Perioperative Management of Antithrombotic Therapy

An American College of Chest Physicians Clinical Practice Guideline

James D. Douketis, MD, FCCP; Alex C. Spyropoulos, MD, FCCP; M. Hassan Murad, MD, MPH; Juan I. Arcelus, MD; William E. Dager, PharmD; Andrew S. Dunn, MD, MPH; Ramiz A. Fargo, MD, FCCP; Jerrold H. Levy, MD; C. Marc Samama, MD; Sahrish H. Shah, MBBS; Matthew W. Sherwood, MD; Alfonso J. Tafur, MD; Liang V. Tang, MD; and Lisa K. Moores, MD, FCCP

BACKGROUND: The American College of Chest Physicians Clinical Practice Guideline on the Perioperative Management of Antithrombotic Therapy addresses 43 Patients-Interventions-Comparators-Outcomes (PICO) questions related to the perioperative management of patients who are receiving long-term oral anticoagulant or antiplatelet therapy and require an elective surgery/procedure. This guideline is separated into four broad categories, encompassing the management of patients who are receiving: (1) a vitamin K antagonist (VKA), mainly warfarin; (2) if receiving a VKA, the use of perioperative heparin bridging, typically with a low-molecular-weight heparin; (3) a direct oral anticoagulant (DOAC); and (4) an antiplatelet drug.

METHODS: Strong or conditional practice recommendations are generated based on high, moderate, low, and very low certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology for clinical practice guidelines.

RESULTS: A multidisciplinary panel generated 44 guideline recommendations for the perioperative management of VKAs, heparin bridging, DOACs, and antiplatelet drugs, of which two are strong recommendations: (1) against the use of heparin bridging in patients with atrial fibrillation; and (2) continuation of VKA therapy in patients having a pacemaker or internal cardiac defibrillator implantation. There are separate recommendations on the perioperative management of patients who are undergoing minor procedures, comprising dental, dermatologic, ophthalmologic, pacemaker/internal cardiac defibrillator implantation, and GI (endoscopic) procedures.

CONCLUSIONS: Substantial new evidence has emerged since the 2012 iteration of these guidelines, especially to inform best practices for the perioperative management of patients who are receiving a VKA and may require heparin bridging, for the perioperative management of patients who are receiving a DOAC, and for patients who are receiving one or more antiplatelet drugs. Despite this new knowledge, uncertainty remains as to best practices for the majority of perioperative management questions. CHEST 2022; 162(5):e207-e243

KEY WORDS: antithrombotic therapy; bleeding; perioperative care; surgery; thrombosis

ABBREVIATIONS: aPTT = activated partial thromboplastin time; ASA = aspirin; ATE = arterial thromboembolism; CABG = coronary artery bypass graft; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥ 65 years, female sex; COI = conflicts of interest; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HR = hazard ratio; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PICO = Patients-Interventions-Comparators-Outcomes; RR = relative risk; UFH = unfractionated heparin; VKA = vitamin K antagonist

AFFILIATIONS: From the Department of Medicine (J. D. D.), St. Joseph's Healthcare Hamilton and McMaster University, Hamilton,

Summary of Key Recommendations

5. In patients receiving VKA therapy for a mechanical heart valve who require VKA interruption for an elective surgery/procedure, we suggest against heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

6. In patients receiving VKA therapy for atrial fibrillation who require VKA interruption for an elective surgery/procedure, we recommend against heparin bridging (Strong Recommendation, Moderate Certainty of Evidence).

7. In patients receiving VKA therapy for VTE as the sole clinical indication who require VKA interruption for an elective surgery/procedure, we suggest against heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

14. In patients receiving VKA therapy who require a pacemaker or ICD implantation, we recommend continuation of VKA over VKA interruption and heparin bridging (Strong Recommendation, Moderate Certainty of Evidence).

15. In patients receiving VKA therapy who require VKA interruption for a colonoscopy with anticipated polypectomy, we suggest against heparin bridging during the period of VKA interruption (Conditional Recommendation, Very Low Certainty of Evidence).

21. In patients receiving LMWH bridging for an elective surgery/procedure, we suggest against routine measurement of anti-factor Xa levels to guide perioperative LMWH management (Conditional Recommendation, Very Low Certainty of Evidence).

22. In patients receiving apixaban who require an elective surgery/procedure, we suggest stopping apixaban for 1 to 2 days before the surgery/procedure over apixaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

23. In patients receiving dabigatran who require an elective surgery/procedure, we suggest stopping dabigatran for 1 to 4 days before the surgery/procedure over dabigatran continuation (Conditional Recommendation, Very Low Certainty of Evidence).

24. In patients receiving edoxaban who require an elective surgery/procedure, we suggest stopping edoxaban for 1 to 2 days before the surgery/procedure over edoxaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

25. In patients receiving rivaroxaban who require an elective surgery/procedure, we suggest stopping rivaroxaban for 1 to 2 days before the surgery/procedure over rivaroxaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

26. In patients who require DOAC interruption for an elective surgery/procedure, we suggest against perioperative heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

27. In patients who had DOAC interruption for an elective surgery/procedure, we suggest resuming DOACs > 24 hours after a surgery/procedure over resuming DOACs within 24 hours (Conditional Recommendation, Very Low Certainty of Evidence).

28. In patients who had DOAC interruption for an elective surgery/procedure, we suggest against routine DOAC coagulation function testing to guide

ON, Canada; Department of Medicine (A. C. S.), Northwell Health at Lenox Hill Hospital, New York, NY; Donald and Barbara Zucker School of Medicine at Hofstra/Northwell (A. C. S.), Hempstead, NY; Institute of Health Systems Science at The Feinstein Institutes for Medical Research (A. C. S.), Manhasset, NY; Mayo Clinic Evidence-Based Practice Center (M. H. M. and S. H. S.), Rochester, MN; Department of Surgery (J. I. A.), Facultad de Medicina, University of Granada, Granada, Spain; Department of Pharmacy (W. E. D.), University of California-Davis, Sacramento, CA; Division of Hospital Medicine (A. S. D.), Department of Medicine, Mt. Sinai Health System, New York, NY; Department of Internal Medicine (R. A. F.), Loma Linda University Medical Center, Loma Linda, CA; Department of Internal Medicine (R. A. F.), Riverside University Health System Medical Center, Moreno Valley, CA; Department of Anesthesiology, Critical Care, and Surgery (Cardiothoracic) (J. H. L.), Duke University School of Medicine, Durham, NC; Department of Anaesthesia, Intensive Care and Perioperative Medicine (C. M. S.), GHU AP-HP, Centre-Université Paris-Cité-Cochin Hospital, Paris, France; Inova Heart and Vascular Institute (M. W. S.), Falls Church, VA; Department of Medicine (A. J. T.), Cardiovascular, NorthShore University HealthSystem, Evanston, IL; Institute of Hematology (L. V. T.), Union Hospital, Tongji Medical College, Huazhong, University of Science and Technology, Wuhan, China; and the F. Edward Hébert School of Medicine (L. K. M.), Uniformed Services University of the Health Sciences, Bethesda, MD.

Drs Douketis and Spyropoulos served as co-primary authors.

CORRESPONDENCE TO: James D. Douketis, MD; email: jdouket@mcmaster.ca

DOI: https://doi.org/10.1016/j.chest.2022.07.025

perioperative DOAC management (Conditional Recommendation, Very Low Certainty of Evidence).

29a. In patients receiving ASA who are undergoing elective non-cardiac surgery, we suggest ASA continuation over ASA interruption (Conditional Recommendation, Moderate Certainty of Evidence).

34. In patients who are receiving ASA and undergoing CABG surgery, we suggest continuation of ASA over interruption; in patients receiving a $P2Y_{12}$ inhibitor drug, we suggest interruption of the $P2Y_{12}$ inhibitor over continuation perioperatively (Conditional Recommendation, Low Certainty of Evidence).

36. In patients receiving antiplatelet drug therapy who are undergoing an elective surgery/procedure, we suggest against the routine use of platelet function testing prior to the surgery/procedure to guide perioperative antiplatelet management (Conditional Recommendation, Very Low Certainty of Evidence).

38. In patients receiving ASA and a $P2Y_{12}$ inhibitor who had coronary stents placed within the last 3 to 12 months and are undergoing an elective surgery/procedure, we suggest stopping the $P2Y_{12}$ inhibitor prior to surgery over continuation of the $P2Y_{12}$ inhibitor (Conditional Recommendation, Very Low Certainty of Evidence).

39. In patients with coronary stents who require interruption of antiplatelet drugs for an elective surgery/procedure, we suggest against routine bridging therapy with a glycoprotein IIb-IIIa inhibitor, cangrelor, or LMWH over routine use of bridging therapy (Conditional Recommendation, Low Certainty of Evidence).

Introduction

The perioperative management of antithrombotic therapy encompasses patients who are receiving a vitamin K antagonist (VKA), a direct oral anticoagulant (DOAC), or an antiplatelet drug and require surgery or an invasive procedure.[1] The scope of this problem is considerable because anticoagulant and antiplatelet drugs are widely used for clinical indications that include atrial fibrillation, VTE, mechanical heart valves, coronary artery disease, and peripheral arterial disease.[2] Moreover, this clinical problem is likely to increase due to an aging population in whom antithrombotic therapy is widely used and in whom the need for a surgery/procedure is most common.[3-7] Approximately 15% to 20% of patients who are receiving anticoagulant therapy will require a surgery/procedure annually,[7-10] and 10% to 15% of patients with coronary stents will require surgery within 2 years of implantation.[11,12]

The current American College of Chest Physicians (CHEST) guidelines on perioperative antithrombotic management have expanded from previous iterations to address 43 Patients-Interventions-Comparators-Outcomes (PICO) questions. New domains that are addressed include the perioperative management of patients who are receiving DOACs (also referred to as non-vitamin K oral anticoagulants), $P2Y_{12}$ inhibitor antiplatelet drugs, and guidance on perioperative laboratory testing.[13-15] The target audience for this guideline is the wide array of clinicians involved in perioperative patient care, but it is also relevant for researchers to identify areas of future study, for patients to access a reliable information resource, and for clinical managers to facilitate the development of standardized patient care paths.[16,17] This guideline will be updated as new evidence emerges in the field of perioperative antithrombotic management in accordance with CHEST guideline policies.[18]

The aims of this practice guideline are: (1) to provide evidence-based recommendations for the perioperative management of patients who are receiving antithrombotic therapy; and (2) to provide practical guidance to clinicians for managing such patients in the perioperative period.

The PICO questions and guideline statements are separated into four broad categories to reflect the dominant patient groups assessed in clinical practice:

- Patients receiving a VKA, focused on warfarin.
- Among patients receiving a VKA, the use of perioperative heparin bridging.
- Patients receiving a DOAC.
- Patients receiving an antiplatelet drug.

The PICO questions are further arranged to reflect practical aspects of perioperative antithrombotic management, which include:

- Interruption and resumption of VKAs before and after an elective surgery/procedure, and need for perioperative heparin bridging.
- For patients in whom heparin bridging is considered, how to manage pre- and post-operative bridging during VKA interruption.

- Interruption and resumption of DOACs before and after an elective surgery/procedure.
- Perioperative management of antiplatelet therapy around non-cardiac surgery, coronary artery bypass graft (CABG) surgery, and in patients with cardiac stents.
- Management of VKAs, DOACs, and antiplatelet drugs around minor procedures (dental, dermatologic, ophthalmologic, GI endoscopy, and cardiac device implantation, the latter comprising pacemakers and internal cardiac defibrillators [ICDs]).

Definitions of Patient Groups, Antithrombotic Agents, and Qualifying Remarks

The following definitions and qualifying remarks are aimed at facilitating an understanding of this practice guideline and the accompanying recommendations.

Patient Groups

For patients who are receiving oral anticoagulant therapy, the recommendations will pertain to those patients who have one (or more) of the following clinical conditions: chronic atrial fibrillation; a mechanical prosthetic heart valve; or VTE. Although there may be patients who are receiving anticoagulant therapy for other conditions (eg, dilated cardiomyopathy), we focus on the most common indications for anticoagulant therapy. For patients who are receiving antiplatelet therapy, the recommendations pertain mainly to patients who have coronary artery disease and require non-cardiac surgery, CABG surgery, or percutaneous coronary interventions and, to a lesser extent, to patients receiving antiplatelet therapy for secondary prevention of cardiovascular disease (eg, peripheral or cerebrovascular disease) who need non-cardiac surgery.

VKAs

Although there are several VKAs available for clinical use, including warfarin, acenocoumarol, fluindione, phenprocoumon, and anisindione,[19] the PICO questions and associated recommendations herein will refer to warfarin when the term VKA is used because most evidence has assessed warfarin-treated patients, with few or no studies involving patients who are receiving other VKAs.[13,14]

DOACs

DOACs that are in clinical use comprise the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the factor IIa (thrombin) inhibitor dabigatran.[20] As these drugs differ in pharmacokinetic and pharmacodynamic properties,[21] recommendations that are specific for each DOAC will be made whenever possible based on evidence from patients who are taking a specific DOAC. Where appropriate, recommendations will be made for DOACs collectively.

Heparin Bridging

We define "heparin bridging" as the administration of a short-acting anticoagulant, typically a low-molecular-weight heparin (LMWH) or, less often, unfractionated heparin (UFH), for an 8- to 10-day perioperative period during interruption of a VKA when the international normalized ratio (INR) is below the therapeutic range.[14] We define a heparin bridging regimen as a therapeutic-dose (or full-dose) LMWH (eg, enoxaparin 1 mg/kg bid or 1.5 mg/kg daily, dalteparin 100 IU/kg bid or 200 IU/kg daily) or full-dose UFH (eg, to achieve a target activated partial thromboplastin time [aPTT] of 1.5- to 2-times the control aPTT or a target anti-factor Xa level of 0.35-0.70 IU/mL).[22] Although there are intermediate-dose LMWH regimens (eg, enoxaparin 40 mg bid) that have been referred to as "bridging," our definition and associated recommendations pertain to use of therapeutic-dose heparin bridging where the intent is to prevent stroke and systemic embolism, referred to in this guideline as arterial thromboembolism (ATE); moreover, this is the bridging dose regimen that has been most widely studied.[1,23] Heparin bridging should also be distinguished from perioperative use of low-dose LMWH (eg, enoxaparin 40 mg daily, dalteparin 5,000 IU daily) that is administered for prophylaxis against postoperative VTE rather than for the prevention of ATE.[24]

Other Definitions

We define the "perioperative period" or the term "perioperatively" as the period before and after a surgery/procedure that, in its entirety, spans from 1 week before until 4 weeks after a surgery/procedure. This 5-week period is when most adverse thrombotic and bleeding outcomes may be attributed to perioperative antithrombotic management.[25] A "surgery" will refer to an intervention that requires anesthesia (ie, general, neuraxial, regional block, local) and may take place with or without overnight hospitalization, whereas a "procedure" will refer to a diagnostic, therapeutic, or device-related intervention that, typically, does not require overnight hospitalization.

Qualifying Remarks

This guideline pertains to patients who are receiving anticoagulant or antiplatelet therapy and require an *elective*, non-urgent, surgery/procedure and does not address patients who require an urgent surgery/procedure, in whom the management paradigm differs considerably from that of the elective clinical setting.[26-28] This guideline further pertains to patients who are receiving long-term, typically ≥ 3 months, antithrombotic therapy and focuses on VKAs (warfarin), DOACs (apixaban, dabigatran, edoxaban, rivaroxaban), and antiplatelet drugs (aspirin [ASA], clopidogrel, prasugrel, ticagrelor). This guideline does not address the management of drugs with anticoagulant or antiplatelet properties that are used infrequently (eg, cilostazol, dipyridamole, pentoxifylline); that, in the case of DOACs, are used as low-dose regimens (eg, rivaroxaban 2.5 mg bid); or that, typically, are used for short periods (eg, nonsteroidal antiinflammatory drugs).[13] Finally, this guideline does not address the perioperative use of low-dose LWMHs, low-dose DOACs, or other antithrombotic strategies that are intended as prophylaxis against postoperative VTE.[24]

Practical Aspects of Perioperative Antithrombotic Management

The management approach described below provides the foundation upon which the guideline recommendations have been applied. This perioperative antithrombotic management approach aims to deliver individualized, patient-centric care with the intent of minimizing perioperative thromboembolism and bleeding. Perioperative antithrombotic management is anchored on the assessment of patients' risk for thromboembolism and surgery/procedure-related bleeding.[1,13,14] The risk classification schemes herein are empiric, requiring prospective validation, but aim to provide individualized perioperative management, in particular to help determine if perioperative anticoagulation interruption is needed and, if so, among VKA-treated patients, if heparin bridging is needed.

Assessing Perioperative Risk for Thromboembolism

This involves estimating the risk for ATE, encompassing stroke and systemic embolism for patients with atrial fibrillation or a mechanical heart valve, and the risk for recurrent VTE for patients with a history of VTE with perioperative interruption of anticoagulant drugs. The risk classification in Table 1 is empiric and separates patients according to estimated risk for ATE (high risk: > 10%/year; intermediate risk: 4%-10%/year; low risk: < 4%/year) and estimated risk for VTE (high risk: > 10%/month; intermediate risk: 4%-10%/month; low risk: < 2%/month); it is derived mainly from studies in a non-perioperative setting that involved patients with atrial fibrillation,[29-32] a mechanical heart valve,[33-35] or VTE[36-38] who were not receiving anticoagulant therapy (eg, placebo instead of a VKA in patients with atrial fibrillation) or less effective antithrombotic therapy (eg, ASA instead of a VKA in patients with a mechanical heart valve).[13,14,25] A perioperative risk classification for patients with coronary artery disease, particularly if they have coronary stents, is available elsewhere and is also empiric.[39,40]

The following qualifying remarks apply to this empiric risk classification:

- The thromboembolic risk classification herein can be overridden based on individual patient characteristics. For example, a "*low-risk*" patient with atrial fibrillation and a CHA_2DS_2VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥ 65 years, female sex) ≤ 4 or a $CHADS_2$ score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack) ≤ 2 with a history of perioperative stroke might be classified as "*high-risk*" and managed accordingly.[13,14]
- The type of surgery can affect thromboembolic risk, especially for patients undergoing cardiovascular surgery, such as CABG surgery or carotid endarterectomy, in whom the risk for stroke or other thromboembolism may be higher irrespective of other patient-related factors.[41-43]
- Patients' thromboembolic risk may be less important in certain perioperative circumstances. This can occur in VKA- or DOAC-treated patients or those receiving antiplatelet therapy who are undergoing a procedure that does not require anticoagulant or antiplatelet interruption. Another situation is in patients who are receiving DOAC therapy, irrespective of the clinical indication (atrial fibrillation or VTE). Since the perioperative time period where such patients are not anticoagulated is short (1-3 days), this minimizes the risk for thromboembolism, irrespective of their baseline risk, as reflected by the CHA_2DS_2VASc or $CHADS_2$ score or proximity of recent VTE and, similarly, obviates the rationale for administering heparin bridging.

TABLE 1] Suggested Risk Stratification for Patient-specific Periprocedural Thromboembolism[13,14,25,a]

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (> 10%/y risk of ATE or > 10%/mo risk of VTE)	Mitral valve *with* major risk factors for stroke[b] Caged ball or tilting-disc valve in mitral/aortic position Recent (< 3 mo) stroke or TIA	CHA_2DS_2VASc score ≥ 7 or $CHADS_2$ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo and especially 1 mo) VTE Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Active cancer associated with high VTE risk[c]
Moderate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Mitral valve *without* major risk factors for stroke[b] Bileaflet AVR *with* major risk factors for stroke[b]	CHA_2DS_2VASc score of 5 or 6 or $CHADS_2$ score of 3 or 4	VTE within past 3-12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation) Active cancer or recent history of cancer
Low (< 4%/y risk of ATE or < 2%/mo risk of VTE)	Bileaflet AVR *without* major risk factors for stroke[b]	CHA_2DS_2VASc score of 1-4 or $CHADS_2$ score of 0-2 (and no prior stroke or TIA)	VTE > 12 mo ago

ATE, arterial thromboembolism; TIA, transient ischemic attack; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥ 65 years, female sex. Adapted with permission from Douketis et al.[14]

[a]Empiric risk stratification that is a starting point for assessing perioperative thromboembolism risk; should be combined with clinical judgment that incorporates individual patient- and surgery/procedure-related factors.

[b]Includes: AF, prior stroke/TIA during anticoagulant interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, age ≥ 75 years.

[c]Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

Assessing Perioperative Risk for Surgery/ Procedure-Related Bleeding

This involves an assessment of the surgery/procedure-related bleed risk. The empiric risk classification shown in Table 2 separates patients into "*high*," "*low-to-moderate*," or "*minimal*" bleed risk categories and is based on the expected 30-day post-operative risk of major bleeding (high-bleed-risk ≥ 2%, low-to-moderate-bleed-risk 0%-2%, and minimal-bleed-risk approximately 0%).[1,25,44,45]

- Minimal-bleed-risk procedures and selected surgeries such as phacoemulsification (cataract) surgery are those in which anticoagulants may be continued perioperatively without any or with minimal (ie, day of procedure only) interruption.[1,46-50]
- Low-to-moderate-bleed-risk surgeries/procedures encompass a broad range of interventions in which shorter periods of pre-operative anticoagulant interruption and post-operative anticoagulant resumption intervals are acceptable due to an overall lower bleed risk.[1]
- High-bleed-risk surgeries/procedures are those which require sufficient pre-operative anticoagulant interruption, so there is minimal-to-no residual anticoagulant effect at the time of the surgery, and delayed post-operative anticoagulant resumption, to account for the longer time required for surgical site hemostasis. Also included in this category are any surgeries performed with neuraxial (spinal or epidural) anesthesia or any other neuraxial (eg, pain management) intervention due to concerns about the risk for epidural hematoma, a rare but devastating complication that can result in lower limb paralysis.[51,52]

The following qualifying remarks apply to this empiric risk classification:

- Selected minimal-bleed-risk procedures may require 1 to 2 days of anticoagulant interruption if there is concern about bleeding: for example, a dental extraction may be more complex in a patient with poor dentition or compromised gingival integrity[53]; a screening colonoscopy in patients with a history of polyps that may require resection[54]; and coronary angiography with a femoral (instead of radial) artery access.[48]
- Surgical procedures (eg, an inguinal hernia repair[55]) may vary widely in complexity and might be justifiably categorized as low-to-moderate- or high-bleed-risk.

TABLE 2] Suggested Risk Stratification for Procedural Bleed Risk, Based on ISTH Guidance Statements[25]

High-bleed-risk surgery/procedure[a] (30-d risk of major bleed ≥ 2%)	Major surgery with extensive tissue injury Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, pancreatic) Major orthopedic surgery, including shoulder replacement surgery Reconstructive plastic surgery Major thoracic surgery Urologic or GI surgery, especially anastomosis surgery Transurethral prostate resection, bladder resection, or tumor ablation Nephrectomy, kidney biopsy Colonic polyp resection Bowel resection Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography Surgery in highly vascular organs (kidneys, liver, spleen) Cardiac, intracranial, or spinal surgery Any major operation (procedure duration > 45 min) Neuraxial anesthesia[b] Epidural injections
Low-to-moderate-bleed-risk surgery/procedure[c] (30-d risk of major bleed 0%-2%)	Arthroscopy Cutaneous/lymph node biopsies Foot/hand surgery Coronary angiography[d] GI endoscopy ± biopsy Colonoscopy ± biopsy Abdominal hysterectomy Laparoscopic cholecystectomy Abdominal hernia repair Hemorrhoidal surgery Bronchoscopy ± biopsy
Minimal-bleed-risk surgery/procedure[e] (30-d risk of major bleed approximately 0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) Ophthalmologic (cataract) procedures Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings Pacemaker or cardioverter-defibrillator device implantation

ISTH = International Society on Thrombosis and Haemostasis.
[a]Minimal to no residual anticoagulant effect at time of procedure (ie, four to five drug half-life interruptions pre-procedure).
[b]Includes spinal and epidural anesthesia or any other neuraxial (eg, pain management) intervention; consider not only absolute risk for major bleeding but potentially devastating consequences of epidural bleeding and associated lower limb paralysis.
[c]Some residual anticoagulant effect allowed (ie, two to three drug half-life interruptions pre-procedure).
[d]Radial approach may be considered minimal-bleed-risk compared with femoral approach.
[e]Procedure can be safely done under full-dose anticoagulation (may consider holding DOAC dose day of procedure to avoid peak anticoagulant effects).

- Flexibility with the timing of post-operative DOAC and LMWH resumption is warranted because a peak anticoagulant effect occurs within 2 to 4 hours after administration[21]; this is especially pertinent if patients develop greater than expected post-operative bleeding.

Practical Aspects of Heparin Bridging

The following management points should be considered when administering heparin bridging:

- Bridging is most often done with an LMWH, typically with a therapeutic-dose regimen (eg, enoxaparin 1 mg/kg bid, dalteparin 100 IU/kg bid), administered with the intent of preventing ATE. Bridging with therapeutic-dose IV UFH is another treatment option; for example, in patients with severe renal insufficiency or who are dialysis-dependent.[14] Other types of heparin bridging may include intermediate-dose regimens (eg, enoxaparin 40 mg bid).[14]
- Heparin bridging should be administered in a manner to minimize the risk for bleeding that would require re-operation or another intervention (eg, wound packing). Avoidance of major bleeding is important because if it occurs, it typically requires a longer period of anticoagulant interruption that, in turn, exposes patients to an increased risk for thromboembolism.[56] Specifically, post-operative heparin bridging should be initiated when there is adequate

surgical/procedure-site hemostasis and the patient is at a relatively low risk for bleeding. Although subjective, this can be determined by assessing the amount, type (serous, serosanguinous, bloody), and progress (continuing, increasing, decreasing) of blood collection in wound bandages or surgical drains.

- The administration of heparin bridging, particularly if only used pre-operatively, does not preclude the administration of post-operative low-dose LMWH (eg, enoxaparin 40 mg daily); for example, in patients at high risk for bleeding (eg, intracranial or spinal or CABG surgery) in whom post-operative therapeutic-dose LMWH bridging might be avoided.

Role of Low-Dose LMWH as VTE Prophylaxis in Perioperative Management

In patients who require perioperative interruption of a VKA or a DOAC and are considered at high risk for post-operative VTE, the need to administer low-dose LMWH as VTE prophylaxis may be obviated once the VKA or DOAC is resumed. However, there may be circumstances when low-dose LMWH can be used in patients at high VTE risk; for example, those having abdominopelvic cancer surgery or hip or knee replacement surgery.[57,58] In such hospitalized patients, low-dose LMWH would be started, typically, 12 to 24 hours post-operatively and continued for 2 to 3 days while the VKA takes effect or until resumption of DOAC therapy. In patients who resume antiplatelet therapy after a surgery, the addition of low-dose LMWH can be justified in high VTE risk situations but is empiric and should consider the risk of bleeding.

Communication and Standardization of Perioperative Management

Perioperative antithrombotic management typically involves a team of health-care professionals, comprising one or more of a surgeon/proceduralist, an internist/cardiologist/hematologist, an intensivist, a pharmacist, an anesthesiologist, and a primary care physician, with multiple transitions of care. Consequently, it is important to have alignment of the proposed management plan among the health-care team and that it is communicated to and agreed upon by the surgeon/proceduralist, so as to avoid miscommunication that may lead to adverse outcomes or a delay of the surgery/procedure.[17,59] This can be facilitated with perioperative antithrombotic clinics,[16,59] which can be administered in-person or virtually,[60] and with the support of online tools (https://thrombosiscanada.ca, http://mappp.ipro.org, http://www.anticoagulationtoolkit.org/). At an institutional level, harmonization of perioperative anticoagulant management care paths that encompass multiple specialties (eg, surgery, internal medicine, anesthesia) will facilitate standardization of patient management.

Standardized management is important because unstructured usual care varies widely, based on surveys,[61-63] with the potential for confusion among clinicians and patients as to the planned management. If anticoagulants are not managed with evidence-based protocols or guidelines in the perioperative clinical setting, patients may be exposed to as much as a 0.5% to 1.0% excess risk for disabling stroke (based on a benchmark risk $\leq$ 0.5%) and a 3% to 6% excess risk for serious bleeding (based on a benchmark risk $\leq$ 1.5%), if anticoagulant interruption is too short or too long or if excessive heparin bridging is used.[1,8,64,65]

Methodology

Selection of Panel Members and Conflicts of Interest Disclosure

The guideline panel was selected to comprise a diverse, multidisciplinary group of clinicians that included internists, thrombosis specialists, cardiologists, anesthesiologists, surgeons, intensivists, and pharmacists, who worked alongside methodologists from the Mayo Clinic Evidence Center.

The CHEST Guidelines Oversight Committee and Professional Standards Committee reviewed nominated panelists according to their qualifications and conflicts of interest (COI) before they were approved to join the panel. Throughout the guideline process, panelists were required to update and disclose potential financial or intellectual COI according to each PICO question. COI were reviewed and categorized as disqualifying, manageable, or approved without management, per CHEST policy (https://www.chestnet.org/-/media/chesnetorg/About ACCP/Documents/Guidelines_COI_Policy.ashx). Panelists with manageable COI were required to abstain from voting on PICO recommendations where such COI were present but could participate in discussions, provided they refrained from strong advocacy. A complete list of the panelists' COI and their management is shown in e-Appendix 1.

Selection of PICO Questions

The PICO questions that anchor these guidelines were based on those used with the last guideline iteration, supplemented by new PICOs proposed by the guideline panel. All panelists voted on whether each PICO should be included in the guideline. For all PICOs, standardized questions were developed using the population-intervention-comparator-outcome format. A listing of all PICO questions is provided in e-Appendix 2.

Data Sources

Multiple databases were searched using text words and controlled vocabulary as outlined in e-Appendix 2. This search was done in two parts: the first was the systematic review of the literature from 1970 to December 2011, used by the 9th Edition of the CHEST Perioperative Antithrombotic Therapy Practice Guidelines; the second was an update of this search strategy to include studies up until end-July 2021. Searches were limited to English-language articles and human subject studies, and by article type (clinical trial, randomized clinical trial, systematic review). The literature search was supplemented by conducting Internet-based searches of relevant studies identified in ClinicalTrials.gov, meeting abstracts and conference proceedings, asking content experts, and reference lists of studies that satisfied inclusion criteria. Indirect evidence was sought for questions that were not supported by direct evidence. Panel members collaborated with the systematic review team to identify and summarize indirect evidence.

Guideline Framework

The guideline followed the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation).[66] For each PICO, the certainty of evidence was rated using GRADE, and an evidence-to-decision framework was developed using the GRADE evidence-to-decision criteria.[67] Certainty of evidence was defined as the extent to which our confidence in the effect estimate was adequate to support a recommendation. For each PICO, a recommendation was classified as a strong, referred to as "*we recommend,*" or conditional, referred to as "*we suggest.*" Overall, evidence synthesis comprised direct evidence related to the PICO question and indirect evidence, the later especially when direct evidence was limited. In addition, factors that included the costs of the interventions and the avoidance of harm were also considered.

Evidence Synthesis

Outcomes from randomized trials and observational studies were expressed as a relative risk (RR) and associated 95% CI. Meta-analysis was conducted when feasible. For non-comparative studies, an overall proportion was determined using the Freeman-Tukey arcsine transformation method. All analyses were done using Open Meta-Analyst. Certainty of evidence was categorized as high, moderate, low, or very low, reflecting the strengths and limitations of evidence that were based on the study design, risk of bias, imprecision, inconsistency, indirectness of results, and likelihood of publication bias. Risk of bias in randomized trials was based on the Cochrane Collaboration's Risk of Bias 2 tool,[68] which considers the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, reported result selection, and other sources of bias. Risk of bias in observational studies was based on the Newcastle-Ottawa Scale, which considers the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure and outcomes, comparability of cohorts, and adequacy of follow-up. Precision was judged based on whether CIs crossed the null as a target of certainty. If there were few events (< 10), we considered rating down by two to three levels unless the sample size was large ($> 2{,}000$-$4{,}000$). An arbitrary RR reduction threshold of 25% was used as a cutoff for lowering certainty in precision by two levels. Sample Evidence Tables that formed the basis of recommendations are shown in e-Appendix 3.

Development of Recommendations

We used a modified Delphi technique to achieve consensus on guideline statements.[18,69] This method minimizes bias related to group interactions and enables anonymity among panelists. Panelists without a primary COI voted on approving PICO-specific guideline statements using a standardized online survey tool (SurveyMonkey, Momentive Inc.). Each panelist could also suggest edits to the guideline statement wording and could suggest additional qualifying remarks or comments as to the implementation of the guideline in clinical practice. To achieve consensus and for inclusion in the final guideline, each guidance statement required at least 80% agreement among at least 75% of eligible panel members (without primary COI).

For the 43 PICO questions and 44 associated recommendations (two recommendations for PICO 29), 39 recommendations achieved consensus in the first

voting round, with the remainder achieving consensus in the second voting round. There were five guideline statements (2, 6, 20, 28, and 34) in which one panel member disagreed with either the strength or direction of the recommendation, and one guideline statement (29a) in which one panel member disagreed with both the strength and direction of the recommendation.

Patients Who Are Receiving a VKA and Require an Elective Surgery or Procedure

Background: The timing of VKA interruption before a surgery/procedure, decided upon with the intent of achieving a normal or near-normal INR at the time of a surgery/procedure, is based on the elimination half-life of VKAs that are typically observed in patients without major comorbidities (eg, impaired liver function), genetic polymorphisms, or drug-drug interactions that might affect VKA metabolism: 36 to 42 hours for warfarin, 8 to 11 hours for acenocoumarol, and 96 to 104 hours for phenprocoumon.[70-73] For patients in whom the intent is to normalize the INR after interruption of warfarin, 5 days of interruption prior to the day of the surgery/procedure is needed for the anticoagulant effect to be eliminated or near-eliminated; 6 or more days of interruption may be needed in selected patients, such as elderly patients or in patients with genetic polymorphisms that may delay warfarin metabolism,[74,75] and in those with an elevated INR (ie, > 3.5) when assessed. The resumption of a VKA after a surgery/procedure implies that attainment of an anticoagulant effect is delayed after the initial two to three doses are given and that a full anticoagulant effect (INR > 2.0) will occur 4 to 8 days after VKA resumption.[76] Given these considerations, routinely measuring the INR in the immediate pre-operative (day before) and post-operative (1-2 days after) period during a surgery/procedure would not be needed. There may be circumstances, however, when such testing may be warranted; for example, in patients with a pre-operative high (ie, > 3.5) INR, in patients who are known to have delayed warfarin elimination, or if after post-operative VKA resumption there is unexpected bleeding.

For patients who require perioperative VKA interruption, the premise of heparin bridging has been to shorten the period before and after a surgery/procedure when patients are not therapeutically anticoagulated, with the aim of mitigating the risk for perioperative ATE primarily, as well as recurrent VTE. However, this premise can be questioned given the multiplicity of factors that can lead to perioperative thromboembolism,[41,77] including the surgery/procedure itself,[43] and the limited capacity of heparin bridging to affect these factors and associated pathophysiological pathways.

Perioperative Interruption and Resumption of VKAs

PICO 1: ***In patients requiring VKA interruption, should VKA be interrupted ≥ 5 days vs < 5 days before an elective surgery/procedure?***

Evidence. No randomized trials compared a 5-day and a < 5-day preoperative interruption of warfarin, and no study has compared the effect of a 5-day and > 5-day interruption on perioperative bleeding outcomes, relying instead on a surrogate outcome (ie, INR) at the time of surgery to determine the appropriateness of VKA interruption. In the non-perioperative setting, indirect evidence supports a 5-day warfarin interruption period to attain a normal or near-normal INR.[78] In a prospective cohort study of 224 patients in whom warfarin was stopped 5 days before a surgery/procedure and had INR testing the day before surgery, 15 (7%) patients had an INR > 1.5.[56] In a randomized trial that compared a 5-day or 1-day pre-operative interruption of warfarin (with the 1-day group receiving 1 mg oral vitamin K the day before surgery), the mean INR was 1.2 at surgery in the 5-day interruption group.[79] A subanalysis of a randomized trial of DOAC vs warfarin therapy for atrial fibrillation that assessed perioperative management found that longer vs shorter (≥ 3 days vs < 3 days) warfarin interruption conferred a decrease risk for major bleeding (RR = 0.29; 95% CI: 0.15-0.55) without affecting ATE risk (RR = 0.49; 95% CI: 0.19-1.3).[80] Other observational studies support a longer ($\geq$ 5-day) interruption interval,[81,82] as do uncontrolled studies of perioperative warfarin management in which $\geq$ 5-day interruption was associated with low rates of major bleeding (approximately 2%) and ATE ($< 0.5\%$).[8,10,56,83-94]

1. In patients requiring VKA (warfarin) interruption for an elective surgery/procedure, we suggest stopping VKAs (warfarin) ≥ 5 days over an interruption of < 5 days before an elective surgery/procedure (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- Providing a perioperative VKA management calendar that is distributed by paper or electronically to patients and clinicians has the potential to minimize VKA dosing errors and optimize communication.

- In selected patients, especially the elderly with comorbidities, patients with very low dose warfarin requirements, and those with a higher target INR range, a longer period of warfarin interruption may be needed.
- The interruption timing for non-warfarin VKAs will differ, as it is shorter for acenocoumarol (2-3 days) and longer for phenprocoumon (10-12 days).

PICO 2: ***In patients who interrupted warfarin before an elective surgery/procedure, should warfarin be resumed 12 to 24 hours after surgery (evening of, or next day) and when there is adequate hemostasis vs resuming warfarin further from the surgery/procedure?***

Evidence. There are no studies comparing early (12-24 hours) with delayed (> 24 hours) postoperative warfarin resumption. In uncontrolled observational studies, resuming warfarin within 24 hours after a surgery/procedure was associated with rates of major bleeding and ATE of 2.7% (95% CI: 1.6-3.9) and 0.1% (95% CI: 0.1-1.8),[56,83,87,90,91,95] whereas those that assessed delayed warfarin resumption reported rates of bleeding and ATE of 8.6% (95% CI: 0-17.7) and 2.4% (95% CI: 0-7.0), respectively.[88,89,96]

2. In patients requiring VKA (warfarin) interruption for an elective surgery/procedure, we suggest resuming VKA (warfarin) within 24 hours over a delay to > 24 hours after an elective surgery/procedure (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- For most patients, resuming VKAs within 24 hours implies resumption on the evening of the surgery/procedure.
- Implicit in the early (within 24 hours) resumption of a VKA is that it takes, typically, 2 to 3 days for a partial anticoagulant effect and 4 to 8 days for a full anticoagulant effect to occur.
- VKA resumption may be delayed in certain post-operative circumstances, such as inadequate surgery/procedure-site hemostasis, an anticipated need for additional intervention, or patient inability to take oral medications.

PICO 3: ***In patients who interrupted warfarin before a surgery/procedure, should warfarin be resumed at double the usual maintenance dose for 1 to 2 days vs resuming warfarin with the usual maintenance dose?***

Evidence. One randomized trial of 98 patients compared post-operative resumption of warfarin at patients' usual dose vs doubling the warfarin dose for the first 2 post-operative days.[97] By the fifth post-operative day, an INR ≥ 2.0 was attained in 13% of the usual-dose group and 50% of the doubling dose group (RR = 0.27; 95% CI: 0.10 to 0.60); by the tenth post-operative day, this occurred in 68% and 87% of these groups (RR = 0.87; 95% CI: 0.65 to 1.00). In a 40-patient randomized trial that compared doubling vs usual-dose post-operative warfarin resumption, the median number of days to reach an INR ≥ 2.0 was not significantly different in the two groups (7.8 vs 9.0 days; 95% CI: −3.1 to 4.9).[98] In observational studies that used post-operative VKA resumption with a double-dose or usual-dose regimen, the mean duration to attain an INR ≥ 2.0 was 4.6 and 5.1 days, respectively.[56,95]

3. In patients requiring VKA (warfarin) interruption for an elective surgery/procedure, we suggest resuming the first post-operative VKA dose at the patient's usual dose over resuming VKA with double the usual dose (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Although post-operative doubling of the warfarin dose for 1 to 2 days may lead to a more rapid attainment of an INR ≥ 2.0 in some patients, there are concerns in applying this approach in practice; for example, in patients with variable warfarin dose regimens and those expected to be hospitalized for > 1 day.

PICO 4: ***In patients who interrupted warfarin before a surgery/procedure and have an elevated INR (ie, > 1.5) 1 to 2 days before surgery/procedure, should vitamin K be administered vs not giving vitamin K?***

Evidence. Among patients who have interrupted VKAs 5 to 6 days before a surgery/procedure, the practice of pre-operative INR measurement, typically on the day before or day of the surgery/procedure, may be done in selected patients; however, few studies have addressed the role of vitamin K in this clinical setting. In an uncontrolled observational study of 43 VKA-treated patients who had an INR of 1.4 to 1.9 on the day before elective surgery and received 1 mg oral vitamin K, the INR was normalized (≤ 1.3) in 76.6% of patients on the day of

surgery.[99] In another observational study of 82 VKA-treated patients who received 1 mg IV vitamin K, on average, 27 hours pre-operatively, a normalized INR for surgery was achieved in 54.9% of patients.[100] Other studies that have assessed vitamin K to normalize an elevated INR have been done in other clinical situations (eg, bleeding, urgent surgery) outside of the elective perioperative setting.[101-104]

4. In patients requiring VKA interruption for an elective surgery/procedure who have an elevated INR (ie, > 1.5) 1 to 2 days before the surgery/procedure, we suggest against routine use of pre-operative vitamin K (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Uncertainty about routine pre-operative vitamin K administration relates to the dose of vitamin K, limited availability of oral vitamin K formulations, and potential for resistance to post-operative re-anticoagulation.

Bridging Anticoagulation During Interruption of VKA Therapy

PICO 5: *In patients with a mechanical prosthetic heart valve, should bridging anticoagulation during interruption of warfarin therapy be administered vs no bridging?*

Evidence. One randomized trial assessed the need for heparin bridging in patients with a mechanical prosthetic heart valve. In the PERIOP-2 trial involving warfarin-treated patients who required an elective surgery/procedure, 20.7% (304 of 1,471) of patients had a mechanical heart valve, of whom 9.0% had a mitral valve and 11.7% had an aortic valve prosthesis.[105] All patients received pre-operative bridging with open-label dalteparin, 200 IU/kg daily (100 IU/kg daily on the day before the surgery/procedure). Post-operatively, patients received dalteparin 200 IU/kg daily (fixed-dose 5,000 IU daily in patients at high-bleed-risk) or placebo, in a double-blind manner, until the INR was $\geq$ 2.0; patient follow-up was for 12 weeks. In patients with a mechanical heart valve, there was no significant difference in the no bridging and bridging groups for the outcomes of major thromboembolism (0% vs 0.67%; $P = .67$) and major bleeding (1.96% vs 0.67%; $P = .62$). In an observational study assessing bridging vs no bridging management in VKA-treated patients which included patients with a mechanical heart valve, those who received perioperative bridging had an increased risk for major bleeding (3.6% vs 1.2%; $P = .0007$).[106] In a meta-analysis of non-randomized studies totaling 12,278 patients that compared bridging vs no bridging in a mixed population of patients, of whom 24% had a mechanical heart valve, there was no significant difference in the risk of ATE in bridged and non-bridged groups (OR = 0.80; 95% CI: 0.42-1.54), but bridging conferred an increased risk of major bleeding (OR = 3.60; 95% CI: 1.52-8.50).[23] In non-randomized studies in which all patients with a mechanical heart valve received perioperative therapeutic-dose heparin bridging, this approach was associated with a pooled incidence of ATE and major bleeding of 0.9% (95% CI: 0.2-1.5) and 2.8% (0.8-4.8), respectively.[56,86-88,107-109]

5. In patients receiving VKA therapy for a mechanical heart valve who require VKA interruption for an elective surgery/procedure, we suggest against heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- In selected patients considered at high risk for thromboembolism (Table 1), as examples, those with (1) an older-generation mechanical heart valve [ie, tilting-disc valve]; (2) a mechanical mitral valve with one or more risk factors for stroke; (3) a recent (< 3 months) thromboembolic event; or (4) other high-risk patients (eg, prior perioperative stroke), pre- and post-operative heparin bridging is suggested (see Guideline Statement 8).

PICO 6: *In patients with atrial fibrillation, should bridging anticoagulation be administered during interruption of VKA therapy vs no bridging?*

Evidence. The BRIDGE trial assessed a heparin bridging vs no bridging strategy in patients with atrial fibrillation who required warfarin interruption for an elective surgery/procedure.[76] In a double-blind manner, patients received bridging with therapeutic-dose LMWH (dalteparin 100 IU/kg bid) for 3 days pre-operatively, with only the morning dose given on the day before surgery/procedure, and for at least 5 days post-operatively until the INR was $\geq$ 2.0. Patient follow-up was for 4 weeks post-operatively. This trial showed that no bridging was noninferior to LMWH

bridging for the outcome of ATE (0.3% vs 0.4%; OR = 0.80; 95% CI: 0.42-1.54), but bridging conferred a threefold increased risk for major bleeding (3.2% vs 1.3%; OR = 3.60; 95% CI: 1.52-8.50). In the PERIOP-2 trial, there was no significant difference between the bridging (n = 670) and no bridging (n = 497) arms in the atrial fibrillation subgroup for the outcomes of major thromboembolism (0.75% vs 1.41%) and major bleeding (1.64% vs 2.62%).[105] In a subanalysis of a randomized trial of DOAC vs VKA therapy for atrial fibrillation that assessed perioperative management in 1,415 VKA-treated patients, those who received heparin bridging compared with those not bridged were at increased risk for major bleeding (6.8% vs 1.6%; OR = 4.4; 95% CI: 2.4-8.1).[110] In an observational study of 2,200 patients with atrial fibrillation who required perioperative VKA interruption, a multivariate analysis found that, compared with no bridging, heparin bridging was associated with higher rates of clinically important bleeding (5.0% vs 1.3%; OR = 3.84; 95% CI: 2.07-7.14) and cardiovascular events (4.6% vs 2.5%; OR = 1.62; 95% CI: 0.95-2.78).[106] The aforementioned meta-analysis found no significant difference in ATE but an increased risk of bleeding for bridging vs no bridging in a mixed population of patients, of whom 44% had atrial fibrillation.[23]

6. In patients receiving VKA therapy for atrial fibrillation who require VKA interruption for an elective surgery/procedure, we recommend against heparin bridging (Strong Recommendation, Moderate Certainty of Evidence).

Guideline Implementation Considerations:

- In selected patients considered at high risk for thromboembolism (Table 1), as examples (1) those with a recent [< 3 month] history of stroke or transient ischemic attack; (2) other high-risk patients (eg, prior perioperative stroke), or (3) with a CHA_2DS_2-VASc score ≥ 7 or $CHADS_2$ score of 5 or 6), pre- and post-operative heparin bridging is suggested (see Guideline Statement 8).
- A perioperative VKA and heparin bridging calendar (paper or electronic) that provides patients and clinicians an easy-to-use timetable for VKA interruption and resumption alongside the heparin bridging dosing regimen has the potential to minimize errors and optimize communication among caregivers.

PICO 7: *In patients with VTE, should bridging anticoagulation be administered during interruption of VKA therapy vs no bridging?*

Evidence. In patients with a history of VTE, bridging anticoagulation has been used during VKA interruption for patients requiring an elective surgery/procedure,[111] but there are no randomized trials to address its efficacy and safety. In an observational study of 755 patients that assessed a bridging (n = 214) vs no bridging (n = 514) approach in VKA-treated patients with VTE who required a surgery/procedure, there was no significant difference in recurrent VTE or bleeding outcomes in the two groups.[112] Other observational studies found that heparin bridging increased the risk for major bleeding with bridging,[113,114] with no significant reduction in recurrent VTE.[113,115,116] In a systematic review totaling 6,195 VKA-treated patients with VTE who required elective surgery, a heparin bridging vs no bridging approach was associated with a higher incidence of any bleeding (3.9% [95% CI: 2.0-7.4] vs 0.4% [95% CI: 0.1-1.7]) and no effect on recurrent VTE (0.7% [95% CI: 0.4-1.2] vs 0.5% [95% CI: 0.3-0.8]).[117]

7. In patients receiving VKA therapy for VTE as the sole clinical indication who require VKA interruption for an elective surgery/procedure, we suggest against heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Suggesting against bridging with a therapeutic-dose heparin regimen does not preclude the use of a low-dose heparin regimen, typically started within 24 hours after surgery and continued for up to 5 days while VKA therapy is resumed, to decrease the risk for post-operative VTE.
- In selected patients considered at high risk for VTE (Table 1), as examples (1) those with a recent (< 3 months) history of VTE,[36,118] or (2) severe thrombophilia, or (3) selected types of active cancer, pre- and post-operative heparin bridging is suggested (see Guideline Statement 8).

PICO 8: *In VKA-treated patients who are considered at high risk for thromboembolism (Table 1), should bridging anticoagulation be given during interruption of VKA therapy vs no bridging?*

PICO 9: *In VKA-treated patients who are considered at low-to-moderate-risk for thromboembolism (Table 1),*

should bridging anticoagulation be given during interruption of VKA therapy vs no bridging?

Evidence. Most studies assessing a bridging vs no bridging perioperative management strategy did not separate patients according to thromboembolic risk; consequently, evidence to inform these related PICOs is derived from studies referred to in the section entitled "Bridging Anticoagulation During Interruption of VKA Therapy," supplemented by uncontrolled observational studies[84,119,120] and meta-analyses[23,121,122] that separated patients and associated management according to thromboembolic risk.

8. In patients receiving VKA therapy who are classified as high risk for thromboembolism and who require VKA interruption for an elective surgery/procedure, we suggest heparin bridging over no heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Stratification of patients according to perioperative thromboembolic risk, as shown in Table 1, is empiric as there are no clinical prediction models that have been validated in this clinical setting. Accordingly, a patient's individual risk profile may inform decisions about heparin bridging. The type of surgery may also affect thromboembolic risk; for example, an anticipated higher risk in patients having open cardiac or major vascular surgery.

9. In patients receiving VKA therapy who are classified as low-to-moderate-risk for thromboembolism and who require VKA interruption for an elective surgery/procedure, we suggest against heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Although patients may be classified empirically as low-to-moderate-risk for thromboembolism, there may be selected patients within this classification grouping (Table 1) in whom heparin bridging may be considered.

Management of Patients Who Are Receiving a VKA and Need Minor Procedures

Dental Procedures: Minor dental procedures include single and multiple tooth extractions, and endodontic (root canal) procedures.

PICO 10: ***In patients who are having minor dental procedures and are receiving a VKA, should VKAs be continued vs stopped 5 to 6 days before the procedure?***

PICO 11: ***In patients who are having minor dental procedures and are receiving a VKA, should VKAs be continued with a pro-hemostatic agent vs an alternative approach (interrupting VKA with or without heparin bridging or continuing VKA without pro-hemostatic agent or co-administering different pro-hemostatic agents)?***

Evidence. Multiple randomized trials and prospective cohort studies have evaluated perioperative anticoagulant management for dental procedures. Management strategies that have been assessed include: continuing VKAs, with or without co-administered pro-hemostatic interventions that comprise antifibrinolytic drugs (eg, tranexamic acid) or local measures (eg, fibrin glue, topical hemostatic agents and sealants, sutures); partial (2-3 days' pre-procedure) VKA interruption; and complete (5 days' pre-procedure) VKA interruption.[14] These studies had limitations, with one or more of the following: small (< 100 patients) study samples; variable definitions of bleeding and other outcomes; and uncertain outcome capture during follow-up.[123-148] Among four randomized trials comparing VKA continuation vs interruption, none showed a significant increase in bleeding with VKA continuation.[123,128,129,131] One meta-analysis (of two studies) comparing continuing vs interrupting VKAs found no significant increased intra-procedural bleeding (RR = 1.67; 95% CI: 0.97-2.89) or post-procedural bleeding (RR = 1.44, 95% CI: 0.71-2.92) with VKA continuation.[149] Taken together, these studies suggest that continuing VKAs is associated with a low (approximately 5%) risk for any bleeding, with such bleeding considered self-limiting. Another approach associated with a low risk for bleeding is partial interruption of the VKA for 2 to 3 days before the dental procedure. In terms of thromboembolic outcomes, these appeared rare (< 0.1%), although it was uncertain if these outcomes were reliably identified during follow-up. If tranexamic acid is used, 10 mL of a 5% mouthwash solution can be given just before the procedure and two to three times daily for 1 to 2 days' post-procedure.[123,150]

10. In patients receiving VKA therapy who need a dental procedure, we suggest continuation of VKA over VKA interruption (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- The risk for dental procedure-related bleeding may vary, being lower with single tooth extractions and higher with multiple tooth extractions or in patients with poor gingival health; accordingly, VKA interruption may be preferred in situations where oral bleeding is expected to be considerable.

11. In patients receiving VKA therapy who need a dental procedure, we suggest using a pro-hemostatic agent with continuation of VKA over alternative management options (eg, discontinuation of VKA with or without heparin bridging) (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- Pro-hemostatic options include pre- and post-procedure administration of oral tranexamic acid mouthwash, two to three times daily, and intervention-specific measures (eg, extra sutures, gauze soaked in tranexamic acid).

Minor Dermatologic Procedures: Minor skin procedures include excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi.

PICO 12: ***In patients who are having a minor dermatologic procedure and are receiving a VKA, should VKA be continued around the time of the procedure vs stopping the VKA 5 to 6 days before the procedure?***

Evidence. No randomized trials have assessed perioperative anticoagulant management. Prospective, controlled cohort studies reported a higher incidence of bleeding in patients who continued VKAs compared with patients with VKA interruption, with most bleeds being self-limiting.[151-154] The incidence of bleeding with the continuation of VKAs appears to be low (< 5%), although there was uncertainty as to the reliability that events were identified.

12. In patients receiving VKA therapy who require a minor dermatologic procedure, we suggest continuation of VKA over VKA interruption (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The risk for dermatologic procedure-related bleeding may vary, being lower with resections of small (1-2 cm) skin cancers and biopsies, and higher with resections of larger (> 3 cm) skin cancers, particularly if skin grafting is required; accordingly, VKA interruption may be preferred in situations where site-related bleeding is expected to be considerable or if lengthy wound healing is expected (eg, skin graft).

Minor Ophthalmologic Procedures: Minor ophthalmologic procedures include cataract surgery (phacoemulsification), which is a largely avascular procedure, and surgery for glaucoma (iridotomy) and diabetic retinopathy (panretinal photocoagulation, vitrectomy). Whereas most eye surgery is done using sub-Tenon's or topical anesthesia or a peribulbar (extraconal) block technique, retrobulbar (intraconal) anesthesia poses a concern in anticoagulated patients due to the potential complication of retrobulbar hematoma,[155] which can lead to loss of vision.

PICO 13: ***In patients who are having a minor ophthalmologic procedure and are receiving a VKA, should VKA be continued around the time of the procedure vs stopping the VKA 5 to 6 days before the procedure?***

Evidence. No randomized trials have assessed perioperative management with cataract surgery.[156] In prospective cohort studies, the incidence of major and non-major bleeding was < 3%.[157-166] In a meta-analysis of observational studies, patients who continued VKAs around cataract surgery had an increased risk for bleeding (OR = 3.26; 95% CI: 1.73-6.16), with an overall incidence of bleeding of 10% (95% CI: 5-19).[46] However, almost all bleeds were self-limiting, consisting of dot hyphemas or subconjunctival bleeds, and no patient had compromised visual acuity related to bleeding.

13. In patients receiving VKA therapy who require a minor ophthalmologic procedure, we suggest continuation of VKA over VKA interruption (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- VKA interruption may be preferred in patients considered at higher risk for bleeding; for example, those having more complex retinal surgery or patients having surgery with retrobulbar anesthesia. Cataract surgery is done usually with topical anesthesia and, less commonly, with retrobulbar anesthesia.

Cardiac Device Procedures: Commonly performed cardiac device procedures include implantation of a permanent cardiac pacemaker or an ICD.

PICO 14: *In patients who are having a cardiac device procedure and are receiving a VKA, should VKA be continued around the time of the procedure vs stopping the VKA 5 to 6 days before the procedure?*

Evidence. The BRUISE CONTROL trial assessed a warfarin interruption-bridging vs warfarin continuation-no bridging strategy in patients with atrial fibrillation or a mechanical heart valve who required implantation of a pacemaker or ICD.[167] In the warfarin interruption-bridging group, patients received therapeutic-dose LMWH (89% of patients) or IV UFH (11% of patients) pre-procedure for 3 days. Post-procedure, bridging was resumed within 24 hours. The primary outcome of clinically significant pocket hematoma occurred in 3.5% (12 of 343) of patients in the warfarin continuation group, and in 16.0% (54 of 338) of patients in the warfarin interruption-bridging group (RR = 0.19; 95% CI: 0.10-0.36). Meta-analyses of observational studies where VKAs were continued around the time of pacemaker/ICD implantation demonstrated similar low (approximately 2% to 6%) rates of pacemaker pocket hematomas.[50,168,169] Smaller randomized trials also reported higher bleeding with VKA interruption and bridging compared with VKA continuation around pacemaker implantation,[170-172] whereas a 467-patient retrospective cohort study reported a 1.6% incidence of major pocket hematomas in patients who did not interrupt warfarin for pacemaker implantation.[173]

14. In patients receiving VKA therapy who require a pacemaker or ICD implantation, we recommend continuation of VKA over VKA interruption and heparin bridging (Strong Recommendation, Moderate Certainty of Evidence).

Guideline Implementation Considerations:

- Continuation of VKAs around cardiac device procedures is based on the premise that the patient's INR at the time of the procedure is < 3.0.

PICO 15: In patients receiving VKA therapy who require VKA interruption for a colonoscopy with anticipated polypectomy, should heparin bridging be given vs no heparin bridging?

Evidence. The management of patients undergoing polypectomy poses specific challenges because of the potential for post-procedure bleeding, which can be delayed when the scar formed over the polyp stalk is dislodged with potential exposure of friable, vascular tissue.[54] One randomized trial compared continuing VKAs with cold snare polypectomy vs VKA interruption and heparin bridging with hot snare polypectomy in 184 patients who needed colonic polyp resection.[174] The incidence of polypectomy-related major bleeding was higher in the VKA interruption-heparin bridging group than in the VKA continuation group (12.0% [95% CI: 5.0-19.1] vs 4.7% [95% CI: 0.2-9.2]); this difference was not statistically significant.

15. In patients receiving VKA therapy who require VKA interruption for a colonoscopy with anticipated polypectomy, we suggest against heparin bridging during the period of VKA interruption (Conditional Recommendation, Very Low Certainty of Evidence).

Perioperative Management of Patients Who Are Receiving Heparin Bridging

Background: The perioperative management of patients who receive heparin bridging is informed by an understanding of the basic pharmacologic properties of bridging agents, LMWH and UFH.[22] LMWHs have an elimination half-life of 3 to 5 hours, which informs pre-operative interruption timing, and a peak action occurring 3 to 4 hours after administration, which informs post-operative initiation timing.[22] UFH has a dose-dependent elimination half-life that is approximately 90 minutes but can vary from 30 to 120 minutes depending on the level of anticoagulation (as reflected by the aPTT or anti-factor Xa levels) at the time of interruption.[22]

Perioperative Use of IV UFH as Bridging Anticoagulation

PICO 16: *In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, should UFH be stopped 4 to 6 hours before surgery vs stopping UFH closer to surgery?*

PICO 17: *In patients who are receiving bridging anticoagulation with therapeutic-dose IV UFH, should UFH be resumed > 24 hours after a surgery/procedure vs within 24 hours after a surgery/procedure?*

Evidence. There are no studies assessing the timing of IV UFH interruption and resumption around the time of a surgery/procedure. Based on the elimination half-life, an infusion of UFH can be stopped 4 to 6 hours before surgery to eliminate any residual anticoagulant effect.[22] Resumption of IV UFH after surgery follows the approach used for LMWH in terms of the timing of post-operative resumption, and with IV UFH resumed

at the same or lower infusion rate as that used pre-operatively.[175,176]

16. In patients receiving therapeutic-dose IV UFH bridging for an elective surgery/procedure, we suggest stopping UFH ≥ 4 hours before a surgery/procedure over stopping IV UFH < 4 hours before a surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

17. In patients receiving therapeutic-dose IV UFH bridging for an elective surgery/procedure, we suggest resuming UFH ≥ 24 hours after a surgery/procedure over resuming UFH within 24 hours after a surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- When resuming UFH post-operatively, we suggest avoiding a bolus dose and commencing with a lower-intensity infusion that is associated with a lower target aPTT than that used for initiation of full-dose UFH administration.

Perioperative Use of LMWH as Bridging Anticoagulation

PICO 18: *In patients who are receiving LWMH bridging, should the last pre-operative dose of LMWH be given 24 hours before surgery vs 12 hours before surgery?*

Evidence. There are no studies assessing the timing of LMWH bridging interruption before a surgery/procedure and its effect on bleeding or other clinical outcomes. In observational studies assessing LMWH bridging, there were no apparent higher bleeding rates (compared with non-bridged controls from other studies) if the last dose of LMWH was given approximately 12 hours (evening) before surgery or approximately 24 hours before a surgery/procedure.[56,95] In studies assessing a surrogate marker for bleeding (anti-factor Xa levels), > 90% of patients who received their last LMWH dose approximately 12 hours before a surgery/procedure had a detectable anticoagulant effect at surgery, with 34% of patients having an elevated (therapeutic level) anticoagulant effect (ie, anti-factor Xa level ≥ 0.50 IU/mL) at the time of surgery.[177,178]

18. In patients receiving LMWH bridging for an elective surgery/procedure, we suggest administering the last pre-operative LMWH bridging dose at approximately 24 hours over administering the last dose 10 to 12 hours before a surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

PICO 19: *In patients who are receiving bridging with therapeutic-dose LMWH and are having high-bleed-risk surgery, should therapeutic-dose LMWH be resumed within 24 hours after surgery vs resuming LMWH > 24 hours after surgery?*

Evidence. No randomized trials have compared an early (within 24 hours) or delayed (> 24 hours) resumption of therapeutic-dose LMWH after a surgery/procedure, irrespective of the type of surgery. The BRIDGE trial used a standardized post-operative heparin resumption regimen where LMWH was resumed 24 hours after a low-to-moderate-bleed-risk surgery/procedure and 48 to 72 hours after a high-bleed-risk surgery/procedure was associated with a 3.2% incidence of major bleeding.[76] In a subanalysis of the RE-LY trial, which compared warfarin and dabigatran for stroke prevention in atrial fibrillation, patients who were receiving (open-label) warfarin and received perioperative LMWH bridging without a standardized bridging regimen had a 6.8% incidence of major bleeding.[110] In an observational study in which all patients received LMWH bridging with enoxaparin 1.5 mg/kg daily, started 12 to 24 hours after all types of surgery, patients who had major (> 1 hour duration) surgery had a 20% (8 of 40) incidence of major bleeding, whereas major bleeding occurred in 0.7% (1 of 148) of patients who had a minor (< 1 hour duration) surgery or procedure.[179] Other observational studies that allowed a flexible post-operative bridging regimen in high-bleed-risk patients, with either delayed resumption of therapeutic-dose LMWH or substitution of a low-dose regimen, found a low (< 5%) incidence of major bleeding.[84,87,88,92,107,120,180,181] Taken together, these studies support flexible postoperative resumption timing of LMWH bridging, to occur after 24 hours or after 48 to 72 hours depending on the surgery/procedure-related bleed risk, and when there is adequate surgical site hemostasis.

19. In patients receiving LMWH bridging for an elective surgery/procedure, we suggest administering the first post-operative LMWH bridging dose at least 24 hours after a surgery/procedure over administering it less than 24 hours after a surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- We suggest waiting at least 24 hours before resuming LMWH bridging in patients having a low-to-moderate-bleed-risk surgery/procedure and waiting at least 48 to 72 hours before resuming LMWH bridging in patients having a high-bleed-risk surgery/procedure (Table 2).
- For patients in whom the management plan is to delay resumption of LMWH bridging for 48 to 72 hours and who are considered at high risk for postoperative VTE, low-dose LMWH can be administered for the initial 2 to 3 days before the transition to LMWH bridging.

PICO 20: *In patients receiving LMWH bridging, should half the total daily dose of LMWH be given on the day before the surgery/procedure vs administering the full dose of LMWH?*

Evidence. The evidence for administering half the total dose of LMWH bridging on the day before the surgery/procedure incorporates the evidence used for Guideline Statement 18, shown above.[56,95,177,178] In addition, in the BRIDGE and PERIOP-2 trials, which gave half the total daily LMWH bridging dose on the day before the surgery/procedure in patients who received pre-operative bridging, this approach was associated with low rates of perioperative major bleeding (3.2%, 1.6%).[76,105]

20. In patients receiving LMWH bridging for an elective surgery/procedure, we suggest administering half the total daily dose of LMWH the day prior to the surgery/procedure over administering the full dose of LMWH the day prior (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This guidance may apply more to patients having a high-bleed-risk surgery, including patients having neuraxial (spinal or epidural) anesthesia, rather than in patients having a low-to-moderate-bleed-risk surgery/procedure (Table 2).
- Administering half the total daily dose of LMWH can be done by giving, on the morning of the day before the surgery/procedure, only the morning dose of a twice-daily LMWH regimen or approximately 50% of the dose of a once-daily LWMH regimen.

PICO 21: *In patients receiving LMWH bridging, should measurement of anti-factor Xa levels be routinely done vs no anti-factor Xa measurements*?

Evidence. There are no studies that have compared a perioperative LMWH bridging strategy with and without pre-operative anti-factor Xa measurements. Large randomized trials and prospective cohort studies did not incorporate anti-factor Xa measurements as part of perioperative management.[23,76,105]

21. In patients receiving LMWH bridging for an elective surgery/procedure, we suggest against routine measurement of anti-factor Xa levels to guide perioperative LMWH management (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- There may be select patients undergoing high-bleed-risk surgeries/procedures (ie, intracranial, spinal) or patients who require an urgent (nonelective) surgery/procedure where anti-factor Xa measurement may be considered.

Patients Who Are Receiving a DOAC and Require an Elective Surgery/Procedure

Background: The interruption of DOACs before an elective surgery/procedure can follow a pharmacokinetic-based approach, as used with the perioperative management of other anticoagulants, whereby the pre-operative interruption interval corresponds to four to five elimination half-lives of each DOAC.[182,183] Given the DOAC half-lives of 9 to 14 hours, withholding DOACs for 2 full days before a surgery/procedure, which corresponds more precisely to a 60- to 68-hour interval (or four to five half-lives) from the last DOAC dose until the surgery, should result in minimal to no residual anticoagulant effect at the time of surgery.[184] This approach can be used for patients having a high-bleed-risk surgery/procedure, whereas for patients having a low-to-moderate-bleed-risk surgery/procedure, withholding DOACs for 1 full day before the procedure, which corresponds to a 30- to 36-hour interruption interval (or approximately three DOAC half-lives), should result in a residual anticoagulant effect which is acceptable clinically for lower bleed risk procedures. In all patients, no DOAC is taken on the day of the surgery/procedure.

There are two important qualifying remarks to this pharmacokinetic-based DOAC interruption management strategy:

- In dabigatran-treated patients with impaired renal function (creatinine clearance [CrCl] $<$ 50 mL/min), interruption for 3 to 4 full days is required to allow for

the longer time required for drug clearance as 75% to 80% of dabigatran clearance is by the kidney.[21,185]

- There may be selected patients in whom a longer duration of pre-operative DOAC interruption may be required, irrespective of the DOAC used. This may include patients with severely impaired renal function (CrCl < 30 mL/min) or hepatic function, and in those who are taking drugs that, through inhibition of CYP3A4 or P-glycoprotein pathways, may interfere with DOAC clearance.[186-188]

An alternative pre-operative management strategy includes measurement of DOAC levels before the surgery/procedure,[189,190] which may be considered in patients who require an urgent (ie, within 24 hours) surgery, such as hip fracture repair.[191] A practical issue with this approach is that routine coagulation function tests such as the INR or aPTT may be insensitive to exclude a residual preoperative DOAC effect,[192] thereby necessitating the need to measure DOAC levels with more sensitive but less widely available tests. These tests consist of DOAC-calibrated anti-factor Xa levels for apixaban, edoxaban, and rivaroxaban, and the dilute thrombin time or ecarin clotting time for dabigatran; however, questions remain as to their clinical utility.[193-195]

Perioperative Interruption and Resumption of DOACs and Heparin Bridging

PICOs 22-25: *In patients who are receiving a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) and require an elective surgery/procedure, should DOACs be interrupted for 1 to 2 days (1-4 days for dabigatran) before a surgery/procedure vs interrupting DOACs earlier?*

Evidence. Two prospective studies assessed a standardized perioperative DOAC management, with standardized DOAC interruption. The first was a prospective management study of 541 dabigatran-treated patients with atrial fibrillation who required an elective surgery/procedure; 24- and 48-hour DOAC interruption intervals were adopted for low- and high-bleed-risk surgeries/procedures, respectively.[185] This approach was associated with low 30-day post-operative rates of ATE (0.2%; 95% CI: 0-0.5) and major bleeding (1.8%; 95% CI: 0.7-3.0). The second study, PAUSE, was a prospective management study of 3,007 patients with atrial fibrillation taking a DOAC (apixaban, dabigatran, or rivaroxaban) who required an elective surgery/procedure and received standardized perioperative management[196]; patients with severe renal insufficiency, in whom DOAC therapy was not clinically indicated, were excluded (CrCl < 25 mL/min if taking apixaban or CrCl < 30 mL/min if taking dabigatran or rivaroxaban). DOACs were interrupted for 1 day before and 1 day after (2 days total) a low-to-moderate-bleed-risk surgery/procedure and for 2 days before and 2 days after (4 days total) a high-bleed-risk surgery/procedure. An exception to this management occurred in a small proportion of patients (2.7% [80 of 3,007]) who were receiving dabigatran and had a CrCl < 50 mL/min in whom the interruption interval was extended by 1 or 2 days depending on the surgery/procedure bleed risk. With this overall management approach, 30-day post-operative incidences of ATE and major bleeding, respectively, were: 0.16% (95% CI: 0-0.48) and 1.35% (95% CI: 0-2.0) in the apixaban cohort (n = 1,257); 0.60% (95% CI: 0-1.33) and 0.9% (95% CI: 0-1.73) in the dabigatran cohort (n = 668); and 0.37% (95% CI: 0-0.82) and 1.85% (95% CI: 0-2.65) in the rivaroxaban cohort (n = 1,082).

Retrospective subanalyses of the major randomized trials assessing DOACs vs warfarin in atrial fibrillation were done to assess perioperative DOAC management but, in general, such management was not standardized as the timing of DOAC interruption and resumption varied and 15% to 20% of patients received heparin bridging.[8,10,80,85,197] A meta-analysis of > 19,000 patients who underwent a procedure in the randomized trials comparing DOACs vs warfarin in atrial fibrillation was reported as well.[198] Taken together, these studies reported rates of perioperative ATE of 0.5% to 1.0% and rates of major bleeding of 2% to 5%, which are comparable to rates observed in patients who receive non-standardized VKA interruption and resumption.[23,198]

Additional evidence relating to pre-operative DOAC management involves patients undergoing catheter ablation for atrial fibrillation. An observational study reported an increase in bleeding with periprocedural DOAC continuation[199] while another reported no difference in bleeding outcomes.[200] A 306-patient randomized trial that compared 1-day DOAC interruption vs no interruption found no significant difference in bleeding outcomes (11.3% vs 9.7%; risk difference = 1.7%; 95% CI –5.5 to 8.8).[201] An observational study assessing pacemaker/ICD implantation and minimal DOAC interruption (ie, skipping or delaying the immediate pre-procedure dose)

reported a low rate (1.6%) of major pocket hematomas.[173] A 25-patient observational study assessing DOAC continuation in patients having cataract surgery identified no bleeding events.[202] An observational study comparing perioperative DOAC interruption and continuation in patients undergoing low-bleed-risk procedures reported lower rates of overall bleeding (OR = 0.59; 95% CI: 0.39 to 0.91) and minor bleeding (OR = 0.59; 95% CI: 0.37 to 0.93) with DOAC interruption, a finding that persisted after adjustment for confounders (OR = 0.62; 95% CI: 0.41 to 0.95).[203]

It is noteworthy that almost all evidence pertaining to perioperative DOAC management involves patients with atrial fibrillation. Few studies, limited to retrospective case series, have assessed perioperative DOAC management in patients with VTE.[204,205] There are no studies assessing perioperative management in patients who are receiving low-dose DOAC therapy (rivaroxaban 2.5 mg bid) and ASA for stable coronary or peripheral arterial disease.[206]

22. In patients receiving apixaban who require an elective surgery/procedure, we suggest stopping apixaban for 1 to 2 days before the surgery/procedure over apixaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The number of days of pre-operative apixaban interruption before the surgery/procedure will depend on the bleed risk associated with the surgery/procedure:
  - o 1 day off before low-to-moderate-bleed-risk;
  - o 2 days off before high-bleed-risk.
- This management may be applied irrespective of whether patients are receiving apixaban for atrial fibrillation or VTE.

23. In patients receiving dabigatran who require an elective surgery/procedure, we suggest stopping dabigatran for 1 to 4 days before the surgery/procedure over dabigatran continuation (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The number of days of pre-operative dabigatran interruption before the surgery/procedure will depend on the bleed risk associated with the surgery/procedure and patient renal function:
  - o 1 day off before low-to-moderate-bleed-risk if CrCl $\geq$ 50 mL/min;
  - o 2 days off before low-to-moderate-bleed-risk if CrCl $<$ 50 mL/min;
  - o 2 days off before high-bleed-risk if CrCl $\geq$ 50 mL/min;
  - o 4 days off for high-bleed-risk if CrCl $<$ 50 mL/min (this extended duration of interruption of $>$ 2 days reflects the unique management of patients who are receiving dabigatran and have a CrCl $<$ 50 mL/min).
- This management may be applied irrespective of whether patients are receiving dabigatran for atrial fibrillation or VTE.

24. In patients receiving edoxaban who require an elective surgery/procedure, we suggest stopping edoxaban for 1 to 2 days before the surgery/procedure over edoxaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The number of days of pre-operative edoxaban interruption before the surgery/procedure will depend on the bleed risk associated with the surgery/procedure:
  - o 1 day off before low-to-moderate-bleed-risk;
  - o 2 days off before high-bleed-risk.
- This management may be applied irrespective of whether patients are receiving edoxaban for atrial fibrillation or VTE.

25. In patients receiving rivaroxaban who require an elective surgery/procedure, we suggest stopping rivaroxaban for 1 to 2 days before the surgery/procedure over rivaroxaban continuation (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The number of days of pre-operative rivaroxaban interruption before the surgery/procedure will depend on the bleed risk associated with the surgery/procedure:
  - o 1 day off before low-to-moderate-bleed-risk;
  - o 2 days off before high-bleed-risk.
- This management may be applied irrespective of whether patients are receiving rivaroxaban for atrial fibrillation or VTE.

PICO 26: *In patients who require DOAC interruption for an elective surgery/procedure, should perioperative bridging be given vs no bridging?*

Evidence. In a subanalysis of the RE-LY trial that assessed patients with AF who were receiving open-

label dabigatran (or warfarin) and required treatment interruption for an elective surgery/procedure, those who received perioperative LMWH bridging were at higher risk for major bleeding than those who did not receive bridging (6.5% vs 1.8%; $P < .001$), and use of bridging had no significant effect on stroke/systemic embolism outcomes (0.5% vs 0.3%; $P = .46$).[110] In a prospective patient registry of 901 DOAC-treated patients who required an elective surgery, perioperative LMWH bridging was associated with an increased risk for major bleeding (OR = 4.6; 95% CI: 1.1-9.9) with no significant effect on thromboembolic outcomes (OR = 1.9; 95% CI: 0.7-5.4).[207] In the aforementioned DOAC meta-analysis, perioperative LMWH bridging was associated with a threefold higher incidence of major bleeding compared with the non-bridged group (4.8% [95% CI: 3.4-6.2] vs 1.6% [95% CI: 1.2-2.0%]), with no differences in the pooled rates of stroke/systemic embolism.[198]

26. In patients who require DOAC interruption for an elective surgery/procedure, we suggest against perioperative heparin bridging (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The rapid offset and rapid onset of action of DOACs obviate the need for heparin bridging with short-acting anticoagulants such as UFH or LMWH in a perioperative setting.

PICO 27: *In patients who had DOAC interruption for an elective surgery/procedure, should DOACs be resumed > 24 hours after a surgery/procedure vs resuming DOACs within 24 hours?*

Evidence. One randomized trial of 662 DOAC-treated patients who required a pacemaker/ICD implantation compared perioperative DOAC continuation (median interval between pre- and post-procedure DOAC doses: 12 hours) and DOAC interruption (median interval: 72 hours) found no significant difference in pacemaker/ICD pocket hematomas (OR = 1.02; 95% CI: 0.36-2.87).[208] Evidence from the PAUSE study, as discussed above, informs the incidence of major bleeding and ATE when DOACs are resumed > 24 hours after a surgery/procedure. Other evidence regarding post-operative DOAC resumption timing is derived from the PAUSE trial in which resumption was standardized at approximately 24 hours (for a low-to-moderate-bleed-risk surgery/procedure) and 48 to 72 hours (for a high-bleed-risk surgery/procedure).

27. In patients who had DOAC interruption for an elective surgery/procedure, we suggest resuming DOACs > 24 hours after a surgery/procedure over resuming DOACs within 24 hours (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The resumption of DOACs post-operatively will depend on the bleed risk associated with the surgery/procedure:
  o at least 24 hours after low-to-moderate-bleed-risk;
  o 48-72 hours after high-bleed-risk.
- DOACs have a rapid onset of action, with a peak effect occurring 1 to 3 hours after intake, thereby requiring cautious administration after a surgery/procedure.

Perioperative Laboratory Measurement of DOAC Therapy

Background: The role of measuring DOAC levels before a surgery/procedure, akin to a pre-operative measurement of the INR in VKA-treated patients, is uncertain.[45,209,210] Unlike with an INR measurement where a level < 1.5 is considered safe to allow most surgery/procedures to proceed,[51] such a threshold with DOACs is uncertain as levels of < 30 ng/mL (the lower limit of detection of DOAC levels for some assays) or < 50 ng/mL have been suggested.[211,212] Although a subanalysis of the PAUSE study suggested that pre-operative DOAC levels < 30 ng/mL or 30 to 50 ng/mL were not associated with an increased risk for perioperative bleeding, this study was underpowered to assess such an association, and additional research is needed to define safe pre-operative DOAC levels according to the surgery/procedure-related risk for bleeding.[213,214]

Potential barriers for the clinical use of DOAC assays, including relatively high costs and limited availability, can be mitigated if laboratories are configured to run these assays with similar 20- to 30-minute turnaround times as with the INR and aPTT, and provide the requisite quality control measures.[215,216]

PICO 28: *In patients who interrupted a DOAC before a surgery/procedure, should the anticoagulant effect of DOACs routinely be measured with coagulation*

function tests vs not measuring the anticoagulant effect of DOACs?

Evidence. Although DOAC-level testing has been assessed in various clinical settings,[217-221] no studies have assessed the clinical utility of measuring the residual anticoagulant effect of a DOAC after its interruption before a surgery/procedure. Specifically, no study has compared the safety of a perioperative DOAC testing-driven strategy with a strategy that does not involve DOAC-level testing.[184] One prospective registry assessed 422 patients who interrupted DOACs with non-standardized intervals (ranging from 1 to 218 hours), according to physician discretion, and had DOAC levels measured just before the surgery. In patients with a 49- to 72-hour interruption interval, only 5% had a residual DOAC level > 30 ng/mL, and none had a level > 50 ng/mL.[222] A receiver-operator curve analysis identified a DOAC interruption interval of 54 hours to best predict a residual anticoagulant level ≤ 30 ng/mL. In the PAUSE study, 85% (n = 2,541) of patients had a DOAC level measured just before the surgery/procedure, but this was not available for clinical use and did not affect the DOAC interruption protocol.[196] In the overall study population, encompassing patients having a low-to-moderate-bleed-risk and high-bleed-risk surgery/procedure, the proportion of patients on apixaban (n = 1,129), dabigatran (n = 563), and rivaroxaban (n = 965) with a pre-operative DOAC level < 50 ng/mL was 90.5%, 95.1%, and 96.8%, respectively. Patients having a high-bleed-risk surgery/procedure or any neuraxial anesthesia, in whom the interval between the last DOAC dose and DOAC-level testing (just before the surgery/procedure) was approximately 60 to 68 hours (corresponding to 2 full days off before the surgery/procedure [4 days off if on dabigatran and CrCl < 50 mL/min]), were considered separately given a heightened concern about bleeding in the event of a significant residual DOAC level at surgery. In this subgroup, the proportion of patients on apixaban (n = 335), dabigatran (n = 183), and rivaroxaban (n = 314) with a DOAC level < 50 ng/mL was 97.9%, 99.4%, and 99.3%, respectively; the proportion with a DOAC level < 30 ng/mL was 93.1%, 98.9%, and 85.3%, respectively.

28. In patients who had DOAC interruption for an elective surgery/procedure, we suggest against routine DOAC coagulation function testing to guide perioperative DOAC management (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- DOAC-level testing may be considered, on a case-by-case basis, in nonelective perioperative clinical situations; for example, in patients who require an urgent/emergency surgery/procedure in whom DOAC-level testing may inform the need for active DOAC reversal with administration of blood products or DOAC-specific reversal agents.

Perioperative Management of Patients Who Are Receiving Antiplatelet Drugs

Background: Knowledge of basic pharmacologic properties of antiplatelet drugs will inform the timing of perioperative interruption and resumption. When interrupting ASA and the $P2Y_{12}$ inhibitors clopidogrel and prasugrel, since these drugs irreversibly inhibit platelet function, 7 to 10 days (ie, platelet life span) of interruption is needed to restore platelet function.[223-225] When interrupting the $P2Y_{12}$ inhibitor ticagrelor, which reversibly inhibits platelet function, at least 2 to 3 days of interruption is needed to restore platelet function.[226,227] When resuming antiplatelet drugs post-operatively, a maximal antiplatelet effect occurs within minutes after taking ASA, within 2 hours after taking ticagrelor, and occurs 4 to 5 days after resuming clopidogrel with a (75 mg) maintenance dose only, and after 3 days after resuming prasugrel.[226,228,229] If a loading dose of clopidogrel is used, the maximal antiplatelet effect occurs between 2 and 6 hours.[230,231] Less commonly used reversible inhibitors of platelet function include cilostazol, dipyridamole, and pentoxifylline, with half-lives of 2 to 10 hours,[232-234] and vorapaxar, which has a prolonged, 3- to 15-day antiplatelet effect.[235] Nonsteroidal antiinflammatory drugs have reversible antiplatelet properties with half-lives that vary from 2 to 6 hours (ibuprofen, ketoprofen, indomethacin), to 7 to 15 hours (celecoxib, naproxen, diflunisal), to approximately 20 hours (meloxicam, nabumetone, piroxicam).[236]

Patients Having Non-cardiac Surgery

PICOs 29-32: ***In patients receiving antiplatelet drugs who require non-cardiac surgery, should antiplatelet drugs be continued perioperatively vs stopping 7 to 10 days before surgery?***

Evidence. One 80-patient trial compared 4 to 5 days vs 10 days of ASA interruption before surgery, with too few cardiovascular (n = 1) or bleeding (n = 0) events for adequate interruption.[237] The PEP trial involved 17,444 patients who required hip fracture

repair or hip/knee joint replacement with patients randomized to receive ASA or placebo started pre-operatively and continued for 35 days.[238] ASA use was associated with a decreased risk for VTE (RR = 0.71; 95% CI: 0.54-0.94) and did not affect the risk for clinically overt myocardial ischemia (RR = 1.57; 95% CI: 0.93-2.65) or stroke (RR = 1.13; 95% CI: 0.69-1.85) but conferred an increased risk for major bleeding (2.9% vs 2.4%; $P = .04$). In a randomized trial of 220 patients who were at high cardiovascular risk and were undergoing surgery, ASA (or placebo) was started 7 days before surgery and continued for 30 days.[239] Patients in the ASA group had a lower risk for major cardiovascular events (1.8% vs 9.0%; 95% CI: 1.3-13.0), but the study was underpowered to detect a difference in bleeding. POISE-2 was a randomized, placebo-controlled trial that assessed immediate pre-operative ASA initiation (200 mg) or ASA continuation in 10,010 patients with known or at risk for coronary artery disease who were having major non-cardiac surgery.[240] Perioperative ASA initiation/continuation did not reduce the risk for non-fatal myocardial infarction or death (7.0% vs 7.1%; RR = 0.99; 95% CI: 0.86-1.2), a finding observed in both initiation and continuation strata, but increased the risk for major bleeding (4.6% vs 3.8%; RR = 1.2; 95% CI: 1.01-1.50). The interpretation of these results involves consideration that post-operative nonsteroidal antiinflammatory drug use occurred in 37% of patients, which may have impaired the cardioprotective effects of ASA[241]; moreover, major bleeding was increased in the ASA initiation stratum (4.6% vs 3.5%; hazard ratio [HR] = 1.34; 95% CI: 1.03-1.74) but not the ASA continuation stratum (4.6% vs 4.1%; HR = 1.11; 95% CI: 0.84-1.48). Smaller, likely underpowered, trials assessing perioperative ASA interruption vs continuation or single-dose pre-operative ASA administration reported no significant difference in thromboembolic or bleeding events.[242-245]

No prospective studies have assessed perioperative management of clopidogrel, prasugrel, or ticagrelor in non-cardiac surgery. Retrospective cohort studies of clopidogrel suggest an increased risk of bleeding with perioperative clopidogrel continuation.[246-248]

29a. In patients receiving ASA who are undergoing elective non-cardiac surgery, we suggest ASA continuation over ASA interruption (Conditional Recommendation, Moderate Certainty of Evidence).

Guideline Implementation Considerations:

- This guidance may be modified on a case-by-case basis. For example, in select patients undergoing a non-cardiac surgery associated with a high-bleed-risk (eg, intracranial, spinal); if ASA interruption is adopted, we suggest interruption for ≤ 7 days.

29b. In patients receiving ASA therapy who are undergoing elective non-cardiac surgery and require ASA interruption, we suggest stopping ASA ≤ 7 days instead of 7 to 10 days before the surgery (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This suggestion may be modified on a case-by-case basis, depending on individual patient circumstance; for example, surgery-related bleeding risk.

30. In patients receiving clopidogrel who are undergoing an elective non-cardiac surgery, we suggest stopping clopidogrel 5 days instead of 7 to 10 days before the surgery (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This suggestion may be modified on a case-by-case basis, depending on individual patient circumstances; for example, surgery-related bleeding risk.

31. In patients receiving ticagrelor who are undergoing an elective non-cardiac surgery, we suggest stopping ticagrelor 3 to 5 days instead of 7 to 10 days before the surgery (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This suggestion may be modified on a case-by-case basis, depending on individual patient circumstances; for example, surgery-related bleeding risk.

32: In patients receiving prasugrel who are undergoing an elective non-cardiac surgery, we suggest stopping prasugrel 7 days instead of 7 to 10 days before the surgery (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This suggestion may be modified on a case-by-case basis, depending on individual patient circumstances; for example, surgery-related bleeding risk.

PICO 33: *In patients receiving antiplatelet drugs who require non-cardiac surgery, should antiplatelet drugs be resumed ≤ 24 hours or > 24 hours after surgery?*

33. In patients who require antiplatelet drug interruption for an elective surgery/procedure, we suggest to resume antiplatelet drugs ≤ 24 hours instead of > 24 hours after the surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Patients Having Coronary Artery Bypass Graft Surgery

PICO 34: ***In patients receiving antiplatelet drugs who require CABG surgery, should antiplatelet drugs be continued perioperatively vs stopping antiplatelet drugs 7 to 10 days before CABG surgery?***

PICO 35: ***In patients receiving antiplatelet drugs who require CABG surgery, should antiplatelet drugs be resumed within 24 hours or ≥ 24 hours after CABG surgery?***

Evidence. Determining whether to continue or stop antiplatelet drugs before CABG surgery is important because of the need to minimize surgical-site bleeding, which can cause life-threatening pericardial tamponade. In a > 8,000-patient cohort study, ASA use within 5 days prior to CABG was associated with a reduction in overall mortality without a concomitant increased risk for re-operation for pericardial bleeding or need for blood transfusion.[249] ATACAS was a randomized, placebo-controlled trial assessing perioperative ASA use in patients who required CABG surgery where patients received ASA 100 mg, starting 1 to 2 hours' pre-CABG (prior ASA users stopped it 4 days' pre-surgery), or placebo, with resumption within 24 hours' post-CABG.[250] After 30 days of follow-up, there was no significant effect of ASA on the outcomes of myocardial infarction (13.8% vs 15.8%; RR = 0.87; 95% CI: 0.71-1.07), death, and other cardiovascular outcomes; ASA use was not associated with an increased risk for re-operation related to bleeding (1.8% vs 2.1%; RR = 0.87; 95% CI: 0.47-1.6). Stopping ASA in prior users for at least 4 days and restarting it just before surgery may question the generalizability of the study results, whereas continuing ASA perioperatively without interruption (as in one of the treatment arms) may have better reflected what is done in clinical practice.

In patients who also are receiving the $P2Y_{12}$ inhibitor clopidogrel, subanalyses of large trials involving patients with acute coronary syndromes who subsequently required CABG reported a 50% higher risk for major bleeding and a 70% higher need for transfusion requirements in patients who received clopidogrel within 5 days before CABG.[251,252] Observational studies have also found increased bleeding in patients who received clopidogrel within 5 days of CABG surgery.[253-255] In a subanalysis of the PLATO trial, which compared ticagrelor with clopidogrel in ASA-treated patients with an acute coronary syndrome who needed CABG surgery, rates of bleeding were similar in patients stopping clopidogrel 7 days before surgery and those stopping ticagrelor 24 to 72 hours before surgery.[256] A meta-analysis of four randomized trials and one observational study totaling 2,632 patients undergoing CABG surgery that compared > 5 days vs < 5 days interruption of clopidogrel found patients with a longer interruption had a lower incidence of re-operation (1.8% vs 3.2%; OR = 0.47; 95% CI: 0.25-0.91) and major bleeding (19.7% vs 30.2%; OR = 0.71; 95% CI: 0.51-0.98) and cardiovascular events.[257]

There are no randomized trials or trial subanalyses that address the resumption of antiplatelet drugs post-operatively. One 100-patient observational study compared resuming ASA 1 hour or 6 hours' post-CABG surgery and reported no significant difference in bleeding or transfusion requirement outcomes.[258]

34. In patients who are receiving ASA and undergoing CABG surgery, we suggest continuation of ASA over interruption; in patients receiving a $P2Y_{12}$ inhibitor drug, we suggest interruption of the $P2Y_{12}$ inhibitor over continuation perioperatively (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- For pre-operative $P2Y_{12}$ interruption prior to the day of surgery/procedure, we suggest:
  - 7 days for prasugrel;
  - 5 days for clopidogrel;
  - 3 to 5 days for ticagrelor.

35. In patients receiving ASA or a $P2Y_{12}$ inhibitor who are undergoing CABG surgery, we suggest resuming the ASA or $P2Y_{12}$ inhibitor within 24 hours after surgery compared to ≥ 24 hours after surgery (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- Resumption of antiplatelet therapy may be delayed in patients who develop post-CABG thrombocytopenia (platelet count < 50,000 × 10^9/L), typically occurring with on-pump surgery.

Perioperative Measurement of Antiplatelet Therapy

PICO 36: *In patients who are receiving antiplatelet therapy, should platelet function assays be routinely used to measure antiplatelet effect vs no routine use of antiplatelet function testing?*

Evidence. Several platelet function assays have been assessed mostly in patients having cardiac surgery or percutaneous coronary interventions.[259,260] One observational study (n = 107) assessed platelet function in patients who received or did not receive ASA around the time of a colorectal surgery and found that impaired platelet function observed with ASA continuation did not affect the incidence of blood transfusion.[261] Other studies have not shown a correlation between platelet function assay results and clinical outcomes.[262,263]

36. In patients receiving antiplatelet drug therapy who are undergoing an elective surgery/procedure, we suggest against the routine use of platelet function testing prior to the surgery/procedure to guide perioperative antiplatelet management (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Platelet function testing could be used with a possible small benefit and little harm in certain scenarios such as patients undergoing CABG surgery who have recently started taking a $P2Y_{12}$ inhibitor. Costs would be moderate for implementation.

Patients With Coronary Stents Having Surgery

PICOs 37-40: *In patients who require surgery within 6 weeks of placement of a bare-metal coronary stent or within 12 months of placement of a drug-eluting coronary stent, should ASA and clopidogrel be continued vs stopping antiplatelet drugs 7 to 10 days before surgery*?

Evidence. Perioperative antiplatelet management aims to minimize the risk for stent thrombosis, which occurs in 2% to 5% of patients and is associated with mortality as high as 50%.[264-269] A subanalysis of the POISE-2 trial assessed 470 patients with a coronary stent who required major non-cardiac surgery, with patients who were allocated to continue ASA perioperatively exhibiting a decrease in the incidence of myocardial infarction (5.1% vs 11.0%; HR = 0.44; 95% CI: 0.22-0.87) and a small increase in major bleeding (4.6% vs 3.8%; HR = 1.22; 95% CI: 1.01-1.48).[270] In observational studies, perioperative antiplatelet therapy interruption for > 5 days was a predictor of major adverse cardiovascular events (OR = 2.11; 95% CI: 1.23-3.63),[271] as was no perioperative antiplatelet therapy (OR = 3.73; 95% CI: 1.26-11.07).[272] A systematic review of patients with coronary stents who required surgery found one randomized trial and 15 observational studies assessing at least six different perioperative antiplatelet management strategies with variable rates of adverse cardiovascular events (0%-21%) and bleeding (0%-22%), and reported no observable pattern of adverse outcome incidence using a given management strategy.[273]

The timing of surgery after coronary stenting balances the urgency of an elective surgery (eg, cancer resection) and the cardiovascular risk relating to the time interval since stenting. Observational studies of patients with coronary stents who required surgery provide evidence to inform this issue. In a retrospective study of 20,590 patients with coronary stents who underwent surgery, the risk for adverse cardiovascular outcomes appeared highest in the initial 6 weeks after stent placement (8%10%) but appeared to plateau at 6 months (1%-2%) and remain stable at 24 months.[274] In a linked administrative database study comparing post-operative rates of adverse cardiovascular outcomes in 4,303 patients with and 20,232 patients without recent (within 1 year) drug-eluting coronary stent placement, stented patients had a higher risk for myocardial infarction (1.6% vs 0.2%; OR = 4.82; 95% CI: 3.25-7.16) and cardiac death (1.0% vs 0.2%; OR = 5.87; 95% CI: 3.60-9.58), and this increased risk was statistically significant only if surgery was done within 1 month of stenting.[275]

Bridging therapy during antiplatelet drug interruption has been assessed with multiple strategies and agents.[276] One randomized trial assessed IV cangrelor, a reversible ultra-short-acting $P2Y_{12}$ inhibitor (elimination half-life of 3-6 minutes), as a bridging agent in patients who were receiving and interrupted $P2Y_{12}$ inhibitor therapy prior to CABG surgery[277,278]; this 198-patient study reported no effect of bridging on CABG-related bleeding (OR = 1.15; 95% CI: 0.47-2.79) or other adverse events (7.8% vs 5.2%; $P = .45$). Observational studies have investigated bridging with IV UFH[279] or subcutaneous LMWH,[280] and bridging with short-acting IV glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide) or cangrelor, with no clear benefits of these approaches.[281-285]

We were unable to address management and outcomes in these studies according to the stent type, whether drug-eluting or bare-metal; consequently, the guideline

statements do not specify management according to stent type. However, coronary stents implanted in current practice are of the drug-eluting type.

37. In patients receiving ASA and a $P2Y_{12}$ inhibitor with coronary stents placed within the last 6 to 12 weeks who are undergoing an elective surgery/procedure, we suggest either continuation of both antiplatelet agents or stopping one antiplatelet agent within 7 to 10 days of surgery (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Either approach is reasonable depending on the bleeding risk associated with the surgery/procedure if antiplatelet therapy is continued and risk for acute coronary syndrome/coronary stent thrombosis if antiplatelet therapy is interrupted.
- Several factors will weigh in the decision about whether to continue dual antiplatelet therapy or interrupt one agent including: the timing of stent placement (whether closer to 6 weeks or 12 weeks); the type of stent (drug-eluting or bare-metal); the location of the stent (whether at a dominant coronary artery or not); and the number and length of stents implanted.

38. In patients receiving ASA and a $P2Y_{12}$ inhibitor who had coronary stents placed within the last 3 to 12 months and are undergoing an elective surgery/procedure, we suggest stopping the $P2Y_{12}$ inhibitor prior to surgery over continuation of the $P2Y_{12}$ inhibitor (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- This guidance is based on indirect evidence and expert-based consensus that stopping $P2Y_{12}$ inhibitors in patients with stents > 3 months' post-implantation is likely safe.
- Several factors will weigh in the decision about whether to continue or interrupt the $P2Y_{12}$ inhibitor, including: the timing of stent placement (whether closer to 3 months or 12 months); the type of stent (drug-eluting or bare-metal); the location of the stent (whether at a dominant coronary artery or not); and the number and length of stents implanted.

39. In patients with coronary stents who require interruption of antiplatelet drugs for an elective surgery/procedure, we suggest against routine bridging therapy with a glycoprotein IIb/IIIa inhibitor, cangrelor, or LMWH over routine use of bridging therapy (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- A bridging approach may be considered in selected high-risk patients; for example, in those with a recent (within 3 months) coronary stent in a critical location.

40. In patients with coronary stents who require continued dual antiplatelet therapy, we suggest delaying an elective surgery/procedure over not delaying the surgery/procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- The duration of surgery/procedure delay is addressed on a case-by-case basis and should consider the urgency of the surgery/procedure, the time elapsed since coronary stenting, and the risk profile of the coronary stenting (eg, critical location, multiple stents).
- Regarding the timing of cessation of $P2Y_{12}$ inhibitors or ASA, we refer to Guideline Statements 29a/b through 33.

Patients Having a Minor Dental, Dermatologic, or Ophthalmologic Procedure

PICOs 41-43: ***In patients who are receiving antiplatelet drugs and require a minor dental, dermatologic, or ophthalmologic procedure, should antiplatelet drugs be continued vs stopping antiplatelet drugs 7 to 10 days before the procedure?***

Evidence. In patients having minor dental procedures, small (< 100 patients) randomized trials and cohort studies suggest no increase in major bleeding with ASA continuation.[146,286-290] In patients having minor skin procedures, prospective cohort studies totaling about 200 patients suggest a low (< 1%) risk for major bleeding with continuation of ASA.[291,292] In patients having phacoemulsification (cataract) surgery, prospective cohort studies have suggested a low (< 1%) incidence of major bleeding with perioperative ASA continuation.[159,160,293] In patients having eyelid surgery, one 42-patient randomized trial compared ASA continuation with no perioperative ASA use and reported no significant effect on bleeding or thromboembolic outcomes.[294] In patients having skin procedures, one meta-analysis of two randomized trials and 28 observational studies totaling > 14,000 patients found no significant increase in bleeding with perioperative ASA continuation.[295] No studies have

assessed the management of patients who are receiving $P2Y_{12}$ inhibitors alone and require minor dental, skin, or eye procedures.

41. In patients receiving an antiplatelet drug (ASA or $P2Y_{12}$ inhibitor) who are undergoing a minor dental procedure, we suggest continuing the antiplatelet drug (ASA or the $P2Y_{12}$ inhibitor) over stopping the antiplatelet agent before the procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Patients who are receiving dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor can continue ASA and interrupt the $P2Y_{12}$ inhibitor.

42. In patients receiving an antiplatelet drug (ASA or $P2Y_{12}$ inhibitor) who are undergoing a minor dermatologic procedure, we suggest continuing the antiplatelet drug (ASA or $P2Y_{12}$ inhibitor) over stopping the antiplatelet drug before the procedure (Conditional Recommendation, Very Low Certainty of Evidence).

Guideline Implementation Considerations:

- Patients who are receiving dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor can continue ASA and interrupt the $P2Y_{12}$ inhibitor.

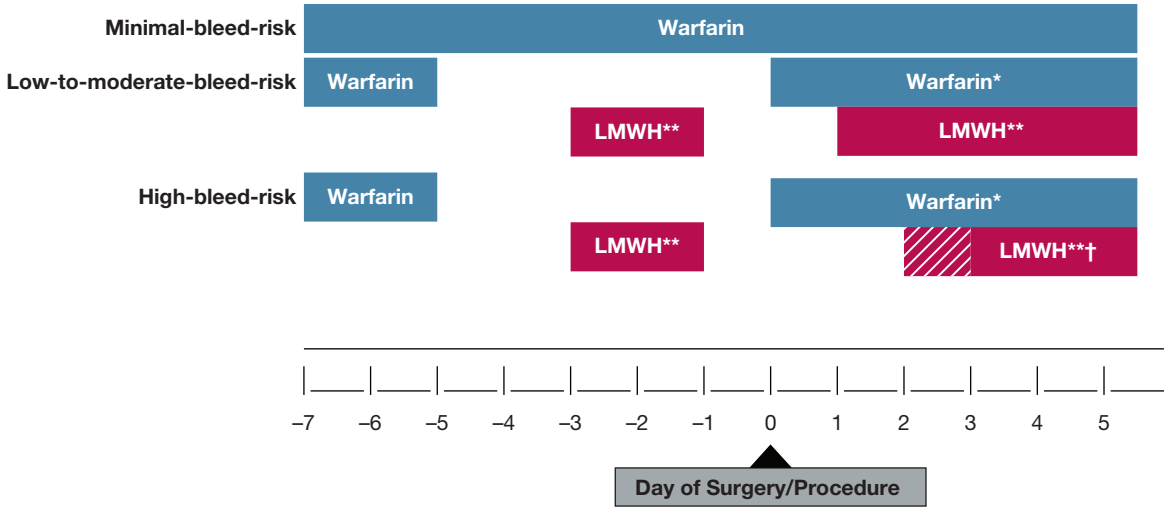
43. In patients receiving an antiplatelet drug (ASA or $P2Y_{12}$ inhibitor) undergoing a minor ophthalmologic procedure, we suggest continuing the antiplatelet drug (ASA or $P2Y_{12}$ inhibitor) throughout the ophthalmologic procedure over stopping the antiplatelet agent before the procedure (Conditional Recommendation, Low Certainty of Evidence).

Guideline Implementation Considerations:

- Patients who are receiving dual antiplatelet therapy with ASA and a $P2Y_{12}$ inhibitor can continue ASA and interrupt the $P2Y_{12}$ inhibitor.

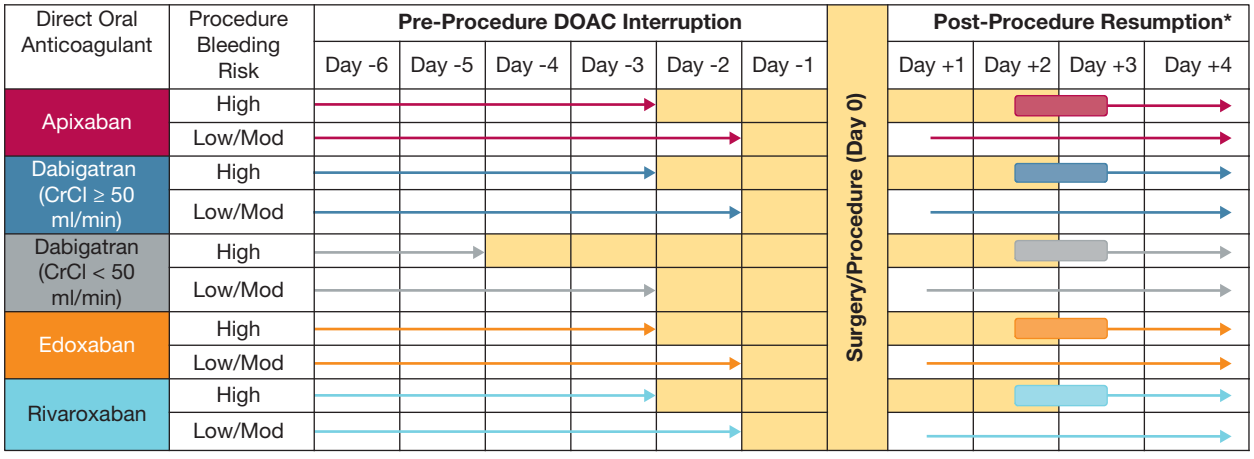
Perioperative Antithrombotic Patient Care Pathways

Based on the evidence presented, perioperative antithrombotic patient care pathways are shown in Figure 1, Figure 2, and Figure 3. These pathways can be used to inform individual patient management and to develop standardized care paths for clinics or institutions. Figure 1 pertains to patients receiving a VKA and provides guidance on whether to interrupt VKA therapy perioperatively, how to interrupt VKA pre-operatively (if interruption is needed), whether to use heparin bridging therapy and how to bridge, and how to restart VKA and bridging therapy (if used) post-



Legend
*Warfarin can be resumed on the evening of procedure (D0) for most patients, or the day after procedure (i.e., D1) at the patient's usual maintenance dose.
**Bridging suggested for high thrombotic risk populations with full-dose, subcutaneous LMWH (e.g., enoxaparin, 1 mg/kg bid or 1.5 mg/kg daily or dalteparin, 100 IU/kg bid or 200 IU/kg daily), with the last dose given the AM of the day prior to the procedure (i.e., D-1) at half the total daily dose.
†Low-dose LMWH (e.g., enoxaparin, 40 mg daily or dalteparin 5,000 IU daily) can be used for VTE prophylaxis for first 24-72 hours post-procedure, with full dose LMWH resumed 2-3 days post-procedure.

Figure 1 – *Perioperative management of vitamin K antagonists (warfarin). LMWH = low-molecular-weight heparin.*

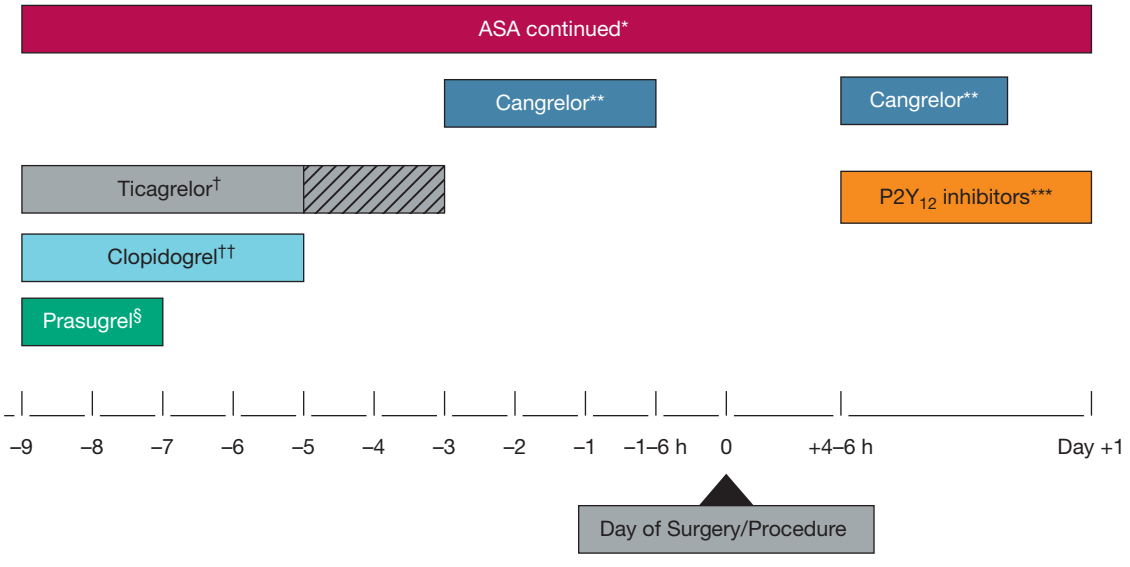


No DOAC administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Figure 2 – *Perioperative management of direct oral anticoagulants (DOACs). CrCl = creatinine clearance.*

operatively. Figure 2 pertains to patients receiving a DOAC and provides guidance on whether to interrupt DOAC therapy perioperatively, and if interruption is needed, how to interrupt DOAC therapy based on surgical/procedural bleed risk in the pre- and post-operative period. Figure 3 pertains to patients who are



Legend:
*Based on surgery/procedure bleed risk assessment.
**Routine use not suggested. If used, initiate within 72 hours from $P2Y_{12}$ inhibitor discontinuation at dose of 0.75 mg/kg/min; resume within 6 hours post-procedure for minimum of 48 hours and maximum of 7 days total. Very low quality data for antiplatelet bridging with glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide, tirofiban).
***$P2Y_{12}$ inhibitors can be resumed within 24 hours post-procedure at a maintenance dose.
†For ticagrelor, 3-5 day interruption
††For clopidogrel, 5 day interruption
§For prasugrel, 7-10 day interruption.

Figure 3 – *Perioperative management of antiplatelet drugs. ASA = aspirin.*

receiving antiplatelet therapy and provides guidance on the timing of peri-operative interruption and resumption based on the type of antiplatelet agent (ie, ASA, clopidogrel, prasugrel, ticagrelor).

Future Research

Although there have been important advances in the perioperative management of anticoagulant and antiplatelet therapy, much work remains to bridge gaps in knowledge. In VKA-treated patients with a mechanical heart valve, there is a need for well-designed studies, especially randomized trials, to further assess the need for perioperative heparin bridging during VKA interruption. In DOAC-treated patients, there is a need for additional research and consensus among clinicians as to safe DOAC interruption intervals before neuraxial anesthesia or regional nerve block procedures, and for patients with severe chronic kidney disease, with a CrCl $<$ 30 mL/min. Further research is also needed as to the perioperative management of patients who are receiving low-dose DOAC regimens, whether in combination with ASA for chronic coronary or peripheral arterial disease or for the secondary prevention of VTE and those who are receiving antiplatelet monotherapy with a $P2Y_{12}$ inhibitor. A challenging area of research is the perioperative management of antiplatelet drugs, especially in those patients with coronary stents who are receiving ASA and a $P2Y_{12}$ inhibitor, as there are multiple factors (timing of stent placement, type of surgery, type of antiplatelet therapy) that make it difficult to undertake randomized trials. In all patient groups, the role of perioperative laboratory testing that includes anti-factor Xa levels during heparin bridging, DOAC anti-factor Xa levels and dilute thrombin time testing, antiplatelet function testing, and viscoelastic testing, remains uncertain. Research is also needed to inform perioperative anticoagulant management of special patient populations (eg, those who are dialysis-dependent). Finally, although beyond the scope of this guideline, research is needed in patients who require an urgent/emergency surgery to inform best practices, including the role of laboratory and point-of-care assays to measure DOAC levels, and the role of anticoagulant and antiplatelet reversal strategies.

Acknowledgments

Author contributions: J. D. D. and A. C. S. served as the co-principal authors; all authors contributed to the development of the guideline methodology, analysis of evidence and writing of the manuscript.

Funding/support: The authors have reported to *CHEST* that no funding was received for this study.

Financial/nonfinancial disclosures: A complete list of the panelists' COI and their management is shown in e-Appendix 1.

Other contributions: The authors thank Dr Ioannis Koulas who is supported by the Broxmeyer Fellowship in Clinical Thrombosis, as well as Jennifer Cookingham, Andrew Dominello, Laura Hyppolite, and Ariana McGinn for their assistance with the tables and figures.

Additional information: The e-Appendixes are available online under "Supplementary Data."

References

1. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost*. 2016;14(5):875-885.
2. Colacci M, Tseng EK, Sacks CA, Fralick M. Oral anticoagulant utilization in the United States and United Kingdom. *J Gen Intern Med*. 2020;35(8):2505-2507.
3. Omling E, Jarnheimer A, Rose J, Bjork J, Meara JG, Hagander L. Population-based incidence rate of inpatient and outpatient surgical procedures in a high-income country. *Br J Surg*. 2018;105(1):86-95.
4. Gao L, Tadrous M, Knowles S, et al. Prior authorization and Canadian public utilization of direct-acting oral anticoagulants. *Healthc Policy*. 2017;13(2):68-78.
5. Proietti M, Laroche C, Opolski G, et al. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace*. 2017;19(5):722-733.
6. Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *Am Heart J*. 2017;194:132-140.
7. Williams BA, Honushefsky AM, Berger PB. Temporal trends in the incidence, prevalence, and survival of patients with atrial fibrillation from 2004 to 2016. *Am J Cardiol*. 2017;120(11):1961-1965.
8. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126(3):343-348.
9. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract*. 2018;72(3):e13070.
10. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014;129(18):1850-1859.
11. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J*. 2014;35(35):2383-2431.
12. Cruden NL, Harding SA, Flapan AD, et al. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ Cardiovasc Interv*. 2010;3(3):236-242.
13. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl 6):299S-339S.

14. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e326S-e350S.
15. Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH: reply. *J Thromb Haemost*. 2015;13(11):2132-2133.
16. Spencer NH, Sardo LA, Cordell JP, Douketis JD. Structure and function of a perioperative anticoagulation management clinic. *Thromb Res*. 2019;182:167-174.
17. Dager WE, Ansell J, Barnes GD, et al. Reduce the Likelihood of Patient Harm Associated with the Use of Anticoagulant Therapy": Commentary from the Anticoagulation Forum on the Updated Joint Commission NPSG.03.05.01 Elements of Performance. *Jt Comm J Qual Patient Saf*. 2020;46(3):173-180.
18. Lewis SZ, Diekemper R, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and expert panel reports. *Chest*. 2014;146(1):182-192.
19. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e152S-e184S.
20. Levy JH, Spyropoulos AC, Samama CM, Douketis J. Direct oral anticoagulants: new drugs and new concepts. *JACC Cardiovasc Interv*. 2014;7(12):1333-1351.
21. Douketis JD. Pharmacologic properties of the new oral anticoagulants: a clinician-oriented review with a focus on perioperative management. *Current Pharm Des*. 2010;16(31): 3436-3441.
22. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl 3):188S-203S.
23. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126(13):1630-1639.
24. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3(23):3898-3944.
25. Spyropoulos AC, Brohi K, Caprini J, et al. Scientific and Standardization Committee Communication: guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. *J Thromb Haemost*. 2019;17(11):1966-1972.
26. Levy JH, Douketis J, Weitz JI. Reversal agents for non-vitamin K antagonist oral anticoagulants. *Nat Rev Cardiol*. 2018;15(5): 273-281.
27. Douketis JD, Healey JS, Brueckmann M, et al. Urgent surgery or procedures in patients taking dabigatran or warfarin: analysis of perioperative outcomes from the RE-LY trial. *Thromb Res*. 2016;139:77-81.
28. Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(3):623-627.
29. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131(7):492-501.
30. 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(1):54. 51.
31. Gage BF, Fihn SD, White RH. Warfarin therapy for an octogenarian who has atrial fibrillation. *Ann Intern Med*. 2001;134(6):465-474.
32. 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(16):2287-2292.
33. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89(2):635-641.
34. Hering 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(1):53-59.
35. Tominaga R, Kurisu K, Ochiai Y, et al. A 10-year experience with the Carbomedics cardiac prosthesis. *Ann Thorac Surg*. 2005;79(3): 784-789.
36. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. *Arch Intern Med*. 2000;160(22):3431-3436.
37. White R. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):14-18.
38. Kyrle PA, Eichinger S. Deep vein thrombosis. *Lancet*. 2005;365(9465):1163-1174.
39. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. *Can J Cardiol*. 2018;34(3):214-233.
40. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213-260.
41. Leary MC, Varade P. Perioperative stroke. *Curr Neurol Neurosci Rep*. 2020;20(5):12.
42. Weiss AJ, Svensson LG, Bakaeen FG. Temporal improvements in perioperative stroke rates following coronary artery bypass grafting. *Curr Opin Cardiol*. 2020;35(6):679-686.
43. Kaatz S, Douketis JD, Zhou H, Gage BF, White RH. Risk of stroke after surgery in patients with and without chronic atrial fibrillation. *J Thromb Haemost*. 2010;8(5):884-890.
44. Chen AT, Patel M, Douketis JD. Perioperative management of antithrombotic therapy: a case-based narrative review. *Intern Emerg Med*. 2022;17(1):25-35.
45. Shaw JR, Kaplovitch E, Douketis J. Periprocedural management of oral anticoagulation. *Med Clin North Am*. 2020;104(4):709-726.
46. Jamula E, Anderson J, Douketis JD. Safety of continuing warfarin therapy during cataract surgery: a systematic review and meta-analysis. *Thromb Res*. 2009;124(3):292-299.
47. Nematullah A, Alabousi A, Blanas N, et al. Dental surgery for patients on anticoagulant therapy with warfarin: a systematic review and meta-analysis. *J Can Dent Assoc*. 2009;75(1):41.
48. Jamula E, Lloyd NS, Schwalm JD, Airaksinen KE, Douketis JD. Safety of uninterrupted anticoagulation in patients requiring elective coronary angiography with or without percutaneous coronary intervention: a systematic review and metaanalysis. *Chest*. 2010;138(4):840-847.
49. Palamaras I, Semkova K. Perioperative management of and recommendations for antithrombotic medications in dermatological surgery. *Br J Dermatol*. 2015;172(3):597-605.
50. Jamula E, Douketis JD, Schulman S. Perioperative anticoagulation in patients having implantation of a cardiac pacemaker or defibrillator: a systematic review and practical management guide. *J Thromb Haemost*. 2008;6(10):1615-1621.
51. Narouze S, Benzon HT, Provenzano D, et al. Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition): guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med*. 2018;43(3):225-262.
52. Bateman BT, Mhyre JM, Ehrenfeld J, et al. The risk and outcomes of epidural hematomas after perioperative and obstetric epidural

catheterization: a report from the Multicenter Perioperative Outcomes Group Research Consortium. *Anesth Analg*. 2013;116(6):1380-1385.

53. Abayon M, Kolokythas A, Harrison S, Elad S. Dental management of patients on direct oral anticoagulants: case series and literature review. *Quintessence Int*. 2016;47(8):687-696.
54. Feagins LA. Colonoscopy, polypectomy, and the risk of bleeding. *Med Clin North Am*. 2019;103(1):125-135.
55. Zollinger RM Jr. An updated traditional classification of inguinal hernias. *Hernia*. 2004;8(4):318-322.
56. 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(12):1658-1663.
57. Douketis JD, Frere C, Farge D; International Thrombosis and Cancer Initiative members. 2019 International clinical practice guidelines for the treatment of venous thromboembolism—authors' reply. *Lancet Oncol*. 2019;20(12):e656.
58. D'Astous J, Liederman Z, Douketis JD. Venous thromboembolism prophylaxis in high-risk orthopedic and cancer surgery. *Postgrad Med*. 2021;133(suppl 1):20-26.
59. Kataruka A, Renner E, Barnes GD. Evaluating the role of clinical pharmacists in pre-procedural anticoagulation management. *Hosp Pract (1995)*. 2018;46(1):16-21.
60. Mihalj M, Carrel T, Gregoric ID, et al. Telemedicine for preoperative assessment during a COVID-19 pandemic: recommendations for clinical care. *Best Pract Res Clin Anaesthesiol*. 2020;34(2):345-351.
61. Flaker GC, Theriot P, Binder LG, Dobesh PP, Cuker A, Doherty JU. Management of periprocedural anticoagulation: a survey of contemporary practice. *J Am Coll Cardiol*. 2016;68(2):217-226.
62. Douketis JD, Syed S, Li N, et al. A physician survey of perioperative neuraxial anesthesia management in patients on a direct oral anticoagulant. *Res Pract Thromb Haemost*. 2021;5(1):159-167.
63. Kurlander JE, Barnes GD, Anderson MA, et al. Mind the gap: results of a multispecialty survey on coordination of care for peri-procedural anticoagulation. *J Thromb Thrombolysis*. 2018;45(3):403-409.
64. Broderick JP, Bonomo JB, Kissela BM, et al. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. *Stroke*. 2011;42(9):2509-2514.
65. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: results from the ROCKET AF trial. *Heart Rhythm*. 2014;11(6):925-932.
66. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ*. 2008;336(7652):1049-1051.
67. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 2016;353:i2089.
68. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
69. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311(7001):376-380.
70. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl 6):160S-198S.
71. Palareti G, Legnani C. Warfarin withdrawal. Pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet*. 1996;30(4):300-313.
72. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet*. 2005;44(12):1227-1246.
73. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. *Br J Haematol*. 2002;117(4):940-946.
74. Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. 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(6):393-400.
75. Kamali F, Wynne H. Pharmacogenetics of warfarin. *Annu Rev Med*. 2010;61:63-75.
76. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373(9):823-833.
77. Selim M. Perioperative stroke. *N Engl J Med*. 2007;356(7):706-713.
78. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. *Ann Intern Med*. 1995;122(1):40-42.
79. Steib A, Barre J, Mertes M, et al. Can oral vitamin K before elective surgery substitute for preoperative heparin bridging in patients on vitamin K antagonists? *J Thromb Haemost*. 2010;8(3):499-503.
80. Douketis JD, Murphy SA, Antman EM, et al. Peri-operative adverse outcomes in patients with atrial fibrillation taking warfarin or edoxaban: analysis of the ENGAGE AF-TIMI 48 Trial. *Thromb Haemost*. 2018;118(6):1001-1008.
81. Garcia DA, Regan S, Henault LE, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med*. 2008;168(1):63-69.
82. Qureshi AI, Jahangir N, Malik AA, Afzal MR, Orfi F, Suri MF. Risk of ischemic stroke in high risk atrial fibrillation patients during periods of warfarin discontinuation for surgical procedures. *Cerebrovasc Dis*. 2016;42(5-6):346-351.
83. Constans M, Santamaria A, Mateo J, Pujol N, Souto JC, Fontcuberta J. 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(2):212-217.
84. Daniels PR, McBane RD, Litin SC, et al. Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. *Thromb Res*. 2009;124(3):300-305.
85. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood*. 2014;124(25):3692-3698.
86. 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(3):285-292.
87. Malato A, Saccullo G, Lo Coco L, et al. Patients requiring interruption of long-term oral anticoagulant therapy: the use of fixed sub-therapeutic doses of low-molecular-weight heparin. *J Thromb Haemost*. 2010;8(1):107-113.
88. Pengo V, Cucchini U, Denas G, et al. Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. *Circulation*. 2009;119(22):2920-2927.
89. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. Observations in 180 operations. *JAMA*. 1978;239(8):738-739.
90. Tinmouth AH, Morrow BH, Cruickshank MK, Moore PM, Kovacs MJ. Dalteparin as periprocedure anticoagulation for patients on warfarin and at high risk of thrombosis. *Ann Pharmacother*. 2001;35(6):669-674.
91. Witt DM, Delate T, McCool KH, et al. Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. *J Thromb Haemost*. 2009;7(12):1982-1989.

92. Wysokinski WE, McBane RD, Daniels PR, et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clin Proc*. 2008;83(6):639-645.

93. 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(4):478-480. A410.

94. 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(5):649-658.

95. 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(12):1319-1326.

96. Beldi G, Beng L, Siegel G, Bisch-Knaden S, Candinas D. Prevention of perioperative thromboembolism in patients with atrial fibrillation. *Br J Surg*. 2007;94(11):1351-1355.

97. Schulman S, Hwang HG, Eikelboom JW, Kearon C, Pai M, Delaney J. Loading dose vs. maintenance dose of warfarin for reinitiation after invasive procedures: a randomized trial. *J Thromb Haemost*. 2014;12(8):1254-1259.

98. Bungard TJ, Mutch J, Ritchie B. A randomized trial of restarting warfarin at maintenance versus loading doses following an elective procedure. *J Thromb Thrombolysis*. 2017;44(4):507-515.

99. Woods K, Douketis JD, Kathirgamanathan K, Yi Q, Crowther MA. 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(2):93-97.

100. Shields RC, McBane RD, Kuiper JD, Li H, Heit JA. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. *Mayo Clin Proc*. 2001;76(3):260-266.

101. Tsu LV, Dienes JE, Dager WE. Vitamin K dosing to reverse warfarin based on INR, route of administration, and home warfarin dose in the acute/critical care setting. *Ann Pharmacother*. 2012;46(12):1617-1626.

102. Kulig CE, Roberts AJ, Rowe AS, Kim H, Dager WE. INR response to low-dose vitamin K in warfarin patients. *Ann Pharmacother*. 2021;55(10):1223-1229.

103. Polito NB, Kanouse E, Jones CMC, McCann M, Refaai MA, Acquisto NM. Effect of vitamin K administration on rate of warfarin reversal. *Transfusion*. 2019;59(4):1202-1208.

104. Meehan R, Tavares M, Sweeney J. Clinical experience with oral versus intravenous vitamin K for warfarin reversal. *Transfusion*. 2013;53(3):491-498. quiz 490.

105. Kovacs MJ, Wells PS, Anderson DR, et al. Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. *BMJ*. 2021;373:n1205.

106. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*. 2015;131(5):488-494.

107. Bui HT, Krisnaswami A, Le CU, Chan J, Shenoy BN. Comparison of safety of subcutaneous enoxaparin as outpatient anticoagulation bridging therapy in patients with a mechanical heart valve versus patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2009;104(10):1429-1433.

108. Ferreira I, Dos L, Tornos P, Nicolau I, Permanyer-Miralda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. *Heart*. 2003;89(5):527-530.

109. Spyropoulos AC, Turpie AG, Dunn AS, et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). *Am J Cardiol*. 2008;102(7):883-889.

110. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. *Thromb Haemost*. 2015;113(3):625-632.

111. Barnes GD, Li Y, Gu X, et al. Periprocedural bridging anticoagulation in patients with venous thromboembolism: a registry-based cohort study. *J Thromb Haemost*. 2020;18(8):2025-2030.

112. McBane RD, Wysokinski WE, Daniels PR, et al. Periprocedural anticoagulation management of patients with venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2010;30(3):442-448.

113. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. *JAMA Intern Med*. 2015;175(7):1163-1168.

114. Tafur AJ, Wysokinski WE, McBane RD, et al. Cancer effect on periprocedural thromboembolism and bleeding in anticoagulated patients. *Ann Oncol*. 2012;23(8):1998-2005.

115. Skeith L, Taylor J, Lazo-Langner A, Kovacs MJ. Conservative perioperative anticoagulation management in patients with chronic venous thromboembolic disease: a cohort study. *J Thromb Haemost*. 2012;10(11):2298-2304.

116. Wysokinska EM, Wysokinski WE, Ketha S, et al. Periprocedural anticoagulation management of patients with thrombophilia. *Am J Med*. 2016;129(9):986-992.

117. Baumgartner C, de Kouchkovsky I, Whitaker E, Fang MC. Periprocedural bridging in patients with venous thromboembolism: a systematic review. *Am J Med*. 2019;132(6):722-732.e7.

118. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA*. 1998;279(6):458-462.

119. Halbritter KM, Wawer A, Beyer J, Oettler W, Schellong SM. Bridging anticoagulation for patients on long-term vitamin-K-antagonists. A prospective 1 year registry of 311 episodes. *J Thromb Haemost*. 2005;3(12):2823-2825.

120. 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(1):11-16.

121. Yong JW, Yang LX, Ohene BE, Zhou YJ, Wang ZJ. Periprocedural heparin bridging in patients receiving oral anticoagulation: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2017;17(1):295.

122. Attaya H, Wysokinski WE, Bower T, et al. Three-month cumulative incidence of thromboembolism and bleeding after periprocedural anticoagulation management of arterial vascular bypass patients. *J Thromb Thrombolysis*. 2013;35(1):100-106.

123. Borea G, Montebugnoli L, Capuzzi P, Magelli C. 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(1):29-31.

124. Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. *Br J Oral Maxillofac Surg*. 2002;40(3):248-252.

125. Sacco R, Sacco M, Carpenedo M, Moia M. Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different INR targets. *J Thromb Haemost*. 2006;4(3):688-689.

126. 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(12):1405-1409.

127. 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(5):504-507.

128. Carter G, Goss A, Lloyd J, Tocchetti R. 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(12):1432-1435.

129. 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(3):257-259.

130. Ramstrom G, Sindet-Pedersen S, Hall G, Blomback M, Alander U. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. *J Oral Maxillofac Surg*. 1993;51(11):1211-1216.

131. Bajkin BV, Popovic SL, Selakovic SD, Bajkin BV, Popovic SL, Selakovic SDJ. Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *J Oral Maxillofac Surg*. 2009;67(5):990-995.

132. Cannon PD, Dharmar VT. Minor oral surgical procedures in patients on oral anticoagulants—a controlled study. *Aust Dent J*. 2003;48(2):115-118.

133. 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(2):107-111.

134. Gaspar R, Brenner B, Ardekian L, Peled M, Laufer D. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. *Quintessence Int*. 1997;28(6):375-379.

135. Saour JN, Ali HA, Mammo LA, Sieck JO. Dental procedures in patients receiving oral anticoagulation therapy. *J Heart Valve Dis*. 1994;3(3):315-317.

136. Street AM, Leung W. Use of tranexamic acid mouthwash in dental procedures in patients taking oral anticoagulants. *Med J Aust*. 1990;153(10):630.

137. Zanon E, Martinelli F, Bacci C, Cordioli G, Girolami A. Safety of dental extraction among consecutive patients on oral anticoagulant treatment managed using a specific dental management protocol. *Blood Coagul Fibrinolysis*. 2003;14(1):27-30.

138. Blinder D, Manor Y, Martinowitz U, Taicher S. 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(6):518-521.

139. 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(11):1275-1278.

140. Martinowitz U, Mazar AL, Taicher S, et al. Dental extraction for patients on oral anticoagulant therapy. *Oral Surg Oral Med Oral Pathol*. 1990;70(3):274-277.

141. Ramli R, Rahman RA. Minor oral surgery in anticoagulated patients: local measures alone are sufficient for haemostasis. *Singapore Dental J*. 2005;27(1):13-16.

142. Russo G, Corso LD, Biasiolo A, Berengo M, Pengo V. Simple and safe method to prepare patients with prosthetic heart valves for surgical dental procedures. *Clin Appl Thromb Hemost*. 2000;6(2):90-93.

143. Zusman SP, Lustig JP, Baston I. Postextraction hemostasis in patients on anticoagulant therapy: the use of a fibrin sealant. *Quintessence Int*. 1992;23(10):713-716.

144. Keiani Motlagh K, Loeb I, Legrand W, Daelemans P, Van Reck J. Prevention of postoperative bleeding in patients taking oral anticoagulants. Effects of tranexamic acid [in French]. *Rev Stomatol Chir Maxillofac*. 2003;104(2):77-79.

145. Garcia-Darennes F, Darennes J, Freidel M, Breton P. Protocol for adapting treatment with vitamin K antagonists before dental extraction [in French]. *Rev Stomatol Chir Maxillofac*. 2003;104(2):69-72.

146. Morimoto Y, Niwa H, Minematsu K, Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. *J Oral Maxillofac Surg*. 2008;66(1):51-57.

147. Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? *J Oral Maxillofac Surg*. 2000;58(2):131-135; discussion 135-136.

148. 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(4):421-424.

149. de Andrade NK, Motta RHL, Bergamaschi CC, et al. Bleeding risk in patients using oral anticoagulants undergoing surgical procedures in dentistry: a systematic review and meta-analysis. *Front Pharmacol*. 2019;10:866.

150. Owattanapanich D, Ungprasert P, Owattanapanich W. Efficacy of local tranexamic acid treatment for prevention of bleeding after dental procedures: a systematic review and meta-analysis. *J Dent Sci*. 2019;14(1):21-26.

151. Alcalay J. Cutaneous surgery in patients receiving warfarin therapy. *Dermatol Surg*. 2001;27(8):756-758.

152. 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(5):381-383; discussion 384-385.

153. Kargi E, Babuccu O, Hosnuter M, Babuccu B, Altinyazar C. Complications of minor cutaneous surgery in patients under anticoagulant treatment. *Aesthetic Plast Surg*. 2002;26(6):483-485.

154. Syed S, Adams BB, Liao W, Pipitone M, Gloster H. A prospective assessment of bleeding and international normalized ratio in warfarin-anticoagulated patients having cutaneous surgery. *J Am Acad Dermatol*. 2004;51(6):955-957.

155. Konstantatos A. Anticoagulation and cataract surgery: a review of the current literature. *Anaesth Intensive Care*. 2001;29(1):11-18.

156. Makuloluwa AK, Tiew S, Briggs M. Peri-operative management of ophthalmic patients on anti-thrombotic agents: a literature review. *Eye (Lond)*. 2019;33(7):1044-1059.

157. Hirschman DR, Morby LJ, Hirschman DR, Morby LJ. A study of the safety of continued anticoagulation for cataract surgery patients. *Nursing Forum*. 2006;41(1):30-37.

158. 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(5):708-711.

159. Katz J, Feldman MA, Bass EB, et al. Risks and benefits of anticoagulant and antiplatelet medication use before cataract surgery. *Ophthalmology*. 2003;110(9):1784-1788.

160. Lumme P, Laatikainen LT. Risk factors for intraoperative and early postoperative complications in extracapsular cataract surgery. *Eur J Ophthalmol*. 1994;4(3):151-158.

161. Rotenstreich Y, Rubowitz A, Segev F, Jaeger-Roshu S, Assia EI. Effect of warfarin therapy on bleeding during cataract surgery. *J Cataract Refract Surg*. 2001;27(9):1344-1346.

162. Kumar N, Jivan S, Pulpa V, Butler J, Khan MY. Intraoperative eye position after sub-Tenon's anesthesia for cataract surgery. *Can J Ophthalmol*. 2006;41(4):476-480.

163. Jonas JB, Pakdaman B, Sauder G. Cataract surgery under systemic anticoagulant therapy with coumarin. *Eur J Ophthalmol*. 2006;16(1):30-32.

164. Barequet IS, Sachs D, Priel A, et al. Phacoemulsification of cataract in patients receiving Coumadin therapy: ocular and hematologic risk assessment. *Am J Ophthalmol*. 2007;144(5):719-723.

165. Kumar N, Jivan S, Thomas P, McLure H. Sub-Tenon's anesthesia with aspirin, warfarin, and clopidogrel. *J Cataract Refract Surg*. 2006;32(6):1022-1025.

166. Robinson GA, Nylander A. Warfarin and cataract extraction. *Br J Ophthalmol*. 1989;73(9):702-703.

167. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013;368(22):2084-2093.

168. Proietti R, Porto I, Levi M, et al. Risk of pocket hematoma in patients on chronic anticoagulation with warfarin undergoing electrophysiological device implantation: a comparison of different

peri-operative management strategies. *Eur Rev Med Pharmacol Sci*. 2015;19(8):1461-1479.

169. Feng L, Li Y, Li J, Yu B. Oral anticoagulation continuation compared with heparin bridging therapy among high risk patients undergoing implantation of cardiac rhythm devices: a meta-analysis. *Thromb Haemost*. 2012;108(6):1124-1131.

170. Tischenko A, Gula LJ, Yee R, et al. Implantation of cardiac rhythm devices without interruption of oral anticoagulation compared with perioperative bridging with low-molecular weight heparin. *Am Heart J*. 2009;158(2):252-256.

171. Schulman S, Healey JS, Douketis JD, Delaney J, Morillo CA. Reduced-dose warfarin or interrupted warfarin with heparin bridging for pacemaker or defibrillator implantation: a randomized trial. *Thromb Res*. 2014;134(4):814-818.

172. Airaksinen KE, Korkeila P, Lund J, et al. Safety of pacemaker and implantable cardioverter-defibrillator implantation during uninterrupted warfarin treatment—the FinPAC study. *Int J Cardiol*. 2013;168(4):3679-3682.

173. Pillarisetti J, Maybrook R, Parikh V, et al. Peri-procedural use of direct anticoagulation agents during cardiac device implantation: vitamin K antagonists vs direct oral anticoagulants. *J Interv Card Electrophysiol*. 2020;58(2):141-146.

174. Takeuchi Y, Mabe K, Shimodate Y, et al. Continuous anticoagulation and cold snare polypectomy versus heparin bridging and hot snare polypectomy in patients on anticoagulants with subcentimeter polyps: a randomized controlled trial. *Ann Intern Med*. 2019;171(4):229-237.

175. 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(2):162-167.

176. 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(2):163-165.

177. O'Donnell MJ, Kearon C, Johnson J, et al. Brief communication: preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. *Ann Intern Med*. 2007;146(3):184-187.

178. Douketis JD, Woods K, Foster GA, Crowther MA. 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(3):528-531.

179. 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*. 2004;5:2211-2218.

180. 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(6):1246-1252.

181. Vink R, Rienstra M, van Dongen CJ, et al. Risk of thromboembolism and bleeding after general surgery in patients with atrial fibrillation. *Am J Cardiol*. 2005;96(6):822-824.

182. Douketis J. Perioperative anticoagulation management in patients who are receiving oral anticoagulant therapy: a practical guide for clinicians. *Thromb Res*. 2002;108(1):3-13.

183. Tafur A, Douketis J. Perioperative management of anticoagulant and antiplatelet therapy. *Heart*. 2018;104(17):1461-1467.

184. Douketis J, Schulman S, Syed S. Reply to Dr Lessire et al. *Reg Anesth Pain Med*. 2016;41(6):788.

185. Schulman S, Carrier M, Lee AY, et al. Perioperative management of dabigatran: a prospective cohort study. *Circulation*. 2015;132(3):167-173.

186. Stollberger C, Finsterer J. Update on drug interactions with non-vitamin-K-antagonist oral anticoagulants for stroke prevention in elderly patients. *Expert Rev Clin Pharmacol*. 2021;14(5):569-581.

187. Li A, Li MK, Crowther M, Vazquez SR. Drug-drug interactions with direct oral anticoagulants associated with adverse events in the real world: a systematic review. *Thromb Res*. 2020;194:240-245.

188. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. *J Am Coll Cardiol*. 2018;71(19):2162-2175.

189. Lessire S, Douxfils J, Dincq AS, Mullier F. Periprocedural management of direct oral anticoagulants should be guided by accurate laboratory tests. *Reg Anesth Pain Med*. 2016;41(6):787-788.

190. Tripodi A, Marongiu F, Moia M, et al. The vexed question of whether or not to measure levels of direct oral anticoagulants before surgery or invasive procedures. *Intern Emerg Med*. 2018;13(7):1029-1036.

191. Griffiths R, Babu S, Dixon P, et al. Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. *Anaesthesia*. 2021;76(2):225-237.

192. Adcock DM, Gosselin RC. The danger of relying on the APTT and PT in patients on DOAC therapy, a potential patient safety issue. *Int J Lab Hematol*. 2017;39(suppl 1):37-40.

193. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol*. 2014;64(11):1128-1139.

194. Albaladejo P, Bonhomme F, Blais N, et al. Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP)—September 2015. *Anaesth Crit Care Pain Med*. 2017;36(1):73-76.

195. Douxfils J, Adcock DM, Bates SM, et al. 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. *Thromb Haemost*. 2021;121(8):1008-1020.

196. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. *JAMA Intern Med*. 2019;179(11):1469-1478.

197. Essebag V, Proietti R, Birnie DH, et al. Short-term dabigatran interruption before cardiac rhythm device implantation: multi-centre experience from the RE-LY trial. *Europace*. 2017;19(10):1630-1636.

198. Nazha B, Pandya B, Cohen J, et al. Periprocedural outcomes of direct oral anticoagulants versus warfarin in nonvalvular atrial fibrillation. *Circulation*. 2018;138(14):1402-1411.

199. Nakamura K, Naito S, Sasaki T, et al. Uninterrupted vs. interrupted periprocedural direct oral anticoagulants for catheter ablation of atrial fibrillation: a prospective randomized single-centre study on post-ablation thrombo-embolic and haemorrhagic events. *Europace*. 2019;21(2):259-267.

200. Yu HT, Shim J, Park J, et al. When is it appropriate to stop non-vitamin K antagonist oral anticoagulants before catheter ablation of atrial fibrillation? A multicentre prospective randomized study. *Eur Heart J*. 2019;40(19):1531-1537.

201. Reynolds MR, Allison JS, Natale A, et al. A prospective randomized trial of apixaban dosing during atrial fibrillation ablation: the AEIOU trial. *JACC Clin Electrophysiol*. 2018;4(5):580-588.

202. Barequet IS, Zehavi-Dorin T, Bourla N, Tamarin I, Moisseiev J, Salomon O. Safety of cataract surgery in patients treated with the new oral anticoagulants (NOACs). *Graefes Arch Clin Exp Ophthalmol*. 2019;257(12):2671-2676.

203. Sheikh MA, Kong X, Haymart B, et al. Comparison of temporary interruption with continuation of direct oral anticoagulants for low bleeding risk procedures. *Thromb Res*. 2021;203:27-32.

204. Shaw J, de Wit C, Le Gal G, Carrier M. Thrombotic and bleeding outcomes following perioperative interruption of direct oral anticoagulants in patients with venous thromboembolic disease. *J Thromb Haemost*. 2017;15(5):925-930.

205. Shaw JR, Douketis J, Le Gal G, Carrier M. Periprocedural interruption of anticoagulation in patients with cancer-associated venous thromboembolism: an analysis of thrombotic and bleeding outcomes. *J Thromb Haemost*. 2019;17(7):1171-1178.

206. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-1330.

207. Ferrandis R, Llau JV, Sanz JF, et al. Periprocedural direct oral anticoagulant management: the RA-ACOD Prospective, Multicenter Real-World Registry. *TH Open*. 2020;4(2):e127-e137.

208. Birnie DH, Healey JS, Wells GA, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). *Eur Heart J*. 2018;39(44):3973-3979.

209. Dubois V, Dincq AS, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. *Thromb J*. 2017;15:14.

210. Squizzato A, Poli D, Barcellona D, et al. Management of DOAC in patients undergoing planned surgery or invasive procedure: FCSA position paper. *Thromb Haemost*. 2022;122(3):329-335.

211. Tripodi A. To measure or not to measure direct oral anticoagulants before surgery or invasive procedures: reply. *J Thromb Haemost*. 2016;14(12):2559-2561.

212. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. To measure or not to measure direct oral anticoagulants before surgery or invasive procedures: comment. *J Thromb Haemost*. 2016;14(12):2556-2559.

213. Tafur AJ, Clark NP, Spyropoulos AC, et al. Predictors of bleeding in the perioperative anticoagulant use for surgery evaluation study. *J Am Heart Assoc*. 2020;9(19):e017316.

214. Shaw JR, Li N, Vanassche T, et al. Predictors of preprocedural direct oral anticoagulant levels in patients having an elective surgery or procedure. *Blood Adv*. 2020;4(15):3520-3527.

215. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. *Chest*. 2017;151(1):127-138.

216. Connors JM. Testing and monitoring direct oral anticoagulants. *Blood*. 2018;132(19):2009-2015.

217. Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants. *Thromb Res*. 2019;173:71-76.

218. Gosselin RC, Adcock DM, Douxfils J. An update on laboratory assessment for direct oral anticoagulants (DOACs). *Int J Lab Hematol*. 2019;41(suppl 1):33-39.

219. Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. *Thromb Haemost*. 2018;118(3):437-450.

220. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

221. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326-1335.

222. Godier A, Martin AC, Leblanc I, et al. Peri-procedural management of dabigatran and rivaroxaban: duration of anticoagulant discontinuation and drug concentrations. *Thromb Res*. 2015;136(4):763-768.

223. 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(14):963-981.

224. 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(3):624-632.

225. Roth GJ, Stanford N, Majerus PW. Acetylation of prostaglandin synthase by aspirin. *Proc Natl Acad Sci U S A*. 1975;72(8):3073-3076.

226. Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy*. 2014;34(10):1077-1090.

227. Teng R. Ticagrelor: pharmacokinetic, pharmacodynamic and pharmacogenetic profile: an update. *Clin Pharmacokinet*. 2015;54(11):1125-1138.

228. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation*. 1999;100(15):1667-1672.

229. Dobesh PP. Pharmacokinetics and pharmacodynamics of prasugrel, a thienopyridine P2Y12 inhibitor. *Pharmacotherapy*. 2009;29(9):1089-1102.

230. von Beckerath N, Taubert D, Pogatsa-Murray G, Schomig E, Kastrati A, Schomig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) trial. *Circulation*. 2005;112(19):2946-2950.

231. Kandzari DE, Berger PB, Kastrati A, et al. Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization. *J Am Coll Cardiol*. 2004;44(11):2133-2136.

232. Lenz TL, Hilleman DE. Aggrenox: a fixed-dose combination of aspirin and dipyridamole. *Ann Pharmacother*. 2000;34(11):1283-1290.

233. Schror K. The pharmacology of cilostazol. *Diabetes Obes Metab*. 2002;4(suppl 2):S14-S19.

234. Ward A, Clissold SP. Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs*. 1987;34(1):50-97.

235. Perez-Rivera JA, Monedero-Campo J, Cieza-Borrella C, Ruiz-Perez P. Pharmacokinetic drug evaluation of vorapaxar for secondary prevention after acute coronary syndrome. *Expert Opin Drug Metab Toxicol*. 2017;13(3):339-350.

236. Brogden RN. Non-steroidal anti-inflammatory analgesics other than salicylates. *Drugs*. 1986;32(Suppl 4):27-45.

237. Gulpinar K, Ozdemir S, Ozis E, Sahli Z, Demirtas S, Korkmaz A. A preliminary study: aspirin discontinuation before elective operations; when is the optimal timing? *J Korean Surg Soc*. 2013;85(4):185-190.

238. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355(9212):1295-1302.

239. Oscarsson A, Gupta A, Fredrikson M, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. *Br J Anaesth*. 2010;104(3):305-312.

240. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370(16):1494-1503.

241. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345(25):1809-1817.

242. Mantz J, Samama CM, Tubach F, et al. Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial. *Br J Anaesth*. 2011;107(6):899-910.

243. Tytgat SH, Laman DM, Rijken AM, et al. Emboli rate during and early after carotid endarterectomy after a single preoperative dose of 120 mg acetylsalicylic acid—a prospective double-blind placebo controlled randomised trial. *Eur J Vasc Endovasc Surg*. 2005;29(2):156-161.

244. Antolovic D, Rakow A, Contin P, et al. A randomised controlled pilot trial to evaluate and optimize the use of anti-platelet agents in the perioperative management in patients undergoing general and abdominal surgery—the APAP trial (ISRCTN45810007). *Langenbecks Arch Surg*. 2012;397(2):297-306.

245. Engheta A, Hadadi Abianeh S, Atri A, Sanatkarfar M. Aspirin use and bleeding volume in skin cancer patients undergoing surgery: a randomized controlled trial. *Daru*. 2016;24(1):20.

246. 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(2):141-145.

247. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. *Am J Cardiol*. 2005;95(6):755-757.

248. Ernst A, Eberhardt R, Wahidi M, et al. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest*. 2006;129(3):734-737.

249. Dacey LJ, Munoz JJ, Johnson ER, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg*. 2000;70(6):1986-1990.

250. Myles PS, Smith J, Knight J, et al. Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial: rationale and design. *Am Heart J*. 2008;155(2):224-230.

251. 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(2):281-286.

252. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation*. 2004;110(10):1202-1208.

253. Purkayastha S, Athanasiou T, Malinovski V, et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. *Heart*. 2006;92(4):531-532.

254. Hongo RH, Ley J, Dick SE, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol*. 2002;40(2):231-237.

255. Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;128(3):425-431.

256. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol*. 2011;57(6):672-684.

257. Cao C, Indraratna P, Ang SC, et al. Should clopidogrel be discontinued before coronary artery bypass grafting for patients with acute coronary syndrome? A systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2014;148(6):3092-3098.

258. Nouraei SM, Gholipour Baradari A, Emami Zeydi A. Does early post-operative administration of aspirin influence the risk of bleeding after coronary artery bypass graft surgery? A prospective observational study. *Med Arch*. 2015;69(6):381-383.

259. Geiger J, Teichmann L, Grossmann R, et al. Monitoring of clopidogrel action: comparison of methods. *Clin Chem*. 2005;51(6):957-965.

260. 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(21):2572-2578.

261. Keeler BD, Simpson JA, Fox SC, et al. An observational study investigating the effect of platelet function on outcome after colorectal surgery. *Int J Surg*. 2015;17:28-33.

262. Watson HG, Greaves M. Can we predict bleeding? *Semin Thromb Hemost*. 2008;34(1):97-103.

263. Price MJ, Price MJ. Monitoring platelet function to reduce the risk of ischemic and bleeding complications. *Am J Cardiol*. 2009;103(suppl 3):35A-39A.

264. Nuttall GA, Brown MJ, Stombaugh JW, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology*. 2008;109(4):588-595.

265. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology*. 2008;109(4):596-604.

266. Brotman DJ, Bakhru M, Saber W, et al. Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents: a retrospective cohort study. *J Hosp Med*. 2007;2(6):378-384.

267. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac surgery after coronary drug-eluting stent implantation. *Am J Cardiol*. 2006;98(9):1212-1213.

268. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol*. 2007;49(1):122-124.

269. Anwaruddin S, Askari AT, Saudye H, et al. Characterization of post-operative risk associated with prior drug-eluting stent use. *JACC Cardiovasc Interv*. 2009;2(6):542-549.

270. Graham MM, Sessler DI, Parlow JL, et al. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. *Ann Intern Med*. 2018;168(4):237-244.

271. Albaladejo P, Marret E, Samama CM, et al. Non-cardiac surgery in patients with coronary stents: the RECO study. *Heart*. 2011;97(19):1566-1572.

272. Rodriguez A, Guilera N, Mases A, et al. Management of antiplatelet therapy in patients with coronary stents undergoing noncardiac surgery: association with adverse events. *Br J Anaesth*. 2018;120(1):67-76.

273. Childers CP, Maggard-Gibbons M, Ulloa JG, et al. Perioperative management of antiplatelet therapy in patients undergoing non-cardiac surgery following coronary stent placement: a systematic review. *Syst Rev*. 2018;7(1):4.

274. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. *J Am Coll Cardiol*. 2014;64(25):2730-2739.

275. Egholm G, Kristensen SD, Thim T, et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. *J Am Coll Cardiol*. 2016;68(24):2622-2632.

276. Rossini R, Tarantini G, Musumeci G, et al. A multidisciplinary approach on the perioperative antithrombotic management of patients with coronary stents undergoing surgery: surgery after stenting 2. *JACC Cardiovasc Interv*. 2018;11(5):417-434.

277. Firstenberg MS, Dyke CM, Angiolillo DJ, et al. Safety and efficacy of cangrelor, an intravenous, short-acting platelet inhibitor in patients requiring coronary artery bypass surgery. *Heart Surg Forum*. 2013;16(2):E60-E69.

278. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA*. 2012;307(3):265-274.

279. Tanaka A, Ishii H, Tatami Y, et al. Unfractionated heparin during the interruption of antiplatelet therapy for non-cardiac surgery after drug-eluting stent implantation. *Intern Med*. 2016;55(4):333-337.

280. Capodanno D, Musumeci G, Lettieri C, et al. Impact of bridging with perioperative low-molecular-weight heparin on cardiac and bleeding outcomes of stented patients undergoing non-cardiac surgery. *Thromb Haemost*. 2015;114(2):423-431.

281. Savonitto S, D'Urbano M, Caracciolo M, et al. Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth*. 2010;104(3):285-291.

282. Wilczynski M, Bochenek T, Goral J, et al. Use of eptifibatide in patients with acute stent thrombosis, requiring urgent surgical revascularisation—report of 2 cases [in Polish]. *Kardiol Pol*. 2009;67(11):1313-1316.

283. Dargham BB, Baskar A, Tejani I, et al. Intravenous antiplatelet therapy bridging in patients undergoing cardiac or non-cardiac surgery following percutaneous coronary intervention. *Cardiovasc Revasc Med*. 2019;20(9):805-811.

284. De Servi S, Morici N, Boschetti E, et al. Bridge therapy or standard treatment for urgent surgery after coronary stent implantation: analysis of 314 patients. *Vascul Pharmacol*. 2016;80:85-90.

285. Walker EA, Dager WE. Bridging with tirofiban during oral antiplatelet interruption: a single-center case series analysis

including patients on hemodialysis. *Pharmacotherapy*. 2017;37(8):888-892.

286. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? *J Am Dent Assoc*. 2000;131(3):331-335.

287. Brennan MT, Valerin MA, Noll JL, et al. Aspirin use and post-operative bleeding from dental extractions. *J Dental Res*. 2008;87(8):740-744.

288. Napenas JJ, Hong CH, Brennan MT, et al. The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. *J Am Dental Assoc*. 2009;140(6):690-695.

289. Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg*. 2005;63(9):1262-1265.

290. Medeiros FB, de Andrade AC, Angelis GA, et al. Bleeding evaluation during single tooth extraction in patients with coronary artery disease and acetylsalicylic acid therapy suspension: a prospective, double-blinded, and randomized study. *J Oral Maxillofac Surg*. 2011;69(12):2949-2955.

291. Bartlett GR. Does aspirin affect the outcome of minor cutaneous surgery? *Br J Plast Surg*. 1999;52(3):214-216.

292. Shalom A, Wong L. Outcome of aspirin use during excision of cutaneous lesions. *Ann Plast Surg*. 2003;50(3):296-298.

293. Narendran N, Williamson TH. The effects of aspirin and warfarin therapy on haemorrhage in vitreoretinal surgery. *Acta Ophthalmol Scand*. 2003;81(1):38-40.

294. Winkler KP, Beaulieu R, Bevill L, Mishulin A, Black EH. Effects of aspirin on postoperative bruising and bleeding complications in upper eyelid surgery. *Ophthalmic Plast Reconstr Surg*. 2020;36(6):575-578.

295. Isted A, Cooper L, Colville RJ. Bleeding on the cutting edge: a systematic review of anticoagulant and antiplatelet continuation in minor cutaneous surgery. *J Plast Reconstr Aesthet Surg*. 2018;71(4):455-467.

Update

Chest
Volume 164, Issue 1, July 2023, Page 267

DOI: https://doi.org/10.1016/j.chest.2023.05.019

CHEST

Corrigendum to: *CHEST*. 2022;162(5):e207-e243

The November 2022 guideline entitled "Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline" contained risk classification schemes for thromboembolism and surgery/procedure-related bleeding that were empiric but not prospectively validated. To provide more clarity and to prevent misinterpretation, the authors have issued the following changes to Table 1:

- The title of the table has been changed from "Adapted American College of Chest Physicians (CHEST) Suggested Risk Stratification for Patient-Specific Periprocedural Thromboembolism" to "Suggested Risk Stratification for Patient-specific Periprocedural Thromboembolism" and additional permission information has been included.
- A footnote (cited in the Table title) has been added, labeled as footnote a: "Empiric risk stratification that is a starting point for assessing perioperative thromboembolism risk; should be combined with clinical judgment that incorporates individual patient- and surgery/procedure-related factors."
- In row 2, column 2, the following has been added to the moderate risk category for "Mechanical Heart Valve": "Mitral valve *without* risk factors for stroke."
- Footnote c has been incorporated into footnote b. Footnote b (cited after "risk factors for stroke" in the low and moderate risk categories) now reads, "Includes AF, prior stroke/TIA during anticoagulant interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, and age ≥ 75 years."
- Footnote a, "Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer" (cited after "Active cancer associated with high VTE risk" in the high-risk category), has been relabeled as footnote c.

The online version of this article has been corrected.

Related Article DOI:

https://doi.org/10.1016/j.chest.2022.07.025