–42
44 Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. Clin Pharmacokinet 1996; 30:300–313
45 Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease–native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):457S–482S
46 Hylek EM, Regan S, Go AS, et al. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. Ann Intern Med 2001; 135:393–400
47 Gadisseur AP, van der Meer FJ, Adriaansen HJ, et al. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br J Haematol 2002; 117:940–946
48 Marietta M, Bertesi M, Simoni L, et al. A simple and safe nomogram for the management of oral anticoagulation prior to minor surgery. Clin Lab Haematol 2003; 25:127–130
49 Deerhake JP, Merz JC, Cooper JV, et al. The duration of anticoagulation bridging therapy in clinical practice may significantly exceed that observed in clinical trials. J Thromb Thrombolysis 2007; 23:107–113
50 Woods K, Douketis JD, Kathirgamanathan K, et al. Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. J Thromb Thrombolysis 2007; 24:93–97

51 Cannegieter SC, Rosendaal FR, Briet I. Thromboembolic and bleeding complications in patients with medical mechanical heart valve prostheses. Circulation 1994; 94:635–641
52 Herin D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude medical valve replacement: results of the German Experience with Low-Intensity Anticoagulation Study. Chest 2005; 127:53–59
53 Tominaga R, Kurisu K, Ochiai Y, et al. A 10-year experience with the Carbomedics cardiac prosthesis. Ann Thorac Surg 2005; 79:784–789
54 Galla JM, Fuhs BE. Outpatient anticoagulation protocol for mechanical valve recipients undergoing non-cardiac surgery [abstract]. J Am Coll Cardiol 2000; 35:531A
55 Spyropoulos AC, Turpie AGG, Dunn AS, et al. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. J Thromb Haemost 2006; 4:1246–1252
56 Ferreira I, Dos L, Tornos P, et al. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. Heart 2003; 89:527–530
57 Jaffer AK, Ahmed M, Brotman DJ, et al. Low-molecular-weight-heparins as periprocedural anticoagulation for patients on long-term warfarin therapy: a standardized bridging therapy protocol. J Thromb Thrombolysis 2005; 20: 11–16
58 Hammerstingl C, Tripp C, Schmidt H, et al. Periprocedural bridging therapy with low-molecular-weight heparin in chronically anticoagulated patients with prosthetic mechanical heart valves: experience in 116 patients from the prospective BRAVE registry. J Heart Valve Dis 2007; 16: 285–292
59 Santamaria MA, Mateo J, Pujol N, et al. Management of anticoagulation in patients who require colonoscopy or gastroscopy: saftey and efficacy of sodic bemiparin [Hibor] [abstract]. Blood 2004; 105:4060
60 Spandorfer JM, Lynch S, Weitz HH, et al. Use of enoxaparin for the chronically anticoagulated patient before and after procedures. Am J Cardiol 1999; 84:478–480
61 Tinmouth AH, Morrow BH, Cruickshank MK, et al. Dalteparin as periprocedure anticoagulation for patients on warfarin and at high risk of thrombosis. Ann Pharmacother 2001; 35:669–674
62 Wilson S, Morgan J, Gray L, et al. A model for perioperative outpatient management of anticoagulation in high-risk patients: an evaluation of effectiveness and safety. Can J Hosp Pharm 2001; 54:269–277
63 Malato A, Anastasio R, Cigna V, et al. Perioperative bridging therapy with low molecular weight heparin in patients requiring interruption of long-term oral anticoagulant therapy. Haematologica 2006; 91:10
64 Constans M, Santamaria A, Mateo J, et al. Low-molecular-weight heparin as bridging therapy during interruption of oral anticoagulation in patients who require colonoscopy or gastroscopy. Int J Clin Pract 2007; 61:212–217
65 Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):338S–400S
66 Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506–1511
67 Baudet EM, Oca CC, Roques XF, et al. A 5/12 year experience with the St. Jude Medical cardiac valve prosthesis: early and late results of 737 valve replacements in 671 patients. J Thorac Cardiovasc Surg 1985; 90:137–144
68 Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999; 131:492–501
69 Pearce LA, Hart RG, Halperin JL. Assessment of three schemes for stratifying stroke risk in patients with nonvalvular atrial fibrillation. Am J Med 2000; 109:45–51
70 Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864–2870
71 Gage BF, Van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004; 110:2287–2292
72 Baudo F, de Cataldo F, Mostarda G, et al. Management of patients on long-term oral anticoagulant therapy undergoing elective surgery: survey of the clinical practice in the Italian anticoagulation clinics. Intern Emerg Med 2007; 2:280–284
73 Garcia DA, Regan S, Henault L, et al. Risk of thromboembolism with short-term interruption of warfarin therapy Arch Intern Med 2008; 168:63–69
74 Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. Neurology 2003; 61:964–968
75 Douketis JD, Gu CS, Schulman S, et al. The risk of fatal pulmonary embolism after stopping anticoagulant therapy in patients with VTE. Ann Intern Med 2007; 147:766–774
76 Douketis JD, Kearon C, Bates S, et al. The risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458–462
77 Douketis JD, Foster GA, Crowther MA, et al. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med 2000; 160:3431–3436
78 Kyrle PA, Eichinger S. Deep vein thrombosis. Lancet 2005; 365:1163–1174
79 White R. The epidemiology of venous thromboembolism. Circulation 2003; 107(suppl 1):14–18
80 Spyropoulos AC, Dunn A, Turpie AG, et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical heart valves on long-term oral anticoagulatns: results from the REGIMEN registry [abstract]. J Am Coll Cardiol 2005;45:352A
81 Halbritter KM, Wawer A, Beyer J, et al. Bridging anticoagulation for patients on long-term vitamin-K-antagonists: a prospective 1 year registry of 311 episodes. J Thromb Haemost 2007; 3:2823–2825
82 Eckman MH, Beshansky JR, Durand-Zaleski I, et al. Anticoagulation for noncardiac procedures in patients with prosthetic heart valves. Does low risk mean high cost? JAMA 1990; 263:1513–1521
83 Katholi RE, Nolan SP, McGuire LB. Living with prosthetic heart valves: subsequent noncardiac operations and the risk of thromboembolism or hemorrhage. Am Heart J 1976; 92:162–167
84 Douketis JD, Crowther MA, Cherian SS. Perioperative anticoagulation in patients with chronic atrial fibrillation who are undergoing elective surgery: results of a physician survey. Can J Cardiol 2000; 16:326–330
85 Douketis JD, Crowther MA, Cherian SS, et al. Physician preferences for perioperative anticoagulation in patients with a mechanical heart valve who are undergoing elective noncardiac surgery. Chest 1999; 116:1240–1246
86 Centers for Disease Control and Prevention. CDC Fact Book, 2001–2002. Atlanta, GA: Centers for Disease Control and Prevention, 2003
87 Kearon C, Ginsberg JS, Julian JA, et al. Comparison of

fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of VTE. JAMA 2006; 296:935–942
88 Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003; 349:1019–1026
89 Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996; 335:540–546
90 O'Donnell M, Oczkowski W, Fang J, et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol 2006; 5:749–754
91 Büller HR, Bousser MG, Bouthier J, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008; 371: 278–280
92 Fanikos J, Tsilimingras K, Kucher N, et al. Comparison of efficacy, safety, and cost of low-molecular-weight heparin with continuous-infusion unfractionated heparin for initiation of anticoagulation after mechanical prosthetic valve implantation. Am J Cardiol 2004; 93:247–250
93 Amorosi SL, Tsilimingras K, Thompson D, et al. Cost analysis of 'bridging therapy' with low-molecular-weight heparin versus unfractionated heparin during temporary interruption of chronic anticoagulation. Am J Cardiol 2004; 93:509–511
94 Spyropoulos AC, Frost FJ, Hurley JS, et al. Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. Chest 2004; 125:1642–1650
95 Spyropoulos AC, Jenkins P, Bornikova L. A disease management protocol for outpatient perioperative bridge therapy with enoxaparin in patients requiring temporary interruption of long-term oral anticoagulation. Pharmacotherapy 2004; 24:649–658
96 Goldstein JL Larson LR, Yamashita BD, et al. Low molecular weight heparin versus unfractionated heparin in the colonoscopy peri-procedure period: a cost modeling study. Am J Gastroenterol 2001; 96:2360–2366
97 Douketis JD, Woods K, Foster GA, et al. Bridging anticoagulation with low-molecular-weight heparin after interruption of warfarin therapy is associated with a residual anticoagulant effect prior to surgery. Thromb Haemost 2005; 94:528–531
98 O'Donnell MJ, Kearon C, Johnson J, et al. Preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. Ann Intern Med 2007; 146:184–187
99 Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of VTE in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002; 162:1833–1840
100 Strebel N, Prins M, Agnelli G, et al. Preoperative or postoperative start of prophylaxis for VTE with low-molecular-weight heparin in elective hip surgery? Arch Intern Med 2002; 162:1451–1456
101 Cruickshank MK, Levine MN, Hirsh J, et al. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med 1991; 151:333–337
102 Anand SS, Yusuf S, Pogue J, et al. Relationship of activated partial thromboplastin time to coronary events and bleeding in patients with acute coronary syndromes who receive heparin. Circulation 2003; 107:2884–2888
103 Dolovich LR, Ginsberg JS, Douketis JD, et al. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of VTE: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000; 160:181–188
104 Tricoci P, Roe MT, Mulgund J, et al. Clopidogrel to treat patients with non-ST-segment elevation acute coronary syndromes after hospital discharge. Arch Intern Med 2006; 166:806–811
105 Fox KA, Goodman SG, Anderson FA Jr, et al. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes; the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003; 24:1414–1424
106 Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006; 295:306–313
107 Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293: 2126–2130
108 Patrono C, Coller B, FitzGerald GA, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects; the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl):234S–264S
109 Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets: I. Acetylation of a particulate fraction protein. J Clin Invest 1975; 56:624–632
110 Roth GJ, Stanford N, Majerus PW. Acetylation of prostaglandin synthase by aspirin. Proc Natl Acad Sci U S A 1975; 72:3073–3076
111 Taggart DP, Siddiqui A, Wheatley DJ. Low-dose preoperative aspirin therapy, postoperative blood loss, and transfusion requirements. Ann Thorac Surg 1990; 50:424–428
112 Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999; 100:1667–1672
113 Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet 2004; 43:963–981
114 Caplain H, Cariou R. Long-term activity of clopidogrel: a three-month appraisal in healthy volunteers. Semin Thromb Haemost 1999; 25(suppl 2):21–24
115 Lenz TL, Hilleman DE. Aggrenox: a fixed-dose combination of aspirin and dipyridamole. Ann Pharmacother 2000; 34: 1283–1290
116 Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, et al. Coronary stent restenosis in patients treated with cilostazol. Circulation 2005; 112:2826–2832
117 Thompson PD, Zimet R, Forbes WP, et al. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol 2002; 90:1314–1319
118. Schrör K. The pharmacology of cilostazol. Diabet Obes Metab 2002; 4(suppl 2):S14–S19
119 Münster T, Furst DE. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics, and drugs used in gout. 8th ed. New York, NY: McGraw-Hill, 2001
120 Münster T, Furst DE. Pharmacotherapeutic strategies for disease-modifying antirheumatic drug (DMARD) combinations to treat rheumatoid arthritis (RA). Clin Exp Rheumatol 1999; 17(6 suppl 18):S29–S36

121 Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999; 100:1667–1672
122 Steinhubl SR, Lauer MS, Mukherjee DP, et al. The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non-Q-wave myocardial infarctions. J Am Coll Cardiol 1998; 32:1366–1370
123 Schühlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. Circulation 1998; 98:104–111
124 Steinhubl SR, Berger PB, Brennan DM, et al. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. J Am Coll Cardiol 2006; 47:939–943
125 Gawaz M, Seyfarth M, Muller I, et al. Comparison of effects of clopidogrel versus ticlopidine on platelet function in patients undergoing coronary stent placement. Am J Cardiol 2001; 87:332–336
126 Müller I, Seyfarth M, Rudiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001; 85:92–93
127 Geiger J, Teichmann L, Grossmann R, et al. Monitoring of clopidogrel action: comparison of methods. Clin Chem 2005; 51:957–965
128 Steinhubl SR, Talley JD, Braden GA, et al. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study. Circulation 2001; 103:2572–2578
129 Kitchen L, Erichson RB, Sideropoulos H. Effect of drug-induced platelet dysfunction on surgical bleeding. Am J Surg 1982; 143:215–217
130 Ferraris VA, Swanson E. Aspirin usage and perioperative blood loss in patients undergoing unexpected operations. Surg Gynecol Obstet 1983; 156:439–442
131 Sharma AK, Ajani AE, Hamwi SM, et al. Major noncardiac surgery following coronary stenting: when is it safe to operate? Catheter Cardiovasc Interv 2004; 63:141–145
132 Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. Am J Cardiol 2005; 95:755–757
133 Ernst A, Eberhardt R, Wahidi M, et al. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 2006; 129:734–737
134 Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics–2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006; 113:e85–e151
135 Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502
136 Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006; 114:774–782
137 Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006; 34:1608–1616
138 Sethi GK, Copeland JG, Goldman S, et al. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting: Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. J Am Coll Cardiol 1990; 15:15–20
139 Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 2002; 13:97–103
140 Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. Circulation 2005; 112:1286–1292
141 Topol E. Aspirin with bypass surgery: from taboo to new standard of care. N Engl J Med 2002; 347:1359–1360
142 Alexander JH, Berger PB, Hafley G, et al. Impact of early clopidogrel use on angiographic and clinical outcomes following coronary artery bypass surgery: findings from PREVENT IV. Am Coll Cardiol 2006; 47(suppl A):932–257
143 Mehta RH, Roe MT, Mulgund J, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol 2006; 48:281–286
144 Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502
145 Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006; 114:774–782
146 Purkayastha S, Athanasiou T, Malinovski V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006; 92:531–532
147 Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol 2002; 40:231–237
148 Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass surgery by intravenous aprotinin during cardiothoracic surgery. Circulation 2004; 110:2004
149 Kapetanakis EI, Medlam DA, Petro KR, et al. Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae? Circulation 2006; 113:1667–1674
150 Akowuah E, Shrivastava V, Jamnadas B, et al. Comparison of two strategies for the management of antiplatelet therapy during urgent surgery. Ann Thorac Surg 2005; 1:149–152
151 van der Linden J, Lindvall G, Sartipy U. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: a double-blind, placebo-controlled, randomized clinical trial. Circulation 2005; 112(suppl I):276–280
152 Mangano DT, Tudor IC. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 254:353–365
153 Spiess BD, Royston D, Levy JH, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion 2004; 44:1143–1148
154 Carless PA, Moxey AJ, Stokes BJ, et al. Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. BMC Cardiovasc Disord 2005; 5:19
155 Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 2007; 115:2801–2813
156 Pleym H, Stenseth R, Wahba A, et al. Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. Anesth Analg 2004; 98:578–584
157 Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358:527–533
158 Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction: the PCI-CLARITY Study. JAMA 2005; 294:1224–1232
159 Kastrati A, von Beckerath N, Joost A, et al. Loading with 600

mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. Circulation 2004; 110:1916–1919
160 Patti G, Colonna G, Pasceri V, et al. A randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) Study. Circulation 2005; 111:2099–2106
161 Kastrati A, Mehilli J, Schulhen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. N Engl J Med 2004; 350:232–238
162 Hausleiter J, Kastrati A, Mehilli J, et al. A randomized trial comparing phosphorylcholine-coated stenting with balloon angioplasty as well as abciximab with placebo for restenosis reduction in small coronary arteries. J Intern Med 2004; 256:388–397
163 Kaluza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000; 35:1288–1294
164 Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003; 42: 234–240
165 Vicenzi MN, Meislitzer T, Heitzinger B, et al. Coronary artery stenting and non-cardiac surgery: a prospective outcome study. Br J Anaesth 2006; 96:686–693
166 McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004; 364:1519–1521
167 Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. Catheter Cardiovasc Interv 2005; 65:516–519
168 Compton PA, Zankar AA, Adesanya AO, et al. Risk of noncardiac surgery after coronary drug-eluting stent implantation. Am J Cardiol 2006; 98:1212–1213
169 Bakhru M, Saber W, Brotman D, et al. Is discontinuation of antiplatelet therapy after 6 months safe in patients with drug-eluting stents undergoing noncardiac surgery? Cleve Clin J Med 2006; 73:S23
170 Fleron MH, Dupuis M, Mottet P, et al. Non cardiac surgery in a patient with coronary stenting: think sirolimus now! Ann Fr Anesth Reanim 2003; 22:733–735
171 Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use of recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004; 110:2361–2367
172 Ferrari E, Benhamou M, Cerboni P, et al. Coronary syndromes following aspiring withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005; 45:456–459
173 Wilson S, Rihal CS, Bell MR, et al. Timing of coronary stent thrombosis in patients treated with ticlopidine and aspirin. Am J Cardiol 1999; 83:1006–1011
174 Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001; 103:1967–1971
175 Schouten O, Bax JJ, Poldermans D. Management of patients with cardiac stents undergoing noncardiac surgery. Curr Opin Anaesthesiol 2007; 20:274–278
176 Bergerson P, Rudondy P, Poyen V, et al. Long-term peripheral stent evaluation using angioscopy. Int Angiol 1991; 10:182–186
177 Ueda Y, Nanto S, Komamura K, et al. Neointimal coverage of stents in human coronary arteries observed by angioscopy. J Am Coll Cardiol 1994; 23:341–346
178 Cattaneo M. Platelet P2 receptors: old and new targets for antithrombotic drugs. Expert Rev Cardiovasc Ther 2007; 5:45–55
179 Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Coll Cardiol 2007; 49:734–739
180 Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. J Am Coll Cardiol 2007; 49:2145–2150
181 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients. J Thromb Haemost 2005; 3:692–694
182 Borea G, Montebugnoli L, Capuzzi P, et al. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery: an alternative method to discontinuing anticoagulant therapy. Oral Surg Oral Med Oral Pathol 1993; 75:29–31
183 Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002; 40:248–252
184 Sacco R, Sacco M, Carpenedo M, et al. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different INR targets. J Thromb Haemost 2006; 4:688–689
185 Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg 2003; 61:1405–1409
186 Carter G, Goss A. Tranexamic acid mouthwash–a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 2003; 32:504–507
187 Carter G, Goss A, Lloyd J, et al. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg 2003; 61:1432–1435
188 Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 92:257–259
189 Ramström G, Sindet-Pedersen S, Hall G, et al. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. J Oral Maxillofac Surg 1993; 51:1211–1216
190 Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? J Oral Maxillofac Surg 2000; 58:131–135
191 Cannon PD, Dharmar VT. Minor oral surgical procedures in patients on oral anticoagulants: a controlled study. Aust Dent J 2003; 48:115–118
192 Devani P, Lavery KM, Howell CJ. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? Br J Oral Maxillofac Surg 1998; 36:107–111
193 Gaspar R, Brenner B, Ardekian L, et al. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. Quintessence Int 1997; 28:375–379
194 Saour JN, Ali HA, Mammo LA, et al. Dental procedures in patients receiving oral anticoagulation therapy. J Heart Valve Dis 1994; 3:315–317
195 Street AM, Leung W. Use of tranexamic acid mouthwash in dental procedures in patients taking oral anticoagulants. Med J Aust 1990; 153:630

196 Zanon E, Martinelli F, Bacci C, et al. Safety of dental extraction among consecutive patients on oral anticoagulant treatment managed using a specific dental management protocol. Blood Coagul Fibrinolysis 2003; 14:27–30
197 Blinder D, Manor Y, Martinowitz U, et al. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. Int J Oral Maxillofac Surg 2001; 30:518–521
198 Della Valle A, Sammartino G, Marenzi G, et al. Prevention of postoperative bleeding in anticoagulated patients undergoing oral surgery: use of platelet-rich plasma gel. J Oral Maxillofac Surg 2003; 61:1275–1278
199 Martinowitz U, Mazar AL, Taicher S, et al. Dental extraction for patients on oral anticoagulant therapy. Oral Surg Oral Med Oral Pathol 1990; 70:274–277
200 Ramli R, Abdul Rahman R. Minor oral surgery in anticoagulated patients: local measures alone are sufficient for haemostasis. Singapore Dent J 2005; 27:13–16
201 Russo G, Corso LD, Biasiolo A, et al. Simple and safe method to prepare patients with prosthetic heart valves for surgical dental procedures. Clin Appl Thromb Haemost 2000; 6:90–93
202 Zusman SP, Lustig JP, Baston I. Postextraction hemostasis in patients on anticoagulant therapy: the use of a fibrin sealant. Quintessence Int 1992; 23:713–716
203 Barrero MV, Knezevic M, Martín MT. Oral surgery in the patients undergoing oral anticoagulant therapy. Medicina Oral 2002; 7:63–70
204 Cieslik-Bielecka A, Pelc R, Cieslik T. Oral surgery procedures in patients on anticoagulants: preliminary report. Kardiologia Polska 2005; 63:137–140
205 Keiani Motlagh K, Loeb I, Legrand W, et al. Prevention of postoperative bleeding in patients taking oral anticoagulants: effects of tranexamic acid. Rev Stomatol Chir Maxillofac 2003; 104:77–79
206 Garcia-Darennes F, Darennes J, Freidel M, et al. Protocol for adapting treatment with vitamin K antagonists before dental extraction. Rev Stomatol Chir Maxillofac 2003; 104:69–72
207 Blinder D, Manor Y, Martinowitz U, et al. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 88:137–140
208 Bodner L, Weinstein JM, Baumgarten AK. Efficacy of fibrin sealant in patients on various levels of oral anticoagulant undergoing oral surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 86:421–424
209 Ardekian L, Gaspar R, Peled M, et al. Does low-dose aspirin therapy complicate oral surgical procedures? J Am Dent Assoc 2000; 131:331–335
210 Madan GA, Madan SG, Madan G, et al. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. J Oral Maxillofac Surg 2005; 63:1262–1265
211 Allard RH, Baart JA, Huijgens PC, et al. Antithrombotic therapy and dental surgery with bleeding. Ned Tijdschr Tandheelkd 2004; 111:482–485
212 Alcalay J. Cutaneous surgery in patients receiving warfarin therapy. Dermatol Surg 2001; 27:756–758
213 Billingsley EM, Maloney ME. Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin, and nonsteroidal antiinflammatory agents: a prospective study. Dermatol Surg 1997; 23:381–383
214 Kargi E, Babuccu O, Hosnuter M, et al. Complications of minor cutaneous surgery in patients under anticoagulant treatment. Aesthetic Plast Surg 2002; 26:483–485
215 Syed S, Adams BB, Liao W, et al. A prospective assessment of bleeding and international normalized ratio in warfarin-anticoagulated patients having cutaneous surgery. J Am Acad Dermatol 2004; 51:955–957
216 Bartlett GR. Does aspirin affect the outcome of minor cutaneous surgery? Br J Plast Surg 1999; 52:214–216
217 Shalom A, Wong L. Outcome of aspirin use during excision of cutaneous lesions. Ann Plast Surg 2003; 50:296–298
218 Alam M, Goldberg LH. Serious adverse vascular events associated with perioperative interruption of antiplatelet and anticoagulant therapy. Dermatol Surg 2002; 28:992–998
219 Hirschman DR, Morby LJ. A study of the safety of continued anticoagulation for cataract surgery patients. Nurs Forum 2006; 41:30–37
220 Kallio H, Paloheimo M, Maunuksela EL. Haemorrhage and risk factors associated with retrobulbar/peribulbar block: a prospective study in 1383 patients. Br J Anaesth 2000; 85:708–711
221 Katz J, Feldman MA, Bass EB, et al. Risks and benefits of anticoagulant and antiplatelet medication use before cataract surgery. Ophthalmology 2003; 110:1784–1788
222 Lumme P, Laatikainen LT. Risk factors for intraoperative and early postoperative complications in extracapsular cataract surgery. Eur J Ophthalmol 1994; 4:151–158
223 Narendran N, Williamson TH. The effects of aspirin and warfarin therapy on haemorrhage in vitreoretinal surgery. Acta Ophthalmol Scand 2003; 81:38–40
224 Wirbelauer C, Weller A, Haberle H, et al. Cataract surgery under topical anesthesia with oral anticoagulants. Klin Monatsbl Augenheilkd 2004; 221:749–752
225 Roberts CW, Woods SM, Turner LS. Cataract surgery in anticoagulated patients. J Cataract Refract Surg 1991; 17: 309–312
226 Rotenstreich Y, Rubowitz A, Segev F, et al. Effect of warfarin therapy on bleeding during cataract surgery. J Cataract Refract Surg 2001; 27:1344–1346
227 Kumar N, Jivan S, Thomas P, et al. Sub-Tenon's anesthesia with aspirin, warfarin, and clopidogrel. J Cataract Refract Surg 2006; 32:1022–1025
228 Davies B. Combined aspirin and clopidogrel in cataract surgical patients: a new risk factor for ocular haemorrhage? Br J Ophthalmol 2004; 88:1226–1227
229 Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2004; 181:492–497
230 Dezee KJ, Shimeall WT, Douglas KM, et al. Treatment of excessive anticoagulation with phytodione (vitamin K): a meta-analysis. Arch Intern Med 2006; 166:391–397
231 Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytodione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 2003; 163:2469–2473
232 Raj G, Kumar R, McKinney WP. Time course of reversal of anticoagulant effect of warfarin by intravenous and subcutaneous phytodione. Arch Intern Med 2000; 159:2721–2724
233 Hongo RH, Ley J, Dick SE, et al. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol 2002; 40:231–237
234 Vilahur G, Choi BG, Zafar MU, et al. Normalization of platelet reactivity in clopidogrel-treated subjects. J Thromb Haemost 2007; 5:82–90
235 Levi MM, Vink R, de Jonge E. Management of bleeding disorders by prohemostatic therapy. Int J Hematol 2002; 76(suppl 2):139–144
236 Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. Drugs 2002; 62:2193–2211
237 Nutescu E, Helgason C. Outpatient dalteparin peri-procedure bridge therapy in patients maintained on long term warfarin. Stroke 2001; 32:328–329

Methodology for Antithrombotic and Thrombolytic Therapy Guideline Development*

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

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The American College of Chest Physicians (ACCP) invited a panel of experts, researchers, information scientists, and guideline methodologists to develop the eighth edition of ACCP evidence-based guidelines on antithrombotic and thrombolytic therapy. The process began with guideline authors specifying the population, intervention and alternative, and outcomes for each clinical question and defined criteria for eligible articles, including methodologic criteria, for each recommendation. The McMaster University Evidence-Based Practice Center, in collaboration with the guideline authors and methodologists, developed strategies and executed systematic searches for evidence. The resulting guidelines are organized in chapters that present a clear link between the evidence and the resulting recommendations. The panel identified questions in which resource allocation issues were particularly important and obtained input from consultants with expertise in economic analysis for these issues. Authors paid careful attention to the quality of underlying evidence and the balance between risks and benefits, both reflected in grades of recommendations. For recommendations that are particularly sensitive to underlying values and preferences, the panel made explicit the values underlying the recommendations. Thus, the process of making recommendations for the ACCP guidelines included explicit definition of questions, transparent eligibility criteria for including studies, comprehensive searches and methodologic assessment of studies, and specification of values and preferences and resource implications underlying recommendations where particularly relevant. In combination with our previous practice of grading recommendations according to their strength and the methodologic quality of the supporting studies, these methods establish our guideline methodology as evidence based. ***(CHEST 2008; 133:113S–122S)***

Key words: evidence-based medicine; grade; guideline development; guidelines; quality of evidence; recommendations

Abbreviations: ACCP = American College of Chest Physicians; EPC = evidence-based practice center; HSP = Health Science Policy; LMWH = low-molecular-weight heparin; RCT = randomized controlled trial; tPA = tissue plasminogen activator

The methodology for the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) built on the innovations of prior conferences. As with other iterations, the changing evidence base in the field of antithrombotic and thrombolytic research led to many updated and new recommendations. To further improve the quality of these guidelines, we have made additional changes to the methodology. Evidence-based approaches to guideline development include acknowledgment of factors other than evidence that inevitably influence recommendations—values and preferences. For the first time, we involved consultants whose role was to focus on patient value and preference issues. We also implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in guideline develop-

ment by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant.[1] To accomplish this task, we involved experts in economic analysis in developing these recommendations.[1,2] In addition, for this iteration of the guidelines, we collaborated with the McMaster University Evidence-Based Practice Center (EPC) [Hamilton, ON, Canada], one of the 13 North American EPCs.

To maintain transparency of the guideline development, we followed explicit rules for managing conflicts of interest. Before participating on the panel, all participants submitted conflict-of-interest statements that were reviewed by the ACCP Health Science and Policy (HSP) Committee. Participants' potential conflicts are listed prominently in the front section of the guideline document.[3] The panelists updated their conflict-of-interest disclosures again before the final conference and before publication. These disclosures are published with the guidelines and posted on the *CHEST* journal Web site (www.chestjournal.org).

The development of evidence-based guidelines includes explicitly defining the question that the guideline or recommendation is addressing; formulating eligibility criteria for evidence to be considered; conducting a comprehensive search for evidence; evaluating study quality; summarizing the studies; balancing the benefits and downsides of the alternative management strategies; and, finally, acknowledging values and preferences underlying the recommendations, including considerations on expenditures.[4–6] This process ends with a recommendation for action and a grading of that recommendation according to the balance of desirable effects (benefits), undesirable effects (harms, burden, and resource expenditures), and the quality of the evidence. We followed the methodology for grading the quality of evidence and strength of recommendations that the ACCP codified during a recent ACCP task force meeting. The grading system adopted was a modification from that developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group.[7–9] This article describes the methodology for guideline development for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)*. Figure 1 summarizes this process.

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Dr. Schünemann is funded by a European Commission: The Human Factor, Mobility and Marie Curie Actions. Scientist Reintegration Grant: IGR 42194—"GRADE."
Manuscript accepted December 20, 2007.

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DOI: 10.1378/chest.08-0666

Guideline Development for the Eighth ACCP Conference on Antithrombotic and Thrombolytic Therapy

Panel Selection Process

The criteria for panel selection were an established track record in the relevant clinical or research area, international and gender representation, prior involvement with the ACCP Conference on Antithrombotic and Thrombolytic Therapy, and absence of conflicts of interest that could not be resolved. The senior editors suggested individual chapter chairs as well as chapter members. Chapter chairs also made suggestions for the inclusion of chapter members. All panel members were approved by the ACCP HSP Committee after review of their curriculum vitae.

Defining the Clinical Question

Developing a clinical practice guideline should begin with specifying a clinical question that defines the relevant population, alternative management strategies (comparison), and outcomes.[10] For the current ACCP guidelines, authors defined one question for each recommendation or set of recommendations. Readers can find these questions in the corresponding table of each chapter containing practice recommendations.

Presentation of Evidence and Recommendations

To provide a transparent, explicit link among questions, evidence, and recommendations, the section numbering in each chapter corresponds to numbers in the corresponding table in the chapters, which specifies the patients, interventions, and outcomes; the section numbering also corresponds to the numbering of the recommendations themselves.

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria. For many recommendations, authors re-

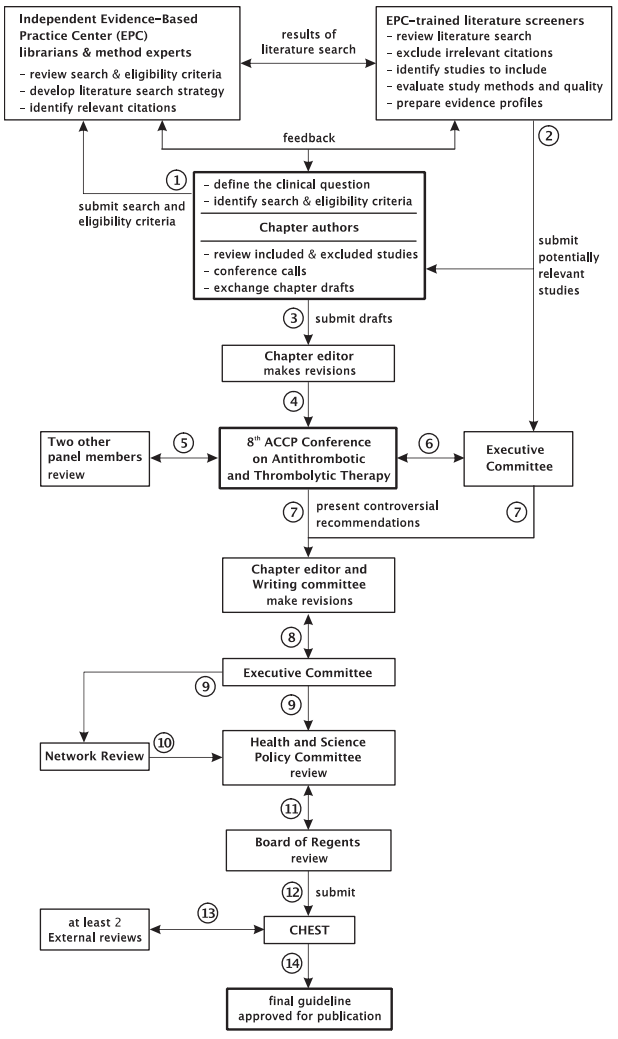

FIGURE 1. Methodology for guideline development and review. Process steps are indicated by the numbers adjacent to arrows in this algorithm. An executive committee comprising methodologists, content experts, and an HSP liaison coordinated the writing of chapters for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)*.[7] After identification of search and eligibility criteria by chapter authors, librarians in collaboration with two of the executive methodologists searched for evidence.[1,2,7] Trained literature screeners reviewed citations and removed irrelevant citations under supervision of one executive methodologist and the chapter editors.[1,2] Chapter authors revised previous chapters or wrote new chapters in close collaboration with all editors and authors of other chapters.[3,4,5,8] The review process includes simultaneous reviews by the appropriate ACCP NetWork and the HSP before advancing to the Board of Regents.[7–11] Both of the latter two committees must approve the manuscript before it can be submitted to *CHEST*.[12] The editor-in-chief of the journal sends the manuscript to at least two external reviewers before acceptance for publication.[13,14]

stricted eligibility to randomized controlled trials (RCTs). For example, as in previous editions, Albers et al[11] considered whether clinicians should offer thrombolytic therapy in acute stroke. They defined *patients* as anyone presenting with acute thrombotic stroke (divided into presentation of < 3 h and > 3 h after onset of symptoms), *intervention* as any thrombolytic regimen compared to no intervention or placebo, and *outcome* as death or functional status based on assessment with a validated functional status instrument. The methodology was restricted to RCTs. This question yielded several recommendations, including whether patients with acute ischemic stroke presenting within 3 h of symptom onset should receive IV tissue plasminogen activator (tPA).

For many questions, randomized trials did not provide sufficient data, and chapter authors included observational studies when randomized trials were not the most appropriate design to address the research question. In particular, randomized trials are not necessarily the best design to understand risk groups, that is, the baseline or expected risk of a given event for certain subpopulations. Because no interventions are typically examined in questions about prognosis, one replaces interventions by the duration of exposure measured in time. For example, to obtain information about the risk of ischemic stroke in patients with atrial fibrillation in specific risk groups, the sensible question was: In patients with atrial fibrillation differing in age, BP, left ventricular function, or history of previous embolic events, what is the risk of stroke or death over a given time period?

Identifying the Evidence

To identify the relevant evidence, a team of librarians and research associates at the McMaster University EPC conducted comprehensive literature searches. Methodologic experts (including the editors) and the EPC librarians reviewed each question to ensure the development of a comprehensive search strategy. For example, for questions about antiplatelet agents, the EPC consulted chapter authors to ensure that the search included all relevant antiplatelet agents. More specifically, authors then decided whether to include dipyridamole in a search that already included aspirin, clopidogrel, and ticlopidine.

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration. These searches updated our more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.[3,6]

The EPC team conducted separate searches for systematic reviews; RCTs; and, if applicable, observational studies. For observational studies, searches were not restricted in terms of methodology. Although increasing the probability of identifying all published studies, this sensitive approach resulted in large numbers of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search using criteria of increased specificity to reduce the number of irrelevant citations that the authors received. These irrelevant citations included press news, editorials, narrative reviews, single-case reports, studies that included fewer participants than specified by authors as an inclusion criterion, animal studies (any nonhuman studies), and letters to the editor. Authors did not include data from abstracts of meetings for the development of recommendations, and we did not explicitly use Internet sources to search for research data. Authors were encouraged, however, to mention abstracts that reported on groundbreaking data that were particularly relevant to a specific question in the chapters in order to alert readers that new, fully published evidence might become available shortly.

Standard Consideration of Study Quality

High-quality clinical guidelines should pay careful attention to the methodologic quality of the studies that form the basis of their recommendations. Using the example of the prevention of venous thromboembolism during air travel, Table 1 shows the criteria for assessment of study quality (randomization, concealment or treatment allocation, blinding, completeness of follow-up, and whether the analysis was performed according to the intention-to-treat principle), and Table 2 shows the presentation of results that were circulated to the authors. Whereas all authors attended to these criteria, we have summarized the results of the quality assessment for only a minority of the recommendations. Readers can find these summaries in an online appendix to the recommendations (see online supplemental data).

In assessing the quality of observational studies, we did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up. Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. We did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label "case series" unless they met the following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

We labeled studies that met these criteria "cohort studies without internal controls." Studies with internal comparisons received the label "cohort studies with concurrent controls" or "cohort studies with historical controls." These cohort studies may succeed or fail to ensure settings, similar time frames, adjustment for differences in patients' characteristics, and follow-up with patients. These features were captured in descriptive tables provided to authors when requested from the EPC.

Summarizing Evidence

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation. For example, Albers et al[11] used a systematic review and metaanalysis as the foundation for their recommendation on IV streptokinase for acute ischemic stroke between 0 and 6 h of symptom onset (chapter on Stroke, Section 1.3). Geerts et al[12] used several metaanalyses for their recommendations (chapter on Prevention of Venous Thromboembolism, *eg*, Section 2).

For the first time for a small number of recommendations (see chapters Ansell et al, Warkentin et al, Geerts et al, Kearon et al, Albers et al, Harrington et al, Becker et al, Sobel and Verhaeghe, and Bates et al), we systematically examined the impact of quality of design and implementation of individual studies, precision, consistency and directness of results, likelihood of reporting bias, and presence of very large effects on the quality of the evidence. For recommendations in which we did so, we present tables that summarize these features. Table 3 provides an example.

Pooled analyses from high-quality systematic reviews formed summary data on which panelists based their recommendations wherever possible. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefits and downsides (risk, burden, and cost). When pooled

Table 1—*Example of Methodologic Evaluation of Studies

Study, yr	Intervention	Randomization Concealed	Blinding	No Outcome, n/N (%)	Analysis	Comments
Travel socks						
Scurr/2001	No prophylaxis Socks: below-knee stockings (ankle pressure, 18–22 mm Hg), starting preflight	Yes: sealed envelope	Subjects: no Outcome assessors: yes	No prophylaxis: 16/116 (14) Socks: 15/115 (13%)	ITT	Designed as a pilot study
Belcaro/2002	No prophylaxis Socks: below-knee stockings (maximum ankle pressure, 25 mm Hg), starting 6–10 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	Combined: 52/885 (6)	NR	Subject recruitment process NR Exclusion criteria NR Method of randomization NR Specific stockings used NR DVT screening test not validated Dropouts/group NR
Belcaro/2002	No prophylaxis Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 17/331 (5) Socks: 11/326 (3)	ITT	Subject recruitment process NR Method of randomization NR DVT screening test not validated Source of funding NR
Cesarone/2003	No prophylaxis Socks: below-knee stockings (ankle pressure, 12–18 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 21/190 (11) Socks: 14/186 (8)	ITT	Subject recruitment process NR Exclusion criteria not defined Method of randomization NR DVT screening test not validated Source of funding NR
Cesarone/2003	No prophylaxis Socks: below-knee travel socks (ankle pressure, 20–30 mm Hg), starting 2–3 h preflight	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 6/144 (4) Socks: 2/140 (1)	ITT	Subject recruitment process NR Exclusion method of randomization NR DVT screening test not validated Unclear how many subjects were randomized in part II (n = 285 or 134) Source of funding NR Criteria not defined
Belcaro/2003	No prophylaxis + video Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 3–4 h preflight + video	Probably not (NR)	Subjects: no Outcome assessors: no	No prophylaxis: 12/114 (11) Socks: 7/110 (6)	ITT	Subject recruitment process NR Exclusion criteria not defined Method of randomization NR DVT screening test not validated Source of funding NR
LMWH vs no prophylaxis						
Cesarone/2002	No prophylaxis Enoxaparin 1 mg/kg, 2–4 h preflight	Probably not (NR)	Subjects: no Outcome assessors: probably not	No prophylaxis: 17/100 (17) Enoxaparin: 18/100 (18)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication Subject recruitment process NR Flight duration NR Method of randomization NR DVT screening test not validated Source of funding NR

Table 1—*Continued*

Study, yr	Intervention	Randomization Concealed	Blinding	No Outcome, n/N (%)	Analysis	Comments
Aspirin vs no prophylaxis						
Cesarone/2002	No prophylaxis Aspirin 400 mg × 3 d, starting 12 h preflight	Probably not (NR)	Subjects: no Outcome assessors: probably not	No prophylaxis: 17/100 (17) Aspirin: 16/100 (16)	Per protocol	Abstract reports an additional subject group (LMWH + socks) not mentioned in publication Subject recruitment process NR Flight duration NR Method of randomization NR DVT screening test not validated Source of funding NR

*ITT = intention to treat; NR = not reported; DVT = deep vein thrombosis.

estimates of effects were not available, the EPC conducted metaanalysis to obtain pooled estimates for specific questions. These were questions that authors had specifically identified. Table 3 presents an example of a Grading of Recommendations Assessment, Development and Evaluation evidence profile prepared by the EPC.[7,13]

Another chapter in this supplement details the basic grading of methodologic quality.[8] In brief, consistent results from RCTs or observational studies with very strong effects result in Grade A recommendations; inconsistent results from RCTs or RCTs with important methodologic limitations receive Grade B, and observational studies without very strong effects result in Grade C quality of evidence.

Group-Specific Recommendations

The absolute magnitude of treatment effects may be very different in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for atrial fibrillation patients is likely close to 50% across risk groups, this translates into absolute risk reductions of $< 1\%$ per year in the lowest risk groups, and in the vicinity of 5% per year in the highest risk groups. Clearly, optimal management must differ across risk groups, and this is reflected in the recommendations of our atrial fibrillation panel.

In general, we have endeavored to make our recommendations as specific as possible for patient subgroups differing according to risk. Whenever valid prognostic data were available, we used them to estimate absolute effects and made recommendations accordingly. Unfortunately, reliable prognostic indexes are not usually available, limiting the extent to which such group-specific recommendations are possible.

Acknowledge Values and Preferences and Resource Use Underlying Recommendations

Under ideal circumstances, knowledge of average patient values and preferences would be available for every recommendation, the panel members would summarize these values and preferences, and they would be integrated into the recommendations that guideline developers make. We asked all chapter chairs before beginning the searches for the relevant literature to identify recommendations that they believed were particularly sensitive to patients' values and preferences. Moderate-quality evidence regarding values and preferences bearing directly on the recommendations proved available for only the chapter that addresses antithrombotic therapy in patients with atrial fibrillation. Our panelists beared in mind what average patient values and preferences may be; the process, however, is speculative.[14]

Our main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation. For example, Albers et al[11] suggest for patients with acute ischemic stroke of > 3 h but < 4.5 h that clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA (Grade 1A). The authors noted in the corresponding values and preferences statement, "This recommendation assumes a relatively low value on small increases in long-term functional improvement, a relatively high value on avoiding acute intracranial hemorrhage and death, and a relatively high degree of risk aversion."

In addition, we involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to

Table 2—*Example Randomized Trials of Thromboprophylaxis in Air Travelers (Partial Presentation of All Trials): Clinical Description and Results

Study Year	Interventions	Risk Group/Flight Duration	Patients Analyzed, No./Total (%)	Time to Screening	DVT, No./Total (%); RR (95% CI)	SVT, No./Total (%); RR (95% CI)	Edema Mean (SD)	Comments
Travel socks								
Scurr, 2001	No prophylaxis Socks: below-knee stockings (ankle pressure 18–22 mm Hg), starting preflight	Low/18–36 h	No prophylaxis: 100/116 (86) Socks: 100/115 (87)	< 48 h	No prophylaxis: 12/100 (12) Socks: 0/100 RR: 0.04 (0.00–0.67)	No prophylaxis: 0/100 Socks: 4/100 (4%) RR: 9.00 (0.49–165.0)	NR	No proximal DVT
Belcaro, 2002	No prophylaxis Socks: below-knee stockings (maximum ankle pressure, 25 mm Hg)	High/10–15 h	Combined: 833/885 (94)	On arrival	No prophylaxis: 19/422 (5) Socks: 1/411 (0%); 0.05 (0.01–0.40)	No prophylaxis: 8/422 (2) Socks: 0/411; 0.06 (0.00–1.04)	NR	Proximal DVT NR
Belcaro, 2002	No prophylaxis Socks: below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 2–3 h preflight	Low to medium/7–12 h	No prophylaxis: 314/331 (95) Socks: 315/326 (97)	On arrival	No prophylaxis: 7/314 (2) Socks: 0/315; 0.07 (0.00–1.16)	No prophylaxis: 5/314 (2) Socks: 0/315; 0.09 (0.01–1.63)	Short flight (7–8 h) No prophylaxis (n = 179): 6.7 (3.1) Socks (n = 179): 2.2 (1.1) [p < 0.005] Long flight (11–12 h) No prophylaxis (n = 135): 8.1 (2.9) Socks (n = 136): 2.6 (1.6) [p < 0.05]	Subjects on 7- to 8-h flights randomized separately from those on 11- to 12-h flights 5/7 DVTs in no-prophylaxis group were proximal

*RR = relative risk; SVT = superficial vein thrombosis; see Table 1 for expansion of abbreviations.

Table 3—*Example of Evidence Profile

Quality Assessment								Summary of Findings				
								Patients, No./Total (%)		Effect†		
No. of Studies	Design	Limitations	Consistency	Directness	Precision	Reporting Bias	Magnitude of Effect	Compression Stockings (Flight Socks)	Control	Relative Risk (95% CI)	Events Prevented per 1,000 Treated	Quality
DVT												
6	RCT	See Table 2	No important inconsistency	No problems	No problems	No reporting bias	Not applicable‡	2/1,239 (0.2)	46/1,245 (3.7)	0.09 (0.03–0.26)	High risk: 50 per 1,000 Low risk: 20 per 1,000	Low
SVT												
5	RCT	See Table 2	Some inconsistency	No problems	Some imprecision§	No reporting bias	Not applicable†	5/754 (0.7)	10/751 (1.3)	0.47 (0.07–3.12)‖	Not significant	Low

*See Tables 1 and 2 for expansion of abbreviations.
†All metaanalyses results are based on random effects models (more conservative), using Cochrane Collaboration Review Manager software (RevMan).
‡Despite the low relative risk, 0.1, do the methodologic limitations lower the confidence in this large effect?
§95% confidence interval includes no effect.
‖Based on metaanalysis of four studies. One study reported no cases of superficial vein thrombosis in either the treatment (0/97 patients) or control group (0/98 patients) and was automatically dropped by RevMan during metaanalysis.

ensure that the guidelines adequately represented the views of patients.[11,15] This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

In previous iterations of these guidelines, we did not have a standard or coherent approach to dealing with resource allocation (cost) issues. For these guidelines, we implemented recommendations of a recent ACCP task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant.[1] We relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that we considered very important to the decision. The methods and examples for this process are described in the article by Matchar and Mark in this supplement.[2] Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Grading Strength of Recommendation

A systematic approach to grading the strength of treatment recommendations can minimize bias and aid interpretation of treatment recommendations. Chapter authors have graded their recommendations as strong (Grade 1, desirable effects much greater than undesirable effects or *vice versa*) and worded the recommendation accordingly as "we recommend" or as weak (Grade 2, desirable effects not clearly greater or less great than undesirable effects) and worded the recommendation as "we suggest." They also have graded the methodologic quality of the underlying evidence. Another chapter in this supplement details our approach to grading recommendations.[8]

Finalizing and Harmonizing Recommendations

After having completed the steps we have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Fig 1 shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each

chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

Review by ACCP and External Reviewers

The ACCP HSP established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the editors, the guidelines underwent review by appropriate NetWorks of the ACCP (for these guidelines, the Cardiovascular and Pulmonary Vascular NetWorks), the HSP, and the Board of Regents. The latter two have the right of approval or disapproval but usually work with the guideline authors and editors to make necessary revisions before final approval. Each group identified primary reviewers who read the full set of chapters as well as individual committee members who were responsible for reviewing one or more chapters. The reviewers considered both content and methodology as well as whether there was balanced, not biased, reporting and adherence to HSP processes. Finally, the *CHEST* editor-in-chief read and forwarded the manuscripts for nonbiased, independent, external peer review before acceptance for publication.

Limitations of These Guideline Development Methods

Limitations of these guidelines include the possibility that some authors followed this methodology more closely than others, although the development process was centralized by an EPC and supervised by the editors. Second, it is possible that we missed relevant studies in spite of the comprehensive searching process. Third, despite our efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines, resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fourth, we performed only few statistical pooling exercises of primary study results. Finally, sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

Future Directions of ACCP Guidelines

Future iterations of the current guidelines will continue to address the limitations of the current iteration. For example, we asked authors making clinical recommendations to consider concealment; blinding; loss to follow-up of individual studies; and precision, consistency, directness, and likelihood of reporting bias when assigning a grade (*ie*, A, B, or C) to the quality of the evidence for a given recommendation. Although final decisions regarding the quality of evidence must remain the prerogative of the panelists, a central process for initially generating these judgments would improve their uniformity. To further improve the quality of these evidence-based recommendations, our next objective is to extend the central assessment of methodologic quality of individual studies, overall judgments of evidence quality, and summaries of findings that we began in this iteration. This initiative will further enhance the consistency and transparency of the approach to grading quality of evidence and strength of recommendations for the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition)*.

Conclusion

For the eighth edition of the *Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*, we have built on the methods of the 7th edition that introduced explicit definition of questions, transparent eligibility criteria for including studies, methodologic evaluation of RCTs included, and specification of values and preferences and resource considerations underlying recommendations where particularly relevant. In combination with our previous practice of grading recommendations according to their strength and the methodologic quality of the supporting studies, these methods establish our guideline methodology as evidence based.

ACKNOWLEDGMENT: We would like to acknowledge the work of Parminder Raina, Mary Gauld, and Dave Cameron at the McMaster University Evidence-Based Practice Center.

Conlict of Interest Disclosures

Dr. Schünemann reports no personal payments from for-profit organizations, but he has received research grants and/or

honoraria that were deposited into research accounts or received by a research group that he belongs to from AstraZeneca (research grant, honoraria), Amgen (research grant), Barilla (research grant), Chiesi Foundation (honorarium), Lily (honorarium), Pfizer (research grant, honorarium), Roche (honorarium), and UnitedBioSource (honorarium) for development or consulting regarding quality-of-life instruments for chronic respiratory diseases and as lecture fees related to the methodology of evidence-based practice guideline development and/or research methodology. He is documents editor for the American Thoracic Society and senior editor of the American College of Chest Physicians Antithrombotic and Thrombolytic Therapy Guidelines, and both organizations receive funding from for-profit organizations. Other institutions or organizations that he is affiliated with likely receive funding from for-profit sponsors that are supporting infrastructure and research that may serve his work.

Dr. Cook discloses that she received grant monies from the Canadian Institutes for Health Research and a dalteparin donation for a peer-review funded trial by the Canadian Institutes for Health Research.

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

References

1 Guyatt G, Baumann M, Pauker S, et al. Addressing resource allocation issues in recommendations from clinical practice guideline panels: suggestions from an American College of Chest Physicians task force. Chest 2006; 129:182–187

2 Matchar D, Mark D. Strategies for incorporating resource allocation and economic considerations: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2008; 133(suppl): 132S–140S

3 Guyatt G, Hirsh J, Albers GW, et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008; 133(suppl):110S–112S

4 Guyatt GR, Richardson W, Green L, et al. Moving from evidence to action. In: Guyatt GR, ed. Users' guide to the medical literature: a manual for evidence-based clinical practice. Chicago, IL: AMA Press, 2002; 175–204

5 Guyatt GS, Cook D, Jaeschke R, et al. Moving from evidence to action: grading recommendations—a qualitative approach. In: Guyatt GR, ed. Users' guide to the medical literature: a manual for evidence-based clinical practice. Chicago, IL: AMA Press, 2002; 599–608

6 Schünemann H, Munger H, Brower S, et al. Methodology for guideline development for the seventh American College of Chest Physicians conference on antithrombotic and thrombolytic therapy: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126(suppl):174S–178S

7 Atkins D, Best D, Briss P, et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328:1490

8 Guyatt G, Cook D, Jaeschke R, et al. Grades of recommendations for antithrombotic agents: American College of Chest Physicians evidenced based clinical practice guidelines. 8th ed. Chest 2008; 133(suppl):123S–131S

9 Guyatt G, Gutterman D, Baumann M, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest 2006; 129:174–181

10 McKibbon A, Hunt D, Richardson SW, et al. Finding the evidence. In: Guyatt GR, ed. Users' guide to the medical literature: a manual for evidence-based clinical practice. Chicago, IL: AMA Press, 2002; 16

11 Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008; 133(suppl):630S–669S

12 Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008; 133(suppl):381S–453S

13 Schünemann H, Hill S, Kakad M, et al. WHO rapid advice guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus. Lancet Infect Dis 2007; 7:21–31

14 Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: developing guidelines. BMJ 1999; 318:593–596

15 Bates S, Greer I, Pabinger I, et al. Venous thromboembolism, thrombophilia, antithrombotic therapy and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008; 133(suppl):844S–886S