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RECOMMENDATIONS AND GUIDELINES

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

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1 | INTRODUCTION

The periprocedural management of patients on chronic oral anticoagulant therapy (OAC)—including Vitamin K antagonists (VKA) such as warfarin and the direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban—is a common clinical problem.[1,2] Both OAC-specific factors as well as patient- and surgery-specific risk factors for bleeding and thromboembolism (TE) should be assessed and risk stratified in any periprocedural anticoagulant management strategy.[2-5] Procedural bleed risk anchors decisions as to *whether* anticoagulants need to be interrupted and, if anticoagulant interruption is deemed necessary, the *timing of perioperative interruption and resumption*.[3,6] Patient-specific TE risk anchors decisions of whether *an aggressive periprocedural antithrombotic approach* such as bridging therapy with treatment doses of unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH), typically during VKA interruption, would be used with the intention of preventing perioperative cardioembolic TE in high-risk patients.[2,4,7] Recent systematic reviews, meta-analyses, and guidance statements on the topic found a lack of uniform definitions of procedural/surgical bleed risk and patient-specific TE risk, identifying a need to apply a standardized risk stratification approach.[2,6-11] Thus, the aim of adopting a standardized periprocedural classification of procedural/surgical bleed risk and patient-specific TE risk

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would ensure: (a) harmonized outcome reporting across clinical trials, observational studies and meta-analyses that would allow comparison and pooling of results; (b) assistance to guideline developers in interpretation of study results as they pertain to patient subgroups undergoing specific procedures; and (c) development of consistent and cost-efficient institutional protocols whereby the risk classification informs periprocedural anticoagulant management approaches.

The objective of this official SSC communication of the ISTH using a multidisciplinary panel of internists, hematologists, anesthesiologists, vascular medicine specialists, and surgeons is to propose a standardized risk stratification scheme for reporting of both procedural/surgical bleed risk and patient-specific TE risk for patients on chronic OAC—either VKA or the DOACs—who need an elective procedure or surgery. This document builds upon previous work of standardized reporting for periprocedural antithrombotic and bridging therapy as part of the Scientific and Standardization Committee of the ISTH.[12]

2 | PROCEDURAL/SURGICAL BLEED RISK STRATIFICATION

Although multiple factors such as patient-specific bleeding diatheses and the type of anaesthesia may contribute to an overall bleed risk estimation in procedural settings, stratification of procedural or surgical bleeding risk is the most important determinant in the overall periprocedural management strategy of a patient on chronic OAC as it anchors *whether* an OAC needs to be interrupted and, if OAC interruption is necessary, the *timing of interruption* of OACs, and the timing of UFH or LMWH bridging therapy in the postprocedural period.[3] Consequently, a three-tier procedural bleed risk classification, empirically designated as "high bleed risk," "low/moderate bleed risk," and "minimal bleed risk" would, in general, distinguish patients who do not need anticoagulant interruption ("minimal bleed risk") from those who need interruption ("high bleed risk" and "low/moderate" bleed risk).[5] Among patients who will need anticoagulant interruption based on the perceived bleeding risk of a procedure or surgery, the procedural classification of "high bleed risk" would distinguish patients on VKA who need a longer interruption period prior to resumption of postprocedural UFH or LMWH bridging therapy or on a DOAC who will need a longer interval for preprocedural interruption and postprocedural resumption of a DOAC. Procedures needing OAC interruption deemed "low/moderate bleed risk" would require shorter intervals for UFH or LMWH bridging postprocedurally for VKA or interruption and resumption of a DOAC.[5]

In terms of minimal bleed risk procedures, data from randomized trials in patients with AF on either VKA and DOACs undergoing pacemaker/defibrillator placement and atrial fibrillation (AF) ablation strongly suggest that these procedures carry a low risk of significant pocket hematoma with continued OAC therapy, with an incidence of ~2.1% to 3.5% (95% confidence interval [CI]: 0.9-4.3) at 30 days[13,14] and an incidence of major bleeding of 0.38%.[15] Moreover, data from systematic reviews and observational studies of periprocedural VKA or DOAC continuation found low rates of procedure site bleeding of ~2.0 to 3.0% (95% CI: 1.1%-5.8%).[16-18] Last, a recent meta-analysis of 4519 procedures in patients with AF deemed at bleed risk low enough to warrant uninterrupted VKA or DOAC, including diagnostic gastrointestinal endoscopic procedures, dermatologic procedures, ophthalmological procedures (cataract removal), and dental/maxillofacial surgical procedures revealed pooled incidence rates of major bleed (MB) at 30 days of 3.3% (95% CI: 2.7-4.0) and 2.0% (95% CI: 1.6-2.4), respectively, which is higher than the perceived bleeding risk.[19] Surgical and procedural societies have included non-specific terms that include "not clinically relevant" and "very low bleed risk" to describe bleed risk in procedures associated with a 2-day MB rate of <1% and, by definition, would not warrant OAC interruption.[11] Other guidance statements on the topic refer to the term "minimal bleed risk" to describe those procedures or surgeries at low enough bleed risk to warrant uninterrupted OAC (or at most a single interruption of DOAC on the day of procedure).[5]

For patients on chronic OAC undergoing procedures or surgeries at high enough bleed risk to warrant OAC discontinuation, data from observational studies, substudies from randomized control trials (RCTs), RCTs, and meta-analyses suggest that the overall 30-day periprocedural background incidence of MB is ~1.0%-3.0%.[5,9,19-23] A recent meta-analysis of substudies of RCTs in patients with AF undergoing 16 479 procedures necessitating warfarin or DOAC interruption found a 30-day incidence of MB of 2.0% (95% CI: 1.7-2.3) and 2.1% (95% CI: 1.8-2.4), respectively.[19] More recently, preliminary results from the large, multicenter PAUSE trial assessing standardized DOAC interruption for an elective procedure or surgery also found a 30-day MB rate of 1.43% (95% CI: 0-1.83).[24]

The bleed risk stratification of procedures and surgeries requiring OAC interruption into non-high bleed risk vs high bleed risk is important because the anticipated background event rates for bleeding would anchor the timing of periprocedural OAC management. Based on early available data of background postprocedural bleed rates, it was suggested that the 2-day risk of MB in patients on chronic OAC without heparin bridging therapy was 0%-2% in low bleed risk procedures and 2%-4% in high bleed risk procedures.[5] Data from the BRIDGE trial revealed a 30-day incidence of MB that was almost threefold higher in patients having high vs low bleed risk procedures or surgeries (5.5% vs 2.0%; OR = 2.9, 95% CI 1.4-5.9, P = .0043).[25] Recent data from the PAUSE Trial with DOACs reveal that for low/moderate bleed risk procedures the 30-day MB incidence was 0.9% (95% CI: 0-1.3), while that of high bleed risk procedures or surgeries was 2.48% (95% CI: 0-3.4).[24]

For surgeries/procedures classified in the low/moderate bleed-risk category, a strategy of OAC interruption of two to three half-lives preprocedure, which would enable some residual anticoagulant effect (ie 3 days off for warfarin, 1 day off for DOACs) and therapeutic-dose anticoagulant resumption within 1 day postprocedurally (for heparin bridging therapy with warfarin and for DOACs in general) would be associated with an acceptably low periprocedural bleeding risk. For procedures/surgeries in the high bleed-risk category, a strategy of OAC interruption of four to five half-lives preprocedure

TABLE 1 Risk stratification for procedural bleed risk as suggested by the ISTH Guidance Statement and BRIDGE Trial[5,22]

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

[a]No residual anticoagulant effect at time of procedure (ie 4-5 drug half-life interruption preprocedure).
[b]Includes spinal and epidural anaesthesia, consider not only absolute MB event rate but catastrophic consequences of a MB.
[c]Some residual anticoagulant effect allowed (ie 2-3 drug half-life interruption preprocedure).
[d]Radial approach may be considered minimal bleed risk compared to 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).

(ie, 5 days off for warfarin and 2 days off for DOACs), and resumption 2 to 3 days postprocedurally in the case of treatment-dose UFH or LMWH bridging therapy for warfarin and for DOACs in general would be associated with an acceptable periprocedural bleeding risk.[5] There are data to suggest that in warfarin-treated patients, resumption of LMWH bridging at treatment doses after high bleed risk procedures within 24 hours postprocedure confers a 20-fold higher risk for MB.[26]

With respect to specific classifications of procedures or surgeries requiring OAC interruption and bleed risk, the terminology and classification used across studies and by procedural and surgical societies was not uniform. Most studies divided procedures/surgeries into a two-tier risk scheme for bleeding, including: (a) "high risk," and (b) "low risk," or "non-high risk." The "high bleed risk" category was relatively uniform and included most major surgeries lasting >45 minutes; major abdominal/pelvic, cardiothoracic, vascular, urologic, and major orthopaedic surgeries; and any surgery or procedure requiring neuraxial anaesthesia. On the other hand, the classification of "low bleed risk" or "non-high bleed risk" procedures or surgeries was less specific and included various invasive procedures and same-day office procedures.[5,6] Some surgical and procedural societies used a three-tier, low-, intermediate-, and high-risk scheme to classify procedure/surgery-related bleed risk.[11] However, there appears to be no advantage of a separate intermediate or moderate bleed-risk category, which would not distinguish management from patients classified as "low" or "non-high" bleed risk.

The classification of procedures and surgeries into low bleed risk and high bleed risk in patients on chronic OAC therapy using bleed-risk–specific anticoagulant interruption and resumption strategies was applied prospectively to warfarin-treated patients who received LMWH bridging in the BRIDGE trial.[22] Bleed-risk-specific management into low and high procedural bleed risk was subsequently applied prospectively to DOAC-treated patients, initially in a proof-of-concept study involving patients on dabigatran, and later in the

recently presented PAUSE trial that involved patients taking apixaban, dabigatran, and rivaroxaban.[21] Additional studies are needed to investigate this bleed-risk classification scheme and determine if it results in low rates of MB in both low/moderate and high bleed-risk categories.

3 | RECOMMENDATIONS FOR STANDARDIZED REPORTING OF PROCEDURAL/SURGICAL BLEED RISK IN ELECTIVE PERIPROCEDURAL SETTINGS

We propose the following recommendations for standardized reporting of surgery/procedure-related bleed risk in randomized trials and observational cohort studies involving patients on chronic OAC therapy (VKA or DOAC) who need an elective procedure or surgery.

1. A three-tiered procedural/surgical bleed-risk scheme as described by our previous ISTH guidance statement[5] and applied to the BRIDGE and PAUSE trials to describe procedural bleed risk as "minimal-bleed-risk," "low/moderate-bleed-risk," and "high-bleed-risk," based on the expected 30-day risk of MB, as shown in Table 1. Examples of procedures and surgeries that would fit into these three categories based on endorsements of various surgical and procedural societies are included, although it is acknowledged that procedure-specific bleed risk can be operator-dependent, and can vary across patients, as well as across time.

4 | PATIENT THROMBOEMBOLIC RISK STRATIFICATION

In periprocedural settings, patients on treatment doses of chronic OAC with VKA or DOACs are in a different TE risk category than patients who are assessed for post-surgical primary venous thromboprophylaxis, for whom validated venous thromboembolism (VTE) risk scores such as the Caprini tool are in use.[27] Patient-specific TE risk stratification would, in theory, inform decisions about whether UFH or LMWH bridging therapy with parenteral anticoagulants should be used to prevent thromboembolism during OAC interruption in high TE risk patients undergoing elective procedures or surgeries.[2,7]

A large systematic review of moderate-to-large (N > 100) periprocedural antithrombotic management studies since 2001 assessed patient TE risk stratification of patient groups on chronic VKA.[9] A total of 34 studies encompassing >12 000 patients were reviewed, including patients with mechanical heart valve (MHV), AF and VTE indications for VKA who had an overall thromboembolic (TE) rate of 0.9% (95% CI: 0.0%-3.4%) in bridged patients and 0.6% (95% CI: 0.0%-1.2%) in non-bridged patients.[5] For TE risk stratification, patients were classified according to a two- or three-tiered TE risk stratification scheme of low-to-intermediate- and high-TE risk, or low-, moderate/intermediate-, and high-TE risk, respectively. For MHV patients, the TE risk stratification schemes included the valve position (aortic or mitral), type of prosthetic valve (caged-ball, tilting disk, or bileaflet) and other major stroke risk factors such as prior stroke or transient ischemic attack (TIA). For patients with AF, the $CHADS_2$ score was used, with higher $CHADS_2$ scores (5 or 6) or recent (within 3 months) stroke or TIA describing high TE risk. For VTE, a recent episode (within 3 months, and especially within 1 month), one associated with severe thrombophilia, and other situations such as the use of venal caval filter can be described as high TE risk. Most studies assessing perioperative anticoagulant management adopted the suggested periprocedural TE risk stratification scheme of the American College of Chest Physicians (ACCP) Antithrombotic Guidelines according to a patient's indication for OAC.[4] More recent guidance statements[10,11] on the topic, which included DOAC management in periprocedural settings, incorporated the CHA_2DS_2VASc score to risk stratify patients with AF, with a CHA_2DS_2VASc score of 7 or more constituting high TE risk and a score of 5 to 6 constituting moderate TE risk, although there was disagreement in what constituted "low TE risk" (a score of ≤1 or ≤4). It was acknowledged that TE risk played a limited role in the periprocedural management of DOACs.[10,11]

There is no validated periprocedural TE risk scheme and suggested TE risk stratification is based mainly on indirect evidence from non-perioperative clinical settings. There are data to suggest that the ACCP TE risk scheme using cut-offs for the $CHADS_2$ score among patients with AF predicts a stepwise increase in the 30-day post-operative risk of stroke, with a $CHADS_2$ score of 0-2 associated with a 30-day post-operative risk of stroke of 1.0%-2.0%, a $CHADS_2$ score of 3-4 with a risk of 2.6%-3.6%, and a $CHADS_2$ score of 5-6 with a risk of 3.6%-7.3%.[28] Although a two-tiered TE approach may seem intuitive, the ACCP-endorsed three-tiered risk scheme that classifies patients into "high," "moderate," and "low" TE risk is based on objective criteria that includes a projected annualized risk of ATE or monthly risk of VTE.[2,4] The ACCP periprocedural TE risk scheme, though empiric, would assist in informing researchers, methodologists, clinicians, and patients to distinguish high TE risk patient groups (who may warrant an aggressive periprocedural antithrombotic approach that may include UFH or LMWH bridging with VKA interruption or need for hospitalization) and low TE risk groups (who warrant a minimalist approach), from moderate TE risk groups in which there is clinical equipoise as to the optimal management strategy.

5 | RECOMMENDATIONS FOR STANDARDIZED REPORTING OF PATIENT THROMBOEMBOLIC RISK IN ELECTIVE PERIPROCEDURAL SETTINGS

We propose the following recommendations for future randomized trials and observational cohort studies for standardized reporting of TE risk in patients on chronic OAC (especially VKA) needing an elective procedure or surgery. We acknowledge this scheme will have a limited role in the interpretation of studies on the periprocedural management of patients on a DOAC.

TABLE 2 Adapted American College of Chest Physicians (ACCP Guidelines) suggested risk stratification for patient-specific periprocedural thromboembolism[2,4]

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/y risk of ATE or >10%/mo risk of VTE)	Any mechanical mitral valve Caged ball or tilting disc valve in mitral/aortic position Recent (<3 mo) stroke or TIA	$CHADS_2$ score of 5 or 6 CHA_2DS_2VASc score of 7 or more Recent (<3 mo) stroke or TIA Rheumatic valvular heart disease	Deficiency of protein C, protein S or antithrombin Antiphospholipid antibodies Multiple thrombophilias Associated with venal caval filter (Active cancer)[a]
Moderate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet AVR *with* major risk factors for stroke[b]	$CHADS_2$ score of 3 or 4 CHA_2DS_2VASc score of 5 or 6	VTE within past 3-12 mo Recurrent VTE Nonsevere thrombophilia Active cancer or recent history of cancer[c]
Low (<4%/y risk of ATE or <2%/mo risk of VTE)	Bileaflet AVR *without* major risk factors for stroke[b]	$CHADS_2$ score of 0-2 (and no prior stroke or TIA) CHA_2DS_2VASc score of 1-4	VTE more than 12 mo ago

[a]Consider pancreatic cancer, myeloproliferative disorders, brain tumor, gastric cancer.
[b]Atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 y.
[c]Within 5 y if history of cancer, excluding non-melanoma skin cancer.

1. A three-tiered TE risk scheme as described by the ACCP[2,4] to describe patient TE risk as high, moderate, and low based on the indication for chronic OAC and expected annualized risk of ATE/monthly risk of VTE should be used in elective periprocedural settings, as shown in Table 2.

6 | DISCUSSION

Standardized and harmonized reporting of procedural/surgical bleed risk and patient-specific TE risk will facilitate comparisons of outcomes across randomized trials and observational studies of periprocedural anticoagulant therapy and would allow for consistent perioperative patient management. This, in turn, would enable more robust assessments of the benefits and harms of different periprocedural antithrombotic management strategies in meta-analyses, would assist guideline developers in interpretation of study outcomes as pertaining to well-defined patient cohorts, and will increase the generalizability and implementation of study results to clinical practice.

For procedural/surgical bleed risk, the term "minimal bleed risk" would best have connotation for those procedures that include pacemaker/ICD placement; coronary angiography; screening colonoscopy; minor dental, skin, and eye procedures;and other outpatient procedures that could safely be done with uninterrupted OAC (or at most interruption of DOAC the morning of procedure) due to the low background MB event rate postprocedure. For other procedures, stratification of bleed risk into low/moderate- or high-risk categories will be helpful in assessing the accompanying background 30-day MB event rates (~1% for low/moderate bleed risk vs 2%-4% or more for high bleed risk, respectively), which will have implications on whether a residual anticoagulant effect can be tolerated and will inform the timing of OAC interruption and resumption as well as administration of postprocedural heparin bridging. A consistent bleed risk classification scheme would also enable easier interpretation of clinical trial results, within and across trials, as well as enabling meta-analysis of results. This, in turn, will inform guideline recommendations on the topic. It is also anticipated that due to improved surgical techniques over time, high bleed risk procedures may have a lower bleed risk, and for this reason it is important to solicit ongoing input from various procedural and surgical societies.

Patient-specific TE risk stratification is helpful for patients on chronic VKA therapy that are perceived to be at high TE risk in whom the need to prevent TE will dominate a management strategy, irrespective of bleed risk, and an aggressive management approach that may include UFH or LMWH bridging is justified. As there are high-quality data from placebo-controlled randomized trials in patients with AF on chronic VKA at mostly low-to-moderate TE risk on the lack of benefits and potential harms of an aggressive periprocedural approach such as LMWH bridging therapy, this TE risk distinction for non-high TE risk patients may become less important in future trial and cohort study designs.[22,29] Last, we acknowledge that this proposed procedural/surgical bleed risk and patient-specific TE risk will be less useful in the design and interpretation of periprocedural studies of patients on chronic DOACs, where other factors such as DOAC pharmacokinetic profiles, procedural bleed risk, and patient renal function will play a more dominant role.[19] In addition, the very low pooled ATE event rate of 0.5% (95% CI: 0.3-0.6) in patients on chronic OAC needing temporary periprocedural interruption

described in a recent large meta-analysis of randomized trials would necessitate large sample sizes.[19]

An acceptable upper boundary for the absolute ATE event and MB rate and their relationship to net clinical benefit, especially in terms of case-fatality or using other approaches such as a bivariate endpoint, is likely needed to design future studies in the field of periprocedural antithrombotic therapy.[30] In addition a placebo-controlled randomized trial of LMWH bridging therapy is needed in high TE risk patients on chronic VKA to definitively assess whether there is benefit (if any) using this approach. These results as well as concerns of generalizability of findings from randomized trials may likely favor large cohort studies to assess benefits and risks and validate an aggressive or minimalist approach in periprocedural antithrombotic management studies.

CONFLICT OF INTEREST

A. C. Spyropoulos—no relevant conflicts for present work. Consultant and advisory board from Janssen, Bayer, Boehringer-Ingelheim, ATLAS Group. Research support from Janssen, Boehringer-Ingelheim. K. Brohi—no relevant conflicts for present work. Consultant for Roche Pharmaceuticals. J. Caprini—no relevant conflicts for present work. Advisory boards for BMS, Janssen, Pfizer, Alexion, Lecture and Travel Support from Sanofi, and a consultant for Recovery Force. C. M. Samama—no relevant conflicts for present work. D. Siegal—no relevant conflicts for present work. Honoraria from BMS-Pfizer, Novartis, Leo Pharma, Bayer, Sanofi, and Aspen Pharma for presentations and consultant meetings. A. Tafur—no relevant conflicts for present work. Research support from Janssen, BMS, Doasense, Idorsia. Consultant for Recovery Force. P. Verhamme—no relevant conflicts for present work. Research funding from Boehringer-Ingelheim, Bayer, Pfizer, BMS, LEO Pharma, Daiichi-Sankyo. Honoraria for consultancy and/or lectures from Boehringer-Ingelheim, Bayer, Pfizer, BMS, LEO Pharma, Daiichi-Sankyo, Portola, Medtronic. J. D. Douketis—no relevant conflicts for present work. Consulting fees or Honoraria from Janssen, Pfizer, Leo Pharma, and Sanofi.

AUTHOR CONTRIBUTIONS

A. C. Spyropoulos, K. Brohi, J. Caprini, C. M. Samama, D. Siegal, A. Tafur, P. Verhamme, and J. D. Douketis contributed to the concept, analysis/interpretation of data, critical writing, and revising intellectual content.

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