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EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

Periprocedural Management of Anticoagulation Writing Committee

John U. Doherty, MD, FACC, *Chair*
Ty J. Gluckman, MD, FACC
William J. Hucker, MD, PhD
James L. Januzzi, Jr, MD, FACC
Thomas L. Ortel, MD, PhD
Sherry J. Saxonhouse, MD, FACC
Sarah A. Spinler, PharmD, AACC

Task Force on Clinical Expert Consensus Documents

James L. Januzzi, Jr, MD, FACC, *Chair*
Luis C. Afonso, MBBS, FACC
Brendan Everett, MD, FACC
Jonathan Halperin, MD, FACC
Adrian Hernandez, MD, FACC
William Hucker, MD
Hani Jneid, MD, FACC
Dharam Kumbhani, MD, SM, FACC
Eva M. Lonn, MD, FACC
Joseph Marine, MD, FACC
James K. Min, MD, FACC
Pamela B. Morris, MD, FACC
Robert Piana, MD, FACC
John Puskas, MD, FACC
Karol E. Watson, MD, FACC
Barbara S. Wiggins, PharmD, AACC

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ABSTRACT

Periprocedural management of anticoagulation is a common clinical conundrum that involves a multidisciplinary team, cuts across many specialties, and varies greatly between institutions in the way it is practiced. Nowhere is

this more evident than in the management of patients with nonvalvular atrial fibrillation. Although they have been found to improve patient outcomes, standardized evidence-based protocols are infrequently in place. The frequency of anticoagulant interruption in preparation for a procedure is high, with an estimated 250,000 patients undergoing temporary interruption annually in North America alone. Knowledge about risk of bleeding and short-term thrombotic risk resides in many specialties, further complicating the issue. Our goal in creating this pathway is to help guide clinicians in the complex decision making in this area. In this document, we aim to: 1) validate the appropriateness of the decision to chronically anticoagulate; 2) guide clinicians in the decision of whether to interrupt anticoagulation; 3) provide direction on how to interrupt anticoagulation with specific guidance for vitamin K antagonists and direct-acting oral anticoagulants; 4) evaluate whether to bridge with a parenteral agent periprocedurally; 5) offer advice on how to bridge; and 6) outline the process of restarting anticoagulation post-procedure.

PREFACE

The American College of Cardiology (ACC) develops a number of policy documents to provide members with guidance on clinical topics. Although clinical practice guidelines remain the primary mechanism for offering evidence-based recommendations, such guidelines may contain gaps in how to make clinical decisions, particularly when equipoise is present in a topic. Expert Consensus Documents are intended to provide guidance for clinicians in areas where evidence may be limited or new and evolving, or where data are insufficient to fully inform clinical decision making.

In an effort to increase the effect of ACC policy on patient care, an ACC Presidential Task Force was formed in 2014 to examine the ACC's clinical documents. The main recommendation of the Task Force was a new focus on concise decision pathways and/or key points of care, instead of the traditional longer documents. The Task Force also established criteria for identifying high-value clinical topics to be addressed, as well as an innovative approach to collecting stakeholder input through a roundtable or think tank meeting. To complement the new focus on brief decision pathways and key points, Expert Consensus Documents were rebranded as "Expert Consensus Decision Pathways."

Although Decision Pathways have a new format, they maintain the same goal of Expert Consensus Documents to develop policy based on expert opinion in areas for which important clinical decisions are not adequately addressed by available data. Expert Consensus Decision Pathways are designed to complement the guidelines and bridge the gaps in clinical guidance that remain. In some cases, topics covered by Expert Consensus Decision Pathways will be addressed subsequently by ACC/American Heart Association (AHA) guidelines as the evidence base evolves. The writing groups are charged with developing algorithms that are more actionable and can be implemented into tools or applications to accelerate the use of these documents at the point of care. Decision Pathways are not intended to provide a single correct answer, but to encourage clinicians to ask certain questions and consider important factors as they come to their own decision on a treatment plan to be recommended and discussed with their patients. There may be multiple pathways that can be taken for treatment decisions, and the goal is to help clinicians make a more informed decision.

James L. Januzzi, JR, MD, FACC
Chair, ACC Task Force on Clinical Expert Consensus Documents

1. INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide (1), substantially increasing in prevalence with age (2) and occurring in 1 in 4 individuals over their lifetime (3). This risk begins at age 40 years and increases thereafter, such that at age 85 years, the prevalence of AF in an otherwise healthy population approaches 18% (3). Antithrombotic therapy is recommended for most patients with AF to reduce the risk of stroke and systemic embolism. By incorporating the known thrombotic risk factors of heart failure, hypertension, age, diabetes, stroke or transient ischemic attack (TIA), vascular disease, and female sex into a scoring system (the CHA_2DS_2-VASc score), strong preference is given to an oral anticoagulant (OAC) over antiplatelet therapy in individuals with a score ≥2 (4–6). Although some controversy exists about the relative importance of these risk factors (7,8), the CHA_2DS_2-VASc score better predicts thromboembolic events than the simpler $CHADS_2$ score, particularly among those with a lower risk score (e.g., 0 to 1) (7,9–12); accordingly, CHA_2DS_2-VASc has become the preferred score in clinical decision making (4,5).

Temporary interruption (TI), the omission of ≥1 dose of an OAC in preparation for a procedure, is frequently necessary (13–18), most often to mitigate bleed risk with surgical or invasive procedures. Although several factors are taken into consideration when making the decision to interrupt anticoagulation (e.g., bleed

risk of the procedure, thrombotic risk associated with anticoagulant interruption, and/or bleed risk specific to the patient), practice varies widely (19). Accordingly, this workgroup was convened to synthesize available data related to periprocedural management of anticoagulant therapy for patients with nonvalvular atrial fibrillation (NVAF) by specifically addressing: 1) whether and when anticoagulant therapy should be interrupted; 2) whether and how anticoagulant bridging with a parenteral agent should be performed; and 3) when and how anticoagulant therapy should be restarted for those who require TI.

2. METHODS

For this document, we have restricted our data review and commentary to patients who are maintained on chronic anticoagulation for NVAF, defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair (4). Although this is a generally accepted definition, trials have varied as to whether patients with more than mild mitral regurgitation were included (20-23). We address anticoagulant management in the preprocedure and postprocedure settings and identify populations in whom TI of anticoagulation is not required. Finally, although this document can be used to guide decision making for those undergoing urgent or emergent surgery, its primary goal is to help direct management in elective, planned procedures. Although TI may be necessary for those taking anticoagulant therapy for other indications (such as prior deep venous thrombosis, pulmonary embolism, or prior valve replacement surgery), our guidance cannot be extrapolated to these populations.

For all patients taking anticoagulant therapy for stroke prophylaxis in NVAF who are scheduled for a procedure, it is important to carefully review the medical history; medication list, including over-the-counter medications and any supplements and herbal preparations; and laboratory test results to identify factors that may increase bleed risk. On the basis of these findings and the type of procedure to be performed, the risks and benefits of TI should be discussed with as well as understood and agreed to by the patient. A collaborative discussion between the patient's anticoagulation management team and the practitioner performing the procedure or surgery should then follow. To minimize treatment errors, it is important to clearly document the anticoagulant management plan and patient concurrence in the patient's medical record before undertaking the procedure.

3. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation, specific assumptions were considered by the writing group in developing the decision pathway.

3.1. General Clinical Assumptions

1. This algorithm is only for patients with NVAF.
2. This algorithm assumes that the patient has a clinical indication for anticoagulation therapy and is on the proper dose of anticoagulant. If the patient has NVAF and no other risk factors, he or she should not be anticoagulated.
3. The algorithm assumes that the patient is not taking concomitant antiplatelet agents or, if they are, that bleed risk estimates may vary.
4. This algorithm is for elective planned procedures, not those occurring urgently or emergently. The section addressing postprocedural anticoagulant management, however, may still be relevant and should be considered for urgent or emergent procedures.
5. The recommendations about withholding and resuming vitamin K antagonist (VKA) therapy refer specifically to warfarin, which is the most common VKA in the United States. If outside of the United States, check the pharmacokinetics of the VKA and adjust accordingly.
6. This algorithm assumes that the clinician will seek additional input from the prescribing physician, cardiologist, and proceduralist to guide clinical judgment, in tandem with patient preference.

3.2. Definitions

Definitions of terms used throughout the indication set are listed here.

Bridging: The process whereby an OAC is discontinued and replaced by a subcutaneous or intravenous anticoagulant before and/or following an invasive procedure.

Temporary interruption: The process whereby an anticoagulant is stopped for ≥1 doses, resulting in full or partial dissipation of anticoagulant effect prior to the invasive procedure.

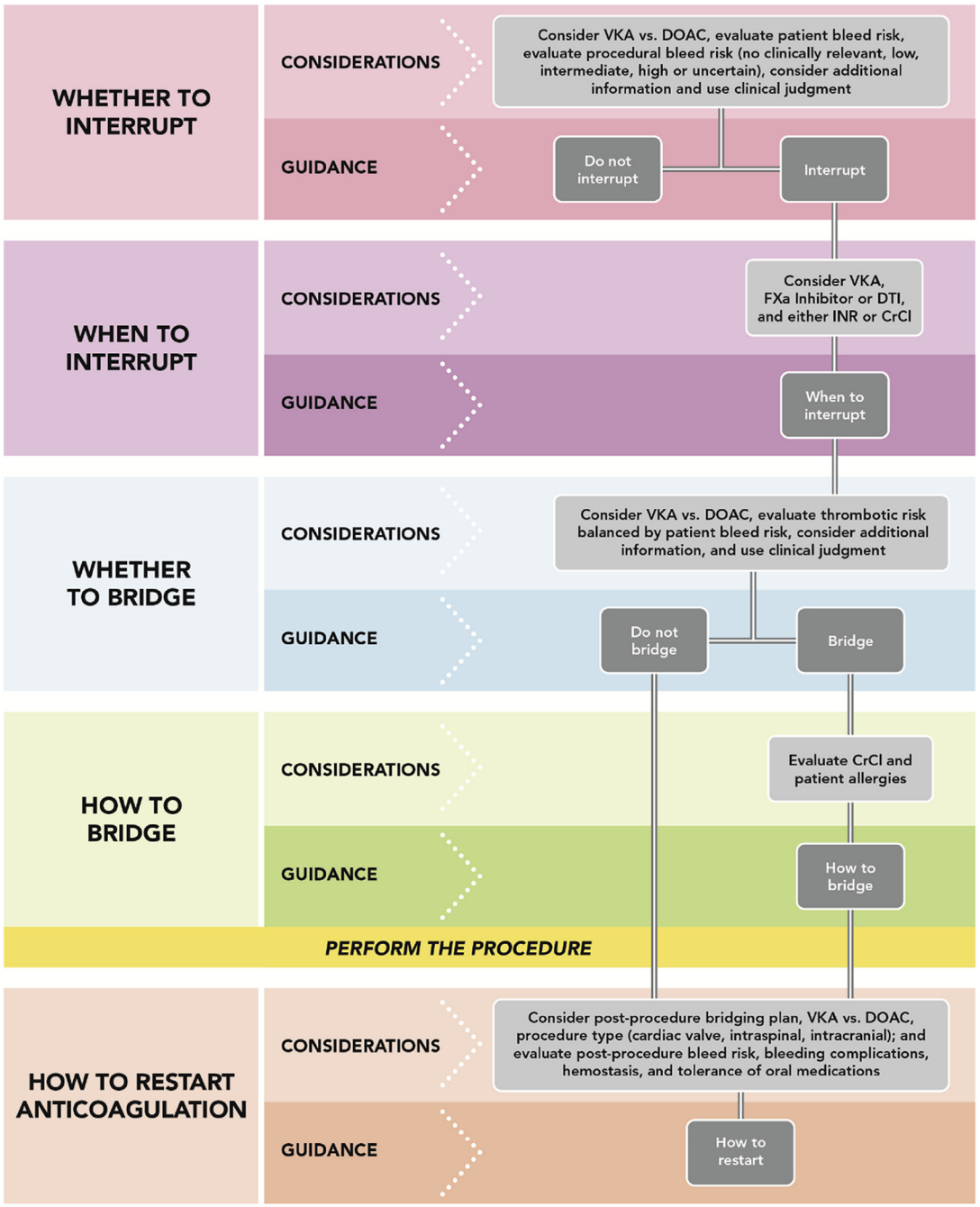
Nonvalvular AF: AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

Periprocedural: The period of time prior to, during, and shortly after an invasive procedure.

4. PATHWAY SUMMARY GRAPHIC

Figure 1 provides an overview of what is covered in the decision pathway. See each section for more detailed considerations and guidance.

FIGURE 1 PMAC Pathway Decision Algorithm Summary



CrCl = creatinine clearance; DOAC = direct oral anticoagulent; DTI = direct thrombin inhibitor
FXa = factor Xa; INR = international normalized ratio; VKA = vitamin K antagonist

5. DESCRIPTION AND RATIONALE

5.1. Periprocedural Interruption of Anticoagulant Therapy

Implicit in any algorithm guiding periprocedural interruption of anticoagulant therapy in NVAF are the following assumptions: 1) the patient has an appropriate clinical indication for the anticoagulant; 2) the anticoagulant is dosed according to the product's prescribing information; and 3) the patient is not actively bleeding.

Current ACC/AHA/Heart Rhythm Society and European Society of Cardiology guidelines (4,5) recommend use of an OAC in those with NVAF and a CHA_2DS_2-VASc score ≥2 (ACC/AHA/Heart Rhythm Society guidelines make a Class of Recommendation [COR] I, Level of Evidence [LOE]: A recommendation for the use of adjusted-dose warfarin, a VKA, and a COR I, LOE: B recommendation for a direct-acting oral anticoagulant [DOAC]; European Society of Cardiology guidelines make a COR I, LOE: A recommendation for a VKA or DOAC). The guidelines differ, however, as to whether an OAC should be used in those with NVAF and a CHA_2DS_2-VASc score of 1 (ACC/AHA/Heart Rhythm Society: COR IIb, LOE: C; European Society of Cardiology: COR IIa, LOE: A).

In a recent retrospective review evaluating 140,420 patients with AF in the Swedish nationwide health registries (6), the annual ischemic stroke rate in those with a CHA_2DS_2-VASc score of 1 was lower (0.1% to 0.2% for women and 0.5% to 0.7% for men) than previously estimated. In addition, a retrospective cohort of Taiwanese patients demonstrated that an age of 65 to 74 years was a more powerful predictor of stroke in both men and women compared with other CHA_2DS_2-VASc score factors (24). As such, it comes as no surprise how difficult it can be to settle on a single risk-benefit ratio for anticoagulation in all populations.

Ultimately, before one can determine whether TI is required for a given procedure, it is important to first understand: 1) the propensity for bleeding with the procedure; 2) the clinical effect of bleeding should it occur; and 3) whether patient factors that impart increased bleed risk are present.

5.2. Assessing Procedural Bleed Risk

Although standardized definitions for bleeding do exist (25,26), they have not been consistently applied to studies evaluating procedural risk; more commonly, such bleeding definitions are used to assess bleeding severity in the context of clinical trials. Most data used to predict procedural bleed risk come from small, observational studies and/or case series involving selected procedures. As a result, most recommendations guiding periprocedural anticoagulation are based on expert consensus (14).

Just as important as the prevalence of bleeding is its consequences. For instance, even small amounts of bleeding in association with neuraxial anesthesia or after cardiac, intraocular, intracranial, or spinal surgery may result in significant morbidity or mortality (27). Therefore, procedures with low rates of bleeding but significant associated sequelae should be categorized as high risk.

A number of professional societies have published consensus documents classifying their most commonly performed procedures by bleed risk and providing guidance regarding periprocedural management of anticoagulant therapy (28-37). Although some of these documents give guidance for patients without AF, their estimates of bleed risk by procedure remain relevant. In these documents, procedures have generally been categorized as high or low bleed risk, with less common inclusion of an intermediate bleed risk category. Unfortunately, there are a number of procedures where disagreement exists about how bleed risk is categorized (e.g., hip/knee replacement, prostate biopsy, and hysterectomy) (38-42). In addition, the bleed risk for many procedures remains uncategorized.

For some procedures, uninterrupted oral anticoagulation with a VKA carries a lower bleed risk than TI with bridging. This was observed in the BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled) trial of patients undergoing implantation of pacemakers or implantable cardioverter defibrillators, where maintenance of therapeutic anticoagulation with a VKA (goal international normalized ratio [INR] ≤3 on the day of the procedure) was associated with significantly less bleeding than TI and bridging with heparin (odds ratio: 0.19; $p < 0.001$) (43). Similar results were noted in the COMPARE (Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation [AF] Patients Undergoing Catheter Ablation) trial, where uninterrupted anticoagulation with a VKA (goal INR of 2 to 3) was associated with lower rates of minor bleeding ($p < 0.001$) and thromboembolic events ($p < 0.001$) than TI and bridging with low molecular weight heparin (LMWH) in those undergoing catheter ablation of AF (44). On the basis of the design of these 2 studies, however, relative bleed risk in those treated with an uninterrupted VKA versus TI alone is unknown.

Prospective data about the safety and efficacy of uninterrupted anticoagulation with the DOACs is more limited. Among patients undergoing catheter ablation of AF in the small VENTURE-AF (Active-Controlled Multicenter Study with Blind-adjudication Designed to Evaluate the Safety of Uninterrupted Rivaroxaban and Uninterrupted Vitamin K Antagonists in Subjects Undergoing Catheter Ablation for Non-Valvular Atrial Fibrillation) trial, patients maintained on either uninterrupted rivaroxaban or a VKA had low rates of major bleeding

(0.4%) and thromboembolic events (0.8%) (45). It is unclear whether such findings can be extrapolated to a broader patient population. Although other trials evaluating periprocedural continuation of DOACs are underway, it is reasonable to consider TI of anticoagulation without bridging in these patients (46,47).

In conjunction with input from multiple professional societies, we classified the most commonly performed procedures into 4 bleeding risk levels: 1) no clinically important bleed risk; 2) low procedural bleed risk; 3) uncertain procedural bleed risk; or 4) intermediate/high procedural bleed risk (Online Appendix). Because the complexity of a given procedure may vary (for instance, not all shoulder surgeries carry the same bleed risk), an important caveat to this categorization is acknowledgement that the proceduralist's opinion of bleed risk may vary from that proposed in this document (Online Appendix).

5.3. Assessing Patient-Related Bleed Risk

Beyond the bleed risks inherent to a given procedure, it is important to also assess patient-related factors that may impart increased bleed risk (**Table 1**). These include a history of prior bleeding events (particularly in the preceding 3 months), bleeding with a similar procedure or with prior bridging, qualitative or quantitative abnormalities of platelet function (e.g., uremia) (48), concomitant use of antiplatelet therapy (or other medications/supplements associated with platelet dysfunction), or for those taking a VKA, an INR in the supratherapeutic range (49–52). If possible, providers should always delay the scheduled procedure to address patient-related factors that can be corrected. Traditionally, the patient characteristics associated with increased bleed risk listed in **Table 1** have been considered important.

TABLE 1 Patient Bleed Risk Factors

HAS-BLED parameters (52)*
Hypertension†
Abnormal renal function‡
Abnormal liver function§
Prior stroke
History of or predisposition to (anemia) major bleeding
Labile INR (VKA)‖
Elderly (>65 years)
Concomitant use of an antiplatelet agent or nonsteroidal anti-inflammatory drug
Alcohol or drug usage history (≥8 drinks/week)¶
Additional items included in the periprocedural management algorithm
Prior bleed event within 3 months (including intracranial hemorrhagic)
Quantitative or qualitative platelet abnormality
INR above the therapeutic range at the time of the procedure (VKA)
Bleed history from previous bridging
Bleed history with similar procedure

*Each bullet is counted as 1 point. A HAS-BLED score ≥3 was shown to be highly predictive of bleeding events, with 1 point being given for the presence of each individual parameter (54). †Defined in HAS-BLED as systolic blood pressure >160 mm Hg. ‡Defined in HAS-BLED as presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L. §Defined in HAS-BLED as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× ULN, AST or ALT >3× ULN). ‖Defined in HAS-BLED as time in the therapeutic range <60%. ¶Defined in HAS-BLED as >8 U/week.

ALT = alanine transaminase; AST = aspartate transaminase; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol; INR = international normalized ratio; ULN = upper limit of normal; and VKA = vitamin K antagonist.

Several risk scores have been proposed to generically evaluate bleed risk in patients with AF (49,50,52). The most widely used among these is the HAS-BLED score (9,52), which incorporates hypertension; renal or hepatic impairment; prior stroke, TIA, or systemic embolization (SE); history of a major bleed; a labile INR; and age >65 years. Because some of these same risk factors increase thrombotic risk, the HAS-BLED score should not be used alone to exclude patients from treatment with an OAC (53). Rather, it should be used to identify risk factors that can be modified to mitigate bleed risk.

Even though the HAS-BLED score has been shown to have predictive value in the periprocedural setting (54), it is limited by its modest discriminatory performance (52) and is not specifically endorsed by current guidelines for this purpose. Instead, cut points for rates of major bleeding have been suggested to differentiate procedures associated with high versus low bleed risk. In 1 review, procedures were considered to be high risk if the major bleed rate within 48 hours was 2% to 4% and low risk if the rate was 0% to 2% (38). In another, high versus low risk levels were defined by procedural rates of major bleeding >1.5% versus ≤1.5%, respectively (39). This latter cut point was based on criteria previously set by the American Society for Gastrointestinal Endoscopy for individuals on no antithrombotic therapy (55), and as such, may not accurately reflect the bleed risk for patients on more complex antithrombotic regimens (36).

For patients taking a VKA:

Warfarin is the most commonly prescribed VKA worldwide. It inhibits the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C and S. It has a half-life of approximately 36 to 42 hours, thus necessitating advanced planning if TI is required. For patients on warfarin, we propose the following approach periprocedurally (**Figure 2**).

Guidance Statement for determining whether a VKA should be interrupted periprocedurally:

1. **Do not interrupt therapy with a VKA in:**
   - **Patients undergoing procedures with: 1) no clinically important or low bleed risk; AND 2) absence**

of patient-related factor(s) that increase the risk of bleeding.

2. **Interrupt therapy with a VKA in:**
   - **Patients undergoing procedures with intermediate or high bleed risk, OR**
   - **Patients undergoing procedures with uncertain bleed risk and the presence of patient-related factor(s) that increase the risk of bleeding.**
3. **Consider interrupting a VKA on the basis of both clinical judgment and consultation with the proceduralist in:**
   - **Patients undergoing procedures with: 1) no clinically important or low bleed risk AND 2) the presence of patient-related factor(s) that increase the risk of bleeding, OR**
   - **Patients undergoing procedures with: 1) uncertain bleed risk AND 2) the absence of patient-related factor(s) that increase the risk of bleeding.**

For all patients on a VKA, an INR level should be measured 5 to 7 days before the procedure. This is performed in individuals not requiring TI so that those with an INR >3.0 may be identified. This is also performed in individuals requiring TI to determine the number of days that the VKA should be stopped prior to the procedure (Figure 2).

Guidance Statement as to how a VKA should be interrupted periprocedurally:

1. **In those with an INR of 1.5 to 1.9, the VKA should be discontinued 3 to 4 days prior to the procedure if a normal INR is desired OR for a shorter period of time if an elevated but subtherapeutic INR is acceptable. The INR should be rechecked within 24 hours before the procedure, particularly if a normal INR is desired. For those with a persistently elevated INR, electively scheduled procedures should be delayed, if possible, until the desired INR is achieved.**
2. **In those with an INR between 2.0 and 3.0, the VKA should be discontinued 5 days prior to the procedure. The VKA may be held for a shorter duration depending on the current INR, the time to the scheduled procedure, and the desired INR for the procedure. The INR should be rechecked within 24 hours before the procedure, particularly if a normal INR is desired. For those with a persistently elevated INR, electively scheduled procedures should be delayed, if possible, until the desired INR is achieved.**
3. **In those with an INR >3.0, the VKA should be discontinued at least 5 days prior to the procedure. The exact duration that is necessary to withhold the VKA depends on the current INR, the time to the scheduled procedure, and the desired INR for the procedure. The INR should be rechecked within 24 hours of the procedure, particularly if a normal INR is desired. For those with a persistently elevated INR, electively scheduled procedures should be delayed, if possible, until the desired INR is achieved.**
4. **In those on a higher VKA maintenance dose (7.5 to 10 mg/day or higher) or for whom the INR is known to normalize more quickly, a shorter discontinuation time may be required prior to the procedure.**

For patients taking a DOAC:

Four DOACs are currently approved to reduce the risk of stroke or systemic embolism in NVAF: 1) apixaban; 2) dabigatran; 3) edoxaban; and 4) rivaroxaban. These agents vary distinctly in their pharmacokinetics, dosing frequency, dependence on renal excretion, and criteria for dose adjustment (33). Their relatively short half-lives should reduce the duration (compared with a VKA) for which preprocedural anticoagulation is withheld when TI is required.

It is important to bear in mind the pharmacokinetics of DOACs. Due to variation between the peak and trough drug levels during the dosing interval with regular once or twice daily dosing, a procedure performed at the trough level (end of a dosing interval) of a DOAC may allow it to be restarted the evening of or the day after the procedure with only 1 or in some cases no dose(s) of the drug missed. For example, in those taking a once-daily DOAC (e.g., 6:00 PM), some procedures could be performed during the afternoon with the prior evening dose given and a plan to restart the DOAC either: 1) later that day (i.e., 10:00 PM) without a missed dose; or 2) the following day (e.g., 6:00 PM) with only 1 missed dose. Alternatively, in those taking a twice-daily DOAC (e.g., 9:00 AM and 9:00 PM), some procedures could be performed during the late morning with the prior evening dose given and a plan to restart the DOAC either: 1) that evening (e.g., 6:00 PM) with a single missed dose; or 2) the following morning (e.g., 9:00 AM) with 2 missed doses.

Since the DOACs became clinically available, 1 persistent concern regarding their use has been the lack of a specific reversal agent in the case of major bleeding complications. This is particularly germane in the periprocedural setting and in patients requiring repeat procedures. Recently, significant progress has been made in this area, with the approval of the monoclonal antibody fragment idarucizumab for the reversal of dabigatran (56). Similar trials are in progress with 2 other novel agents, andexanet alfa and ciraparantag, for reversal of the anticoagulant effects of LMWHs and factor Xa inhibitors (57,58).

For patients on a DOAC who require TI of anticoagulant therapy, it is imperative that renal function be assessed to determine the anticipated duration of anticoagulant effect once the agent has been discontinued (~4 to 5 drug half-lives) (Table 2). This should be done using the Cockcroft-Gault equation (with actual body weight) to estimate creatinine clearance (CrCl).

The exact duration for which a DOAC should be withheld depends upon the procedural bleed risk, specific agent, and estimated CrCl. Because few data exist to provide guidance on periprocedural management of DOACs in patients with stage V chronic kidney disease (CrCl <15 mL/min or on dialysis), consideration should be given to specific laboratory testing (e.g., dilute thrombin time for dabigatran and agent-specific calibrated chromogenic anti-factor Xa activity for apixaban, edoxaban, and rivaroxaban) in patients taking these agents, when available, and interpreting such tests in consultation with a hematologist familiar with qualitative and quantitative DOAC coagulation tests.

Rather than first assessing procedural bleed risk as in those on a VKA, we recommend starting with assessment of patient-related factors that increase bleed risk in those taking a DOAC (Table 1). This stems largely from a paucity of data guiding which procedures can be performed safely in patients taking DOACs without TI. In the coming years, with greater numbers of procedures being performed on uninterrupted DOAC therapy, this approach will need to be refined.

The recommended duration of TI for each DOAC relates to: 1) the drug's expected clearance/metabolism; 2) the bleed risk of the procedure; and 3) patient-related factors that increase bleed risk. In patients with higher bleed risk, electively scheduled procedures should be delayed, if possible, to correct patient factors that potentiate bleed risk. If the procedure cannot be delayed or patient-related factors are not correctable, the DOAC should be interrupted as dictated by clinical judgment. Although this document concerns itself with elective, planned procedures, the use of idarucizumab could be considered in patients receiving dabigatran who are undergoing an urgent/emergent procedure associated with higher bleed risk, requiring normal hemostasis, and for which the procedure could not be delayed for at least 8 hours (56). Other reversal agents for factor Xa inhibitors, such as andexanet, have not been studied for this indication.

In patients without patient-related factors that increase bleed risk, it is important to next assess procedural bleed risk. In those undergoing procedures with no clinically important risk of bleeding (Online Appendix), the DOAC may only need to be held for a single dose. Alternatively, the procedure could be performed without TI but timed to coincide with the predicted nadir of the DOAC's drug level. Procedures routinely performed with a predictably low risk of bleeding (e.g., cataract surgery) are arguably best performed with no or limited interruption, but experience with this approach using DOACs is limited. For those undergoing procedures with low, intermediate, high, or uncertain bleed risk, we propose the approach in Figure 3.

Guidance Statement for interruption of a DOAC periprocedurally:

1. **Interrupt therapy for low bleed-risk procedures in:**
   - **Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).**
2. **Interrupt therapy for intermediate, high, or uncertain bleed-risk procedures in:**
   - **Patients treated with any of the approved DOACs for a duration based on the estimated CrCl (Table 2).**

5.4. Periprocedural DOAC Use With Neuraxial Procedures

Use of anticoagulants in the setting of neuraxial anesthesia raises the risk of a spinal or epidural hematoma, which could be catastrophic. All currently available DOACs carry a black box warning regarding their use in the setting of neuraxial anesthesia. The American Society of Regional Anesthesia and Pain Management has developed guidelines regarding the periprocedural management of antiplatelet and anticoagulant medications around interventional pain procedures. Their guidelines recommend discontinuing a DOAC prior to neuraxial procedures (for 4 to 5 days for dabigatran and 3 to 5 days for factor Xa inhibitors), with reinitiation 24 hours postprocedure (33). This recommended drug-free interval is longer than the typical drug-free interval before a procedure and may stem from the high-risk, surgical nature of some interventional pain procedures. However, given the potential consequences of a bleed, caution is certainly justified and this strategy is very reasonable, especially for a patient with low thrombotic risk. If a patient is at an elevated thrombotic risk, considering a drug-free interval of 2 to 3 half-lives prior to the procedure or considering bridging parenteral anticoagulation with LMWH may be reasonable to keep the risk of a spinal hematoma low (59).

FIGURE 2 **Detailed Algorithm: Whether to Interrupt and How to Interrupt for VKAs**

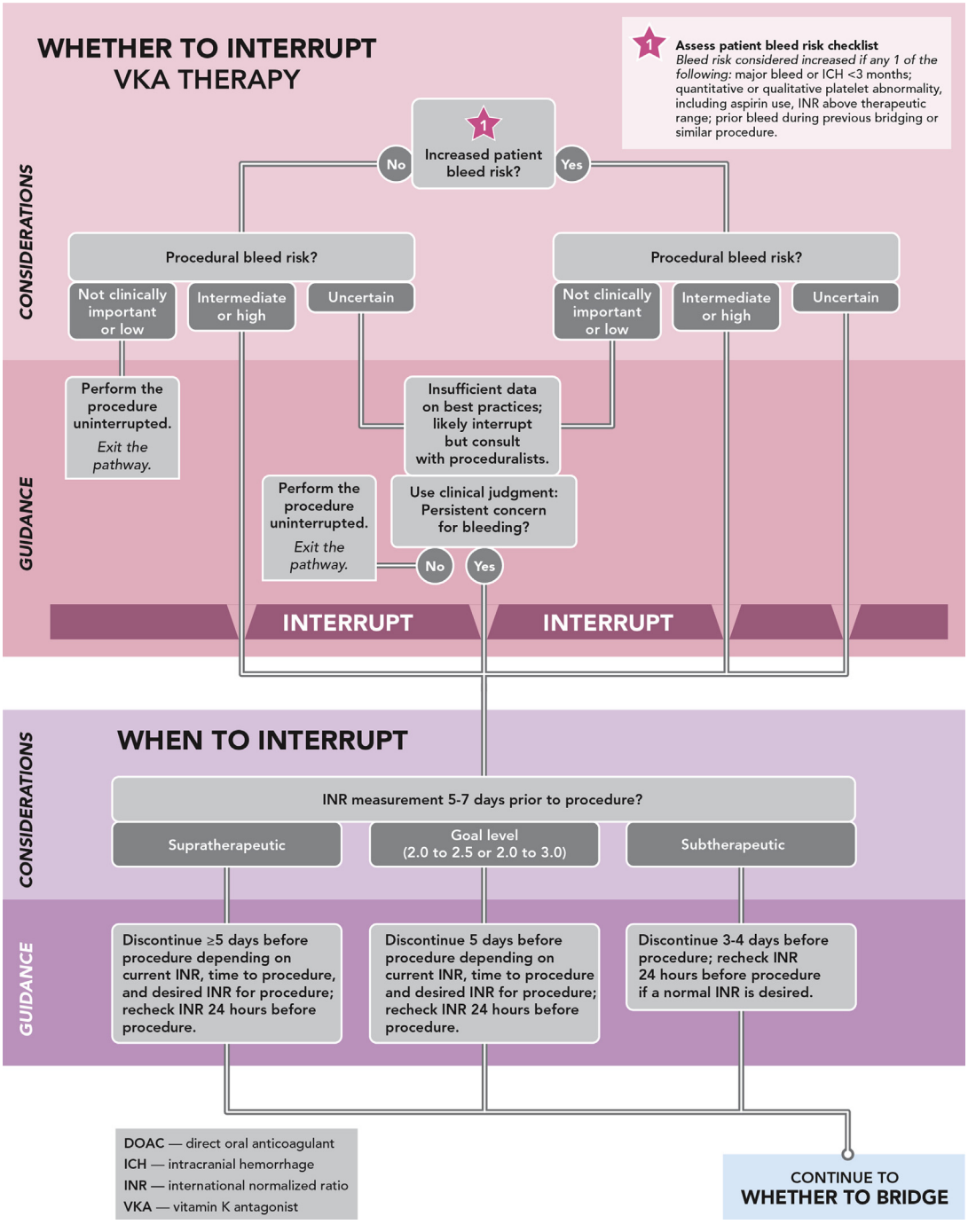


FIGURE 3 **Detailed Algorithm: Whether to Interrupt, and How to Interrupt for DOACs**

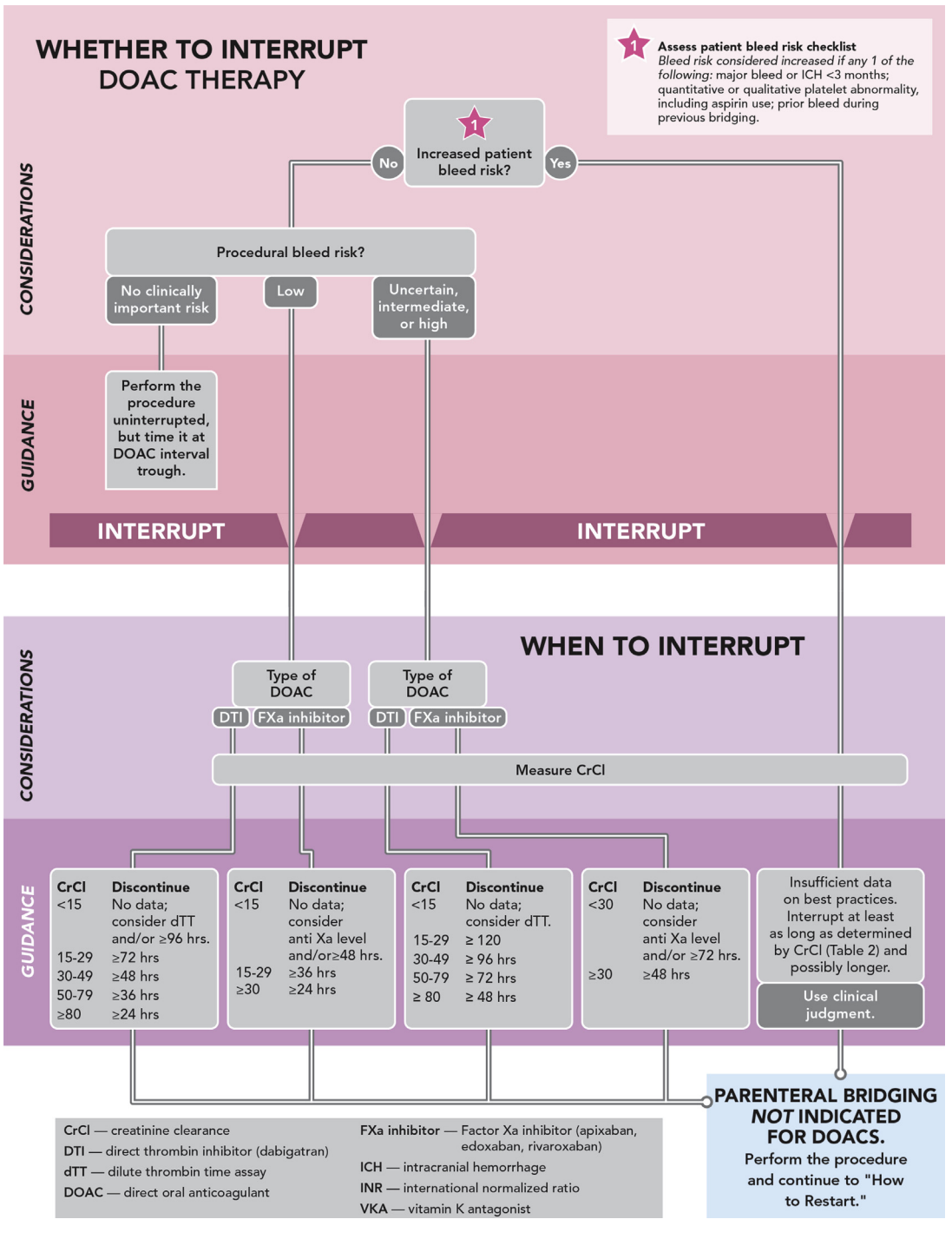


TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (46,60-67).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

5.5. Parenteral Bridging Anticoagulation in the Periprocedural Setting (Figure 4)

Once the decision has been made to discontinue OAC therapy around the time of the procedure, the next step is to develop a strategy that will: 1) minimize perioperative thrombotic risk while the OAC is being withheld; and 2) minimize perioperative bleeding risk. The DOACs have short half-lives that obviate the need to administer an alternative anticoagulant during TI in the majority of situations. In contrast, the anticoagulant effect of a VKA takes longer to dissipate once it is stopped and longer to become therapeutic when restarted. Consequently, patients on a VKA who have a higher risk of thromboembolic events may benefit from bridging using parenteral agents in the periprocedural setting.

Assessment of a patient's thrombotic and bleed risk is essential to determine the need for bridging therapy while the VKA is being held. Although the timing of OAC interruption and the decision to bridge with a parenteral anticoagulant is based on the patient's estimated risk of thromboembolism, there are no validated assessment schemes to determine this risk. Extrapolating risk for a thrombotic event as a function of the period of interruption based on the annual risk may be attractive but has not been validated. Although not validated in the perioperative setting, the CHA_2DS_2-VASc score can be used to assess an individual patient's thrombotic risk overall. As the thrombotic risk increases, the need for bridging becomes more apparent, unless a compelling risk of bleeding is present (36).

5.6. Interruption and Bridging for Patients on DOACs

Given the short-half lives of DOACs, bridging with a parenteral agent is rarely, if ever, needed prior to procedures. Reinitiation of these agents after the procedure, however, may need to be delayed owing to the risk of postprocedural bleeding. Reinitiation might also be delayed depending upon: 1) the need for additional procedures; and/or 2) the patient's ability to tolerate oral medications. In these latter 2 circumstances, a short-acting parenteral anticoagulant (e.g., unfractionated heparin [UFH]) may be needed either between procedures or post-procedure, when thrombotic risk remains high. Depending on the indication (e.g., venous thromboembolism prophylaxis), a prophylactic dose of UFH or LMWH may be sufficient. These are very specific scenarios that are uncommon in routine clinical practice.

5.7. Interruption and Bridging for Patients on a VKA

5.7.1. Patients at Low Thrombotic Risk

Long-term thrombotic risk in NVAF rises proportionally with the CHA_2DS_2-VASc score, especially among patients with prior stroke, TIA, or systemic embolism (14,68,69). For patients with a CHA_2DS_2-VASc score ≤4 and no prior history of ischemic stroke or TIA, the risk for a thrombotic event is low (<5%/year) (8). As such, these patients may discontinue the VKA prior to the procedure as articulated, with resumption when it is felt to be safe from a procedural bleed risk standpoint, as discussed in the following text. Therefore, under most circumstances, no preprocedural or postprocedural parenteral anticoagulation is recommended.

Guidance Statement for determining appropriateness for bridging in those on a VKA who are at low risk for thromboembolism:

1. **For patients who are at low risk for thromboembolism (<5%/year), with a CHA_2DS_2-VASc score ≤4 or and no prior history of ischemic stroke, TIA, or SE, discontinue the VKA prior to the procedure and resume as discussed in the following text, without bridging.**

5.7.2. Patients at Moderate Thrombotic Risk

For individuals who are at moderate risk for thrombotic events with a CHA_2DS_2-VASc score of 5 to 6 or prior history of embolic ischemic stroke, TIA, or systemic embolism (≥3 months previously), it is important to assess the patient's bleed risk to determine the optimal approach to

perioperative management of anticoagulant therapy. In this group, individuals with higher bleed risk should have their VKA withheld without parenteral bridging. For those without significant bleed risk undergoing TI of their VKA, bridging: 1) should likely be performed in those with prior stroke or TIA; and 2) should likely be withheld in those without prior stroke or TIA.

Guidance Statement for determining appropriateness for bridging in those on a VKA at moderate risk for thromboembolism (5% to 10%/year) with a CHA_2DS_2-VASc score of 5 to 6 or history of prior ischemic stroke, TIA, or peripheral arterial embolism (3 or months previously).

Determine the patient's bleed risk to determine the appropriateness of bridging therapy.

1. **If increased risk of bleeding, interruption of the VKA without bridging is recommended.**
2. **If no significant bleed risk:**
   a. **In patients with prior stroke, TIA, or SE, consider use of a parenteral anticoagulant for periprocedural bridging (use clinical judgment, likely bridge);**
   b. **In patients with no prior stroke, TIA, or SE, the use of a parenteral anticoagulant for periprocedural bridging is not advised (use clinical judgment, likely do not bridge.).**

5.7.3. Patients at High Thrombotic Risk

Patients who are at high thrombotic risk for stroke or SE, such as those with a CHA_2DS_2-VASc ≥7 or with a recent (within 3 months) thrombotic event, have a risk of thromboembolic complications that should generally be considered for bridging. Importantly, for those with a recent (within 3 months) thrombotic event, the elective procedure should ideally be delayed, if possible, to move beyond this timeframe. For those with a recent (within 3 months) intracranial hemorrhage, the procedure should be performed either with no bridging or with post-procedural bridging only. Clinical judgment should be used to guide bridging in those who are at high bleed risk, but without recent intracranial hemorrhage.

Guidance Statement for determining appropriateness for bridging in those on a VKA at high risk for thromboembolism:

1. **For patients who are at high risk of stroke or systemic embolism (>10% per year) with a CHA_2DS_2-VASc score of 7 to 9 or recent (within 3 months) ischemic stroke, TIA, or SE, parenteral bridging anticoagulation should be considered.**

5.8. Specific Recommendations Regarding Bridging

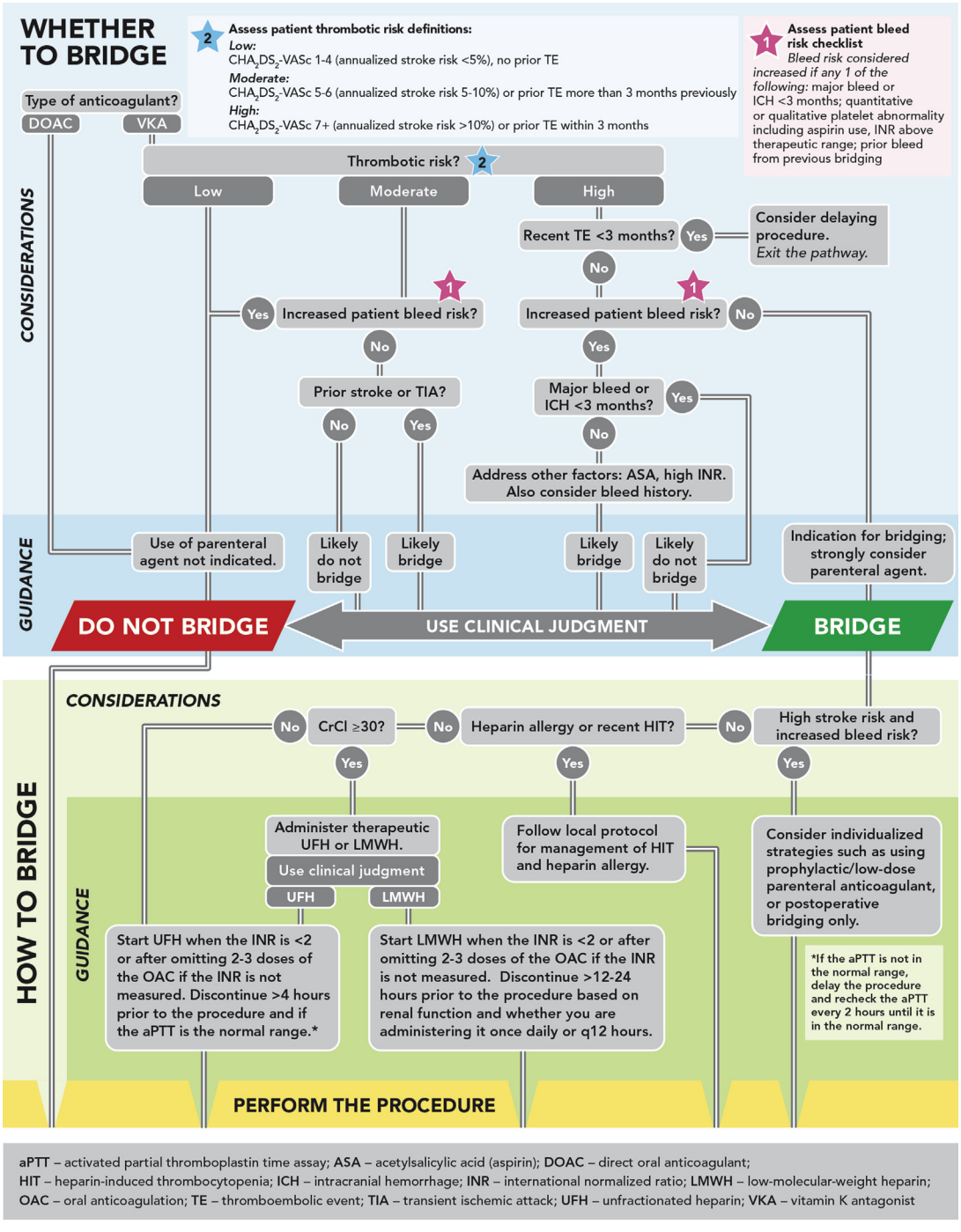
Use of bridging with a parenteral anticoagulant is common, yet the bulk of current evidence suggests that it is associated with an increased risk of both major adverse cardiovascular events and major bleeding, without a significant decrease in thromboembolic events (17,18,42,70). For instance, in the BRIDGE (Bridging Anticoagulation in Patients Who Require Temporary Interruption of VKA Therapy for an Elective Invasive Procedure or Surgery) trial, the overall rate of thromboembolism in patients with NVAF was 0.4%, with no difference noted between bridged and nonbridged patients (42). Importantly, the average $CHADS_2$ score in this trial was 2.3 in the nonbridged group and 2.4 in the bridged group, with <15% of the total cohort having a $CHADS_2$ score ≥4. Therefore, these results may not be applicable to patients with higher thromboembolic risk. In a separate, large observational registry of patients with AF, the overall rate of thrombotic events was 0.6% in bridged and nonbridged patients managed with TI of OAC therapy (18). In contrast, a higher rate of thromboembolism (2.3%) was observed in a smaller nonrandomized study of patients treated with bridging (71). Even with these differences, the rate of periprocedural thromboembolism is relatively low, and as such, this risk must be weighed against the risk of bleeding.

Multiple prior observational studies have evaluated various parenteral agents, dosing schemes, and timings for periprocedural parenteral anticoagulation; yet, no single agent or dosing regimen has been deemed to be superior (71–75). Most commonly, UFH or a LMWH is used. For a patient with an active or remote history of heparin-induced thrombocytopenia, an alternative nonheparin anticoagulant should be selected in accordance with hospital policy and consideration of renal and hepatic function. In those with NVAF, use of an LMWH has been associated with decreased length of hospitalization, with similar rates of thromboembolism and bleeding rates compared with UFH (74). For those using an LMWH in the periprocedural setting, close attention to renal function is necessary to ensure proper dosing.

The parenteral anticoagulant may be started 24 hours (or more) following the first missed dose of warfarin. This timing will be procedure specific and is determined in consultation with the proceduralist. The decision to use UFH rather than an LMWH as the bridging agent depends upon: 1) renal function (based on CrCl); 2) the parenteral bridging setting (inpatient versus outpatient); 3) patient comfort with self-injections; and 4) insurance coverage. If CrCl is <30 mL/min, UFH is preferred over an LMWH; however, dosing guidance for an LMWH is available for patients with a CrCl of 15 to 30 mL/min, although caution is advised when using an LMWH in this setting.

Therapeutic anticoagulation is recommended until the time of procedure. UFH may be discontinued 4 to 6 hours prior to the procedure, with guidance using the activated partial thromboplastin time for earlier time points. If an LMWH is used for bridging, it will need to be discontinued at least 24 hours prior to the procedure (and potentially earlier in those with renal insufficiency), with the option,

FIGURE 4 Algorithm: Whether to Bridge and How to Bridge for DOACs and VKAs



aPTT – activated partial thromboplastin time assay; ASA – acetylsalicylic acid (aspirin); DOAC – direct oral anticoagulant; HIT – heparin-induced thrombocytopenia; ICH – intracranial hemorrhage; INR – international normalized ratio; LMWH – low-molecular-weight heparin; OAC – oral anticoagulation; TE – thromboembolic event; TIA – transient ischemic attack; UFH – unfractionated heparin; VKA – vitamin K antagonist

if necessary, of assessing residual anticoagulation by checking antifactor Xa levels. In patients with heparin-induced thrombocytopenia, if nonheparin anticoagulants are used for bridging, such drugs should be discontinued with knowledge of specific routes of clearance (renal, hepatic) and known half-life for each drug (Table 2).

Guidance Statement for preprocedural management of parenteral bridging anticoagulation for those on a VKA:

1. **Although UFH or a LMWH is most commonly used for bridging, for those with an active or remote history of heparin-induced thrombocytopenia, nonheparin**

anticoagulants should be used and selected in accordance with hospital policy and consideration of renal and hepatic function.

2. **Start parenteral anticoagulant therapy when the INR is no longer therapeutic (e.g., <2.0 in those with NVAF).**
3. **Discontinue UFH ≥4 hours prior to the procedure; the residual anticoagulant effect may be measured by the activated partial thromboplastin time.**
4. **Discontinue LMWH at least 24 hours prior to the procedure; the residual anticoagulant effect may be measured by an LMWH-specific antifactor Xa assay.**

5.9. Postprocedural Reinitiation of Anticoagulant Therapy

Restarting anticoagulation in the postprocedural setting may place the patient at significant risk for bleeding. In patients managed with TI of anticoagulation, recent studies have documented an overall major bleed risk of 1.2% to 1.3% without bridging, with even higher rates in patients bridged with parenteral anticoagulation (18,42,71). Importantly, postprocedural bleed risk depends on: 1) the timing of anticoagulation reinitiation; 2) the type of procedure performed; 3) intraprocedural findings, changes to the planned procedure, or complications; and 4) the anticoagulant used. Together, these factors determine the postprocedural risk for bleeding. Often, the postprocedural bleed risk will reflect the preprocedural bleed risk of the procedure (e.g., high or low bleed risk); however, details of the particular procedure that the patient underwent may shift that risk in 1 direction or the other.

The algorithm for postprocedural reinitiation of anticoagulation is provided in Figure 5. Postprocedural reinitiation of anticoagulation must first begin with a careful assessment of the procedure site to determine adequacy of hemostasis. This necessitates a team-based approach involving the primary managing service and the proceduralist. It is also important to assess the consequences of bleeding. For instance, bleeding after spinal or intracranial procedures carries a significantly higher risk of morbidity and mortality. Finally, one should assess patient characteristics that increase bleed risk. Any history of recent bleeding, qualitative or quantitative abnormalities in platelets (including effects of antiplatelet medications), or abnormalities in coagulation studies should influence when anticoagulation is resumed.

However, when considering resumption of anticoagulation after TI in patients with NVAF, it is important to consider the thrombotic risk as well. Fortunately, as mentioned in the previous text, the overall rate of thromboembolism was quite low in both bridged and nonbridged patients in recent studies (18,42). Therefore, waiting to ensure complete hemostasis before reinitiating anticoagulation for the majority of patients is a prudent strategy to expose the patient to as little risk as possible for a periprocedural bleed or thrombotic complication.

Guidance Statement for restarting anticoagulation postprocedure:

1. **Ensure procedural site hemostasis.**
2. **Consider bleeding consequences, especially with high bleed-risk procedures such as open cardiac surgical, intracranial, or spinal procedures.**
3. **Consider patient-specific factors that may predispose the patient to bleeding complications (e.g., bleeding diathesis, platelet dysfunction, antiplatelet medications).**

5.10. Restarting VKA Therapy

Once hemostasis is achieved and no obvious bleeding complications are present, reinitiation of a VKA may be done following the procedure, typically at the patient's regular therapeutic dose without the need for a loading dose (14,42). The timing of reinitiation may be procedure-specific, and should be determined in consultation with the proceduralist and care team. Early postprocedural initiation of a VKA will not increase the early risk of bleeding because its anticoagulant effect typically begins 24 to 72 hours after initiation of therapy. In general, the full therapeutic effect occurs 5 to 7 days after initiation, assuming the INR was normal at the time of initiation. The anticoagulant effect of a VKA is closely related to hepatic function, antibiotic use, nutritional status, and interactions with other medications, all of which can change in the postprocedural setting. If this occurs, the VKA dosing may need to be adjusted.

In the setting of: 1) any intraprocedural or postprocedural bleeding complication; 2) a procedure at high risk for bleeding; or 3) the presence of patient-specific factors that increase the risk of postprocedural bleeding, delayed reinitiation of anticoagulation may be considered.

Guidance Statement for the postprocedural timing of VKA reinitiation:

1. **In most situations, a VKA can be restarted in the first 24 hours after the procedure at the patient's usual therapeutic dose.**

5.11. Indications for Postprocedural Parenteral Bridging and Unique Postprocedural Indications

For many patients, postprocedural bridging is not necessary and may increase the risk of significant bleeding complications. Thus, careful selection based on

thrombotic and bleed risks is essential to determine the best strategy for most patients. Patients on a VKA who are at moderate or high risk for stroke or systemic thromboembolism may resume parenteral agents until the target INR is achieved. If there is concern about the use of postprocedural parenteral bridging because of high bleed risk, one should consider reinitiation of the VKA without bridging. In selected circumstances, patients may have a second procedure scheduled during the same period and will need to continue the parenteral anticoagulant between procedures without resuming their OAC.

Guidance Statement for consideration of postprocedural parenteral anticoagulation:

1. **Postprocedural bridging with a parenteral agent can be considered in patients with moderate or high risk of stroke or thromboembolic event.**
2. **VKA therapy should be resumed (in most cases at the patient's usual therapeutic dose) without use of parenteral anticoagulation in cases associated with high risk for bleeding.**

5.12. Use of Parenteral Anticoagulation Postprocedure in Patients With Moderate or High Thrombotic Risk: Clinical Factors and Monitoring

Timing the initiation of postprocedural parenteral anticoagulation depends on the type of procedure performed as well as the extent of hemostasis (14). If parenteral anticoagulation is used after procedures with low bleed risk (Online Appendix), we recommend its initiation within 24 hours after the procedure, assuming hemostasis has been achieved and the postprocedural bleed risk is still deemed to be low. In contrast, we recommend delaying therapeutic parenteral anticoagulation, if possible, for at least 48 to 72 hours following procedures with high bleed risk (Online Appendix) (14,42). Although earlier initiation of a parenteral agent is considered to result in a higher bleed risk, this is particularly of concern in patients undergoing a high-bleed-risk procedure, and is associated with an increased risk of major bleeding (14,71). When bleed risk is elevated but thrombotic risk is also considered to be high, individualized strategies may be considered. Options to minimize bleed risk include: 1) initiation of UFH without a bolus dose; 2) administration of UFH or a LMWH at a lower dose (such as those used for deep venous thrombosis prophylaxis); or 3) initiation of a VKA alone (14,73).

Frequent monitoring of coagulation is required during bridging anticoagulation. In addition to monitoring the activated partial thromboplastin time with UFH or argatroban, a chromogenic factor X assay may be used when transitioning between argatroban and a VKA because argatroban elevates the INR (76). However, the INR must also be routinely monitored during bridging when the VKA is restarted, because the risk of bleeding increases as the INR enters the therapeutic range (77). In the BRIDGE trial, the median time to a major bleed was 7.0 days, with the majority of these events occurring in patients randomized to bridging anticoagulation (42). This suggests that the time of highest risk for bleeding is when the therapeutic INR is nearly reached.

Guidance Statement for the initiation of postprocedural therapeutic parenteral anticoagulation in patients with moderate or high thrombotic risk:

1. **Establish that hemostasis has been achieved, procedure-specific bleeding complications have been considered, patient-specific bleeding factors have been evaluated, and the proceduralist and the primary managing service are involved in the decision to restart anticoagulation.**
2. **Following procedures with a lower postprocedural risk of bleeding, therapeutic parenteral anticoagulation, if indicated, can be started within the first 24 hours after the procedure in collaboration with the proceduralist and care team.**
3. **Following procedures with a higher postprocedural risk of bleeding, therapeutic parenteral anticoagulation should be delayed for at least 48 to 72 hours after the procedure.**
4. **When VKA therapy is reinitiated, careful monitoring of the INR during bridging is required to mitigate bleed risk.**
5. **LMWH or UFH should be discontinued when the INR is within goal range (≥2.0). This approach is modified if argatroban is used since argatroban elevates the INR (see the previous text).**

5.13. Reinitiation of DOAC Therapy

Similar to a VKA, reinitiation of a DOAC first requires hemostasis at the procedural site. Thereafter, it is important to consider the consequences of procedural site bleeding and patient-related factors that increase the likelihood of bleeding complications. Unlike therapy with a VKA, use of a DOAC will render the patient therapeutically anticoagulated within hours after the first full DOAC dose. Therefore, the timing of postprocedural DOAC reinitiation should be considered similarly to the timing of parenteral anticoagulation discussed previously, and in most clinical situations, no parenteral agent is needed if resumption of DOAC therapy is planned. Due to the pharmacokinetics observed, bridging after DOAC interruption is not necessary and may be hazardous. Renal function must be carefully monitored in the postprocedural setting, as renal impairment affects the dosing of all DOACs.

5.13.1. Dabigatran

Several studies have investigated the TI of DOACs in the periprocedural setting. A substudy of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial analyzed 4,591 patients who had OAC therapy interrupted for a procedure. Similar rates of major bleeding were observed with dabigatran 150 mg twice daily and VKA therapy (3.8% vs. 3.3%), with shorter interruption of anticoagulation needed with dabigatran (13). In this study, dabigatran was restarted after the procedure once hemostasis was achieved. The details of how dabigatran was resumed were not specified. A separate analysis of this population found that the use of parenteral bridging anticoagulation together with dabigatran resulted in >3 times more major bleeding (6.5% in bridged patients vs. 1.8% in those not bridged), with no statistical difference in thromboembolic events. On the basis of pharmacokinetics of DOACs, bridging with parenteral agents is not necessary and, based on this study, is hazardous (70).

A predefined postprocedure management algorithm for dabigatran has been reported previously (78). For low bleed-risk procedures (including use of neuraxial anesthesia), dabigatran was resumed at a reduced dose of 75 mg on the night of the procedure (≥4 hours after neuraxial anesthesia), with resumption of the full dose the following morning. In contrast, dabigatran was resumed at full dose 48 to 72 hours after the procedure for high bleed-risk procedures. Using this algorithm, the incidences of major bleeding and thromboembolism were 1.8% and 0.2%, respectively, both of which compare favorably with outcomes from other studies of periprocedural VKA therapy.

5.13.2. Rivaroxaban

Similar to dabigatran, a substudy of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) analyzed periprocedural outcomes after TI in 4,692 patients. Similarly low rates of thromboembolism were noted with rivaroxaban and VKA therapy during the at-risk period (0.3% vs. 0.4%), with no difference in major bleeding (15). Although this data provides support that TI is relatively safe with rivaroxaban, details about how it should be resumed postprocedure are not known.

A large registry of patients (n = 2,179) treated with a DOAC (the majority of whom were on rivaroxaban) reported frequent TI, with resumption of therapy most commonly occurring 1 day after the procedure (17). This approach was associated with a 1.2% rate of major bleeding in the 30 days following the procedure, with 0%, 0.5%, and 8% rates of major bleeding following minimal (n = 135), minor (n = 641), and major (n = 87) procedures in the study, respectively. Following major procedures, 6 of the 7 major bleeding events occurred in patients who received some form of bridging anticoagulation, and there was no difference in rates of major cardiovascular events with bridging. It is important to note that a majority (90%) of procedures in this study were considered to pose minor bleed risk. Furthermore, most of these procedures would qualify as low bleed-risk procedures by the classification outlined in this document, underscoring the difficulty in comparing bleeding rates across studies. Unlike with dabigatran, there are no data on the use of reduced doses of rivaroxaban beginning on the evening after low bleed-risk procedures in the setting of NVAF. However, this strategy has been used for deep venous thrombosis prophylaxis after orthopedic procedures associated with high bleed risk. Pooled analysis of several randomized trials found a trend toward more major bleeding with rivaroxaban 10 mg started 6 to 8 hours after the procedure when compared with LMWH, although the overall risk of major bleeding was low with both approaches (79).

5.13.3. Apixaban

In a prespecified analysis from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, apixaban (compared with VKA therapy) was associated with similar rates of thromboembolism and major bleeding in the periprocedural period, establishing it as a relatively safe option if TI is required (16). Despite the lack of an approved reversal agent for apixaban, periprocedural bleeding outcomes were similar between apixaban and a VKA, with no difference in the rate of thromboembolism regardless of whether anticoagulation was stopped periprocedurally. Notably, however, only 10% of procedures in this study were classified as “major,” which was defined by the need for general anesthesia.

Similar to rivaroxaban, apixaban has been studied in the prophylaxis of deep venous thrombosis after orthopedic surgery, with initiation of therapy 12 to 24 hours after surgery. Initiation of anticoagulation should follow consultation with the proceduralist. Although no significant increase in bleeding relative to LMWH has been observed in this population, no dosing for postprocedural thromboprophylaxis in NVAF has been published (46).

5.13.4. Edoxaban

To date, no data has been published regarding edoxaban in the periprocedural period; however, an analysis of the ENGAGE-AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial

Fibrillation-Thrombolysis In Myocardial Infarction 48) trial suggests that procedures performed on edoxaban had similar outcomes to those performed on VKA therapy in patients with or without TI (80). Similar to other DOACs, manufacturer recommendations as well as expert consensus suggest that after complete hemostasis is achieved, it is reasonable to resume full-dose edoxaban 6 to 8 hours after a procedure. Following procedures with a high risk of bleeding, however, it is reasonable to delay resumption of full-dose edoxaban for 48 to 72 hours (46).

Guidance Statement for restarting DOAC therapy postprocedure:

1. **Establish that hemostasis has been achieved, procedure-specific bleeding complications have been considered, patient-specific bleeding factors have been evaluated, and the proceduralist and primary managing service have been involved in the decision to restart anticoagulation.**
2. **Following procedures with low postprocedural bleed risk where TI is indicated, it is reasonable to resume DOAC therapy at full dose on the day following the procedure.**
3. **Following high postprocedural bleed-risk procedures, it is reasonable to wait at least 48 to 72 hours before resuming DOAC therapy at full dose if complete hemostasis has been achieved.**
4. **DOAC dosing should reflect postprocedural renal function.**
5. **Bridging therapeutic anticoagulation with a parenteral agent is generally not required.**

5.14. Scenarios Requiring Special Consideration for DOAC Reinitiation

5.14.1. Prolonged Period of Inability to Take Oral Medications Following a Procedure in Patients Taking a DOAC

A parenteral agent is not typically required when using a DOAC; however, in patients who are unable to tolerate oral medications for a prolonged period postprocedurally (e.g., postoperative ileus after abdominal surgery) or who are anticipated to need a second procedure or multiple interventions during hospitalization, the use of a parenteral agent may be necessary to manage TI of anticoagulation. In these situations, we recommend that therapeutic anticoagulation with a parenteral agent begin within the first 24 hours following a procedure with low bleed risk and within 48 to 72 hours after a procedure with high bleed risk (46,60,81). In patients who are receiving or have received procedural neuraxial anesthesia (see the following text), careful attention to the timing of catheter placement and withdrawal is necessary, with referral to the product-specific prescribing information and the American Society of Regional Anesthesia and Pain Medicine guidelines (33,61,62,82,83).

If an LMWH is used postprocedure, the chosen dose should reflect the patient's renal function in the postprocedural setting. When the patient can tolerate oral medications, the LMWH should be discontinued and the DOAC can be resumed at the time that the next scheduled LMWH dose would have been administered. If UFH is used, the DOAC can be started at the time that UFH is discontinued (20-23). Of note, rivaroxaban must be taken with a meal to have full therapeutic effect. Rivaroxaban and apixaban may be crushed and administered through a feeding tube (61,82).

5.14.2. Postprocedural Venous Thromboembolism Prophylaxis

Resumption of a DOAC or therapeutic parenteral anticoagulation for NVAF obviates the need for other anticoagulants for venous thromboembolism (VTE) prophylaxis postprocedure. For procedures resulting in immobility that require VTE prophylaxis in those who are at high risk of bleeding, nonpharmacological measures, such as an intermittent pneumatic compression device, may be used if appropriate. For some patients, there may be a need to provide prophylactic doses of anticoagulation prior to the resumption of therapeutic anticoagulation. During TI of DOAC therapy, it is reasonable in these cases to use prophylactic doses of an LMWH or UFH starting 6 to 8 hours following the procedure for VTE prophylaxis provided that adequate hemostasis has been achieved (46). In the setting of NVAF, only dabigatran has been specifically tested at a prophylactic dose after low bleed-risk procedures, with a low overall rate of major bleeding (1.8%) (78). Following orthopedic surgery, apixaban 2.5 mg twice daily, edoxaban 15 mg or 30 mg daily, and dabigatran 150 mg or 220 mg daily for VTE prophylaxis have rates of major or clinically relevant nonmajor bleeding similar to those for prophylactic doses of enoxaparin. In contrast, rivaroxaban 10 mg daily has a higher rate of major or clinically relevant nonmajor bleeding (84,85). Rivaroxaban 10 mg daily and apixaban 2.5 mg twice daily demonstrated significantly more major or clinically relevant non-major bleeding than prophylactic enoxaparin for VTE prophylaxis in medically ill patients (86). It is worth noting that postprocedural prophylactic doses of UFH or an LMWH as well as DOACs administered in doses lower than indicated for NVAF may not fully protect against thromboembolic events (87).

5.14.3. Neuraxial Anesthesia

The use of anticoagulants in the setting of neuraxial anesthesia raises the risk of a spinal or epidural hematoma, which can have dire consequences. All currently available DOACs carry a black box warning regarding their use in the setting of neuraxial anesthesia. The prescribing information for each oral factor Xa inhibitor (apixaban, edoxaban,

and rivaroxaban) provides specific guidance on the minimum length of time after the last DOAC dose that an epidural catheter may be removed, as well as, the minimum length of time after catheter removal when the DOAC can be restarted. In the case of dabigatran, the prescribing information does not provide specific timing recommendations for epidural catheter removal or anticoagulation reinitiation. It is important to note that if an epidural catheter is still in place, DOAC use should be avoided.

The American Society of Regional Anesthesia and Pain Management has developed guidelines regarding the periprocedural management of antiplatelet and anticoagulant medications around interventional pain procedures. Their guidelines recommend waiting to reinitiate DOAC therapy until 24 hours postprocedure or after catheter removal (33). Of note, this recommendation is for a longer delay than that recommended by the package inserts for the DOACs (61,62,82,83) and may stem from the surgical nature of some interventional pain medicine procedures (e.g., permanent implantation of spinal cord stimulator). In trials of DOACs for deep vein thrombosis prophylaxis following orthopedic procedures, DOACs were started ≥4 to 8 hours after epidural catheter removal at prophylactic doses without issue (88–90). Nevertheless, restarting a DOAC 24 hours after the procedure is similar to the guidance of restarting DOAC therapy after a low-risk procedure and therefore is a reasonable time point for most patients. If the stroke risk of the patient is significantly elevated, starting a prophylactic dose of a DOAC 12 hours after the procedure may be a reasonable consideration (33,78).

5.14.4. Restarting Anticoagulation After a Procedure With an Unknown Bleed Risk

The timing of restarting anticoagulation discussed in the previous text is largely based on the bleed risk of the procedure performed. However, for procedures with an unknown bleed risk, it is difficult to provide precise guidance regarding the timing of restarting anticoagulation. As previously noted, published rates of periprocedural thromboembolism are low, yet the bleed risk following these procedures is unknown. Therefore, in the absence of evidence-based data, we recommend approaching reinitiation of anticoagulation as was previously recommended for high bleed-risk procedures. This will delay the reinitiation of anticoagulation after the procedure; however, it will not significantly increase the thromboembolic risk for most patients.

5.14.5. Restarting DOAC Therapy Following Cardiac Surgery

The indication for a DOAC should be re-evaluated after cardiac surgery, especially if the patient has undergone a valvular procedure. The RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) study evaluated dabigatran versus warfarin in patients with an existing mechanical mitral valve and in patients undergoing mechanical aortic or mitral valve placement. The dabigatran group had more thromboembolic events and more major bleeding (all within the pericardial space) than did the warfarin group, leading to early cessation of the trial (91). Based on these results, all DOACs are contraindicated in patients with mechanical valves. In addition, there are limited data on DOACs in valvular AF of any kind. Patients with valvular AF were completely excluded from the RE-LY and ROCKET-AF trials, and subpopulations of valvular AF patients were excluded from the ARISTOTLE and ENGAGE-AF-TIMI 48 trials (20–23). Therefore, in patients who have undergone valve surgery, we currently recommend transitioning a patient who was on a DOAC to warfarin after the procedure.

For patients who have undergone a different type of cardiac surgery, such as coronary artery bypass graft surgery, resumption or initiation of a DOAC to treat NVAF is becoming more commonplace. There is not a strong evidence base for this practice, and the increased number of major bleeding events seen in the RE-ALIGN trial (all in the pericardial space) may be relevant to bypass surgery as well. This may, however, be a safe strategy when initiated at least 72 hours after surgery when hemostasis has been achieved (92). Further study of this practice is needed, with the use of a VKA in this setting more strongly supported by existing evidence.

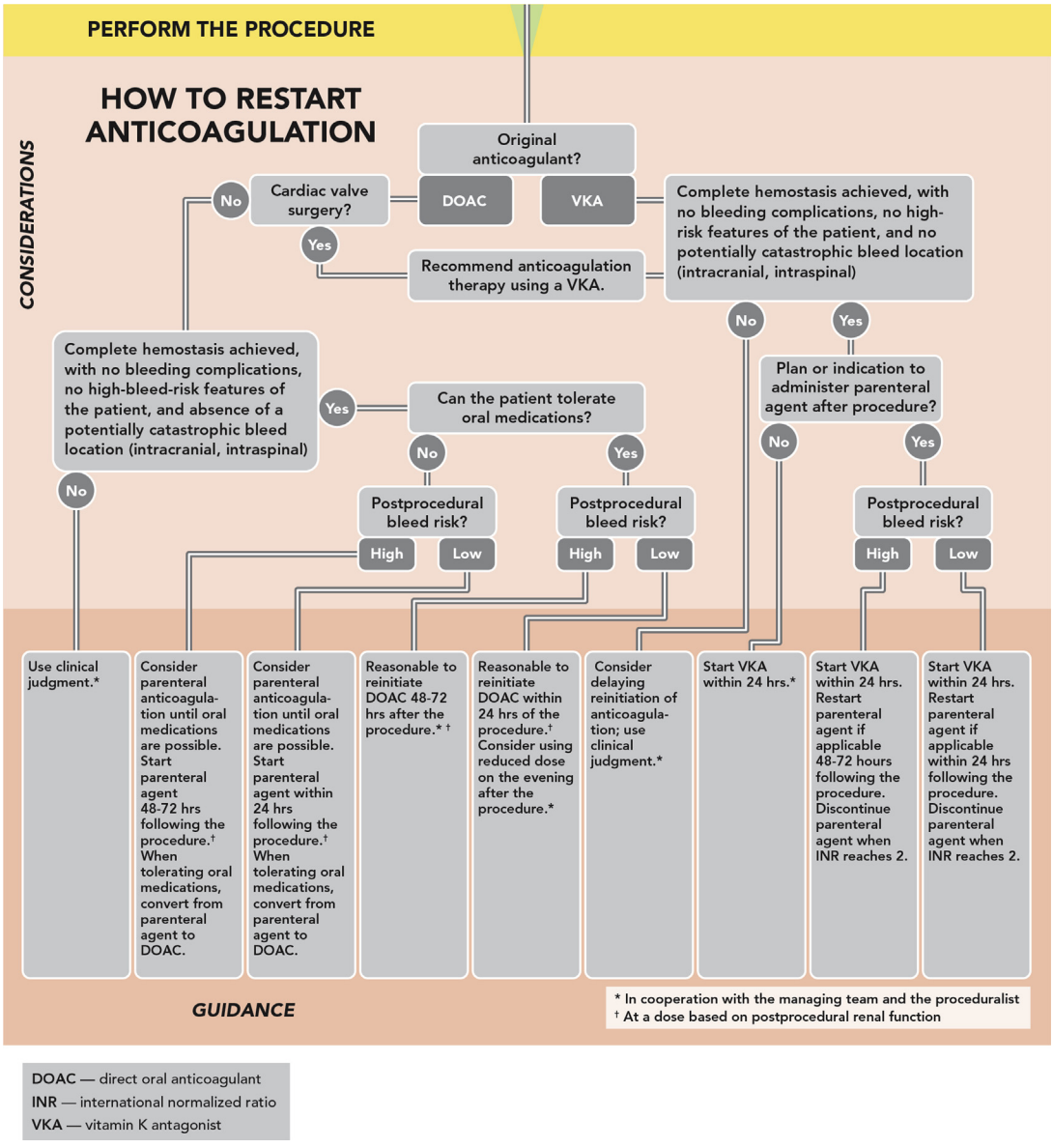
5.14.6. Bleeding Complications

In the event of postprocedural bleeding complications, resumption of DOAC therapy will most often be delayed until adequate hemostasis has been achieved. Clinical judgment and coordinated decision-making by the primary management team and the proceduralist will be required to determine the “best” time to restart DOAC therapy. When the DOAC is resumed, flexible dosing regimens (such as starting with lower doses than are typically used for orthopedic VTE prophylaxis or with reduced renal function) may be considered to reduce the possibility of further bleeding complications. Careful attention should be given to ensuring that the patient resumes the most appropriate dose for stroke prevention in NVAF as soon as possible.

6. DISCUSSION AND IMPLICATION OF PATHWAY

The primary objective of this document was to provide a framework for the multiple decisions that need to be made when managing a patient on anticoagulation who is undergoing a procedure. Management of anticoagulation crosses many different specialties. We have attempted to cite the literature to offer direct guidance when possible

FIGURE 5 Algorithm: How to Restart Anticoagulation



and to highlight areas in which clinical judgment is needed. As more information becomes available, especially regarding the DOACs, many of these areas will be clarified. This is a clinical area of high volume, with multiple transitions of care and several providers involved in the patient's care, which creates potential risk. It is hoped that this document will aid in the management of our patients.

PRESIDENT AND STAFF

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KEY WORDS anticoagulation, atrial fibrillation, bleeding risk, bridging, direct-acting anticoagulants, surgical procedures, thrombotic risk, warfarin

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2017 ACC EXPERT CONSENSUS DECISION PATHWAY FOR PERIPROCEDURAL MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
John U. Doherty, Chair	Jefferson Medical College of Thomas Jefferson University—Professor of Medicine	None	None	None	None	None	None
Ty J. Gluckman	Providence Heart and Vascular Institute—Medical Director	None	None	None	None	None	None
William J. Hucker	Massachusetts General Hospital—Fellow in Cardiovascular Medicine	None	None	None	None	None	None
James L. Januzzi Jr.	Massachusetts General Hospital—Director, Dennis and Marilyn Barry Fellowship in Cardiology Research, Cardiology Division; Harvard Medical School—Hutter Family Professor of Medicine	None	None	None	None	■ Boehringer Ingelheim (DSMB)* ■ Janssen Pharmaceuticals, (DSMB)	None
Thomas L. Ortel	Duke University Medical Center—Chief, Division of Hematology; Professor of Medicine and Pathology; Medical Director, Clinical Coagulation Laboratory	None	None	None	None	None	None
Sherry J. Saxonhouse	Carolinas HealthCare System Sanger Heart & Vascular Institute—Cardiac Electrophysiology Associate Professor of Medicine	None	None	None	None	None	None
Sarah A. Spinler	University of the Sciences Philadelphia College of Pharmacy—Professor of Clinical Pharmacy	■ Boehringer Ingelheim Pharmaceuticals, Inc. ■ Daiichi Sankyo	None	None	None	None	None

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*Significant relationship.

DSMB = data and safety monitoring board.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2017 ACC EXPERT CONSENSUS DECISION PATHWAY FOR PERIPROCEDURAL MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Richard J. Kovacs	Official Reviewer—ACC Board of Trustees	Indiana University School of Medicine—Q.E. and Sally Russell Professor of Cardiology; Krannert Institute of Cardiology—Clinical Director	■ Biomedical Systems* ■ Theravance, Inc.	None	None	■ Armaron Pharmaceuticals† ■ AstraZeneca (DSMB) ■ Biotie (DSMB) ■ Lilly (DSMB)* ■ Siemens† ■ Teva Pharmaceutical (DSMB)	■ Cook Incorporated-Med Institute*	None
John D. Puskas	Official Reviewer—ACC Task Force on Clinical Expert Consensus Documents	Mount Sinai Hospital—Chair, Cardiothoracic Surgery; Icahn School of Medicine—Professor	None	None	None	None	■ Scanlan*	None
Eugene Yang	Official Reviewer—ACC Board of Governors	University of Washington Medicine, Eastside Specialty Center—Medical Director; University of Washington Medical Center—Clinical Associate Professor of Medicine, Division of Cardiology	■ Bristol-Myers Squibb ■ CTI ■ NSCI ■ RubiconMD	None	None	■ Amgen* ■ Gilead*	None	■ Defendant, determination if CV event death was work-related, 2015*
Neena Abraham	Organizational—American Society for Gastrointestinal Endoscopy; ACC	Mayo Clinic College of Medicine—Professor of Medicine; Mayo Foundation—Arizona Site Kern Center for the Science of Healthcare Delivery—Director; "*The Science of Best Practice*"—Consultant, Division of Gastroenterology and Hepatology, Department of Medicine	None	None	None	None	None	None
Honorio T. Benzon	Organizational—American Society of Regional Anesthesia and Pain Medicine	Northwestern University Feinberg School of Medicine—Professor of Anesthesiology	None	None	None	None	None	None
Adam Cuker	Organizational—American Society of Hematology	University of Pennsylvania Perelman School of Medicine—Assistant Professor	■ Amgen ■ Biogen Idec ■ Genzyme*	None	None	■ Spark Therapeutics* ■ T2 Biosystems†	None	None
Bruce Davidson	Organizational—American College of Chest Physicians	University of Washington School of Medicine—Clinical Professor of Medicine, Division of Pulmonary and Critical Care Medicine	■ Bayer HealthCare Pharmaceuticals ■ Janssen	None	None	None	None	None
Paul Dobesh	Organizational—ACC Anticoagulation Workgroup	University of Nebraska Medical Center—AQ Cardiology Professor of Pharmacy Practice, College of Pharmacy	■ AstraZeneca Pharmaceuticals ■ Boehringer Ingelheim ■ Daiichi Sankyo ■ Janssen ■ Pfizer	None	None	None	None	None

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APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ann T. Farrell	Organizational—U.S. Food and Drug Administration	U.S. Food and Drug Administration—Director, Office of Hematology and Oncology; Products Director, Division of Hematology Products; Products Director, Center for Drug Evaluation and Research, Office of New Drugs	None	None	None	None	None	None
Bruce Jacobs	Organizational—American Urological Association	University of Pittsburgh School of Medicine—Assistant Professor, Department of Urology	■ Via Oncology	None	None	None	None	None
Abhishek Khemka	Organizational—ACC Anticoagulation Workgroup	Indiana University Krannert Institute of Cardiology—Assistant Professor of Medicine	None	None	None	None	None	None
Andrea Russo	Organizational—Heart Rhythm Society	Cooper Medical School of Rowan University—Professor of Medicine; Director, Cardiac Electrophysiology and Arrhythmia Services; Director; CCEP Fellow	■ ABIM* ■ Biotronik ■ Medtronic ■ St. Jude ■ UpToDate	None	None	■ Boehringer Ingelheim* ■ Boston Scientific* ■ Medtronic*	■ Biotronik ■ Medtronic* ■ Heart Rhythm Society†	None
Michael Streiff	Organizational—ACC Anticoagulation Workgroup	Johns Hopkins Medicine—Medical Director, Anticoagulation Management Service and Outpatient Clinics; Associate Professor of Medicine; National Comprehensive Cancer Center Network Venous Thromboembolism Guideline Committee	■ Janssen* ■ Merck	None	None	■ BiO2 Medical (DSMB)* ■ CSL Behring (DSMB)	None	None
Jack E. Ansell	Content Reviewer—Individual	Hofstra-NorthShore/LIJ School of Medicine—Professor of Medicine	■ Alere ■ Boehringer Ingelheim ■ Bristol-Myers Squibb ■ Daiichi Sankyo ■ Instrumentation Laboratory ■ Janssen ■ Perosphere Inc.* ■ Pfizer ■ Roche Diagnostics	None	None	None	None	None
Yong-Mei Cha	Content Reviewer—ACC Electrophysiology Council	Mayo Clinic—Consultant, Department of Cardiovascular Diseases; Professor, Department of Medicine; Director, Cardiac Device Service	■ Research†	None	None	None	None	None

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APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
George H. Crossley III	Content Reviewer—ACC Electrophysiology Council	Vanderbilt University—Associate Professor of Medicine	■ Boston Scientific ■ Medtronic	■ Medtronic	None	■ ARCA Biopharma† ■ Boston Scientific† ■ Medtronic† ■ NHLBI† ■ St. Jude† ■ Thoratec† ■ Vanderbilt† ■ Vanderbilt/ Medtronic† ■ Zio Patch†	None	■ Defendant, right-sided pneumothorax during left-sided pacemaker, 2015
Sondra M. DePalma	Content Reviewer—ACC Cardiovascular Team Council	Penn State Health—Assistant Director of Advanced Practice, Milton S. Hershey Medical Center; Penn State Heart and Vascular Institute—Physician Assistant and Clinical Lipid Specialist	■ American Society of Hypertension	None	None	None	■ Accreditation Council for Clinical Lipidology†	None
Richard A. Lange	Content Reviewer—ACC Coronary Artery Bypass Graft Guideline	Texas Tech University Health Sciences Center El Paso Paul L. Foster School of Medicine—Dean	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer—ACC Percutaneous Coronary Intervention Guideline; Dual Antiplatelet Therapy Guideline	Baylor College of Medicine—Professor of Medicine; Michael E. DeBakey Veterans Affairs Medical Center—Director, Cardiac Care Unit	None	None	None	None	None	None
Kristine Anne Scordo	Content Reviewer—ACC Cardiovascular Team Council	Wright State University—Professor and Director, AG-ACNP Program	None	None	None	None	None	None
L. Samuel Wann	Content Reviewer—ACC Atrial Fibrillation Guideline	Columbia St. Mary's Healthcare, Milwaukee—Clinical Cardiologist	■ United Healthcare	None	None	None	None	None
Nanette Kass Wenger	Content Reviewer—ACC Management of Patients With Non-ST-Elevation Acute Coronary Syndromes Guideline	Emory University School of Medicine—Professor of Medicine (Cardiology) Emeritus; Emory Heart and Vascular Center—Consultant	■ Amgen ■ AstraZeneca ■ Gilead ■ Merck	None	None	■ Alnylam Pharmaceuticals ■ Gilead* ■ NHLBI* ■ Pfizer* ■ Society for Women's Health Research*	None	None
Barbara S. Wiggins	Content Reviewer—ACC Task Force on Clinical Expert Consensus Documents	Medical University of South Carolina—Clinical Pharmacy Specialist, Cardiology Department of Pharmacy Services	None	None	None	None	None	None

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APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kim Williams	Content Reviewer—Individual	Rush University Medical Center—James B. Herrick Professor; Chief, Division of Cardiology	None	None	None	None	None	None
Daniel M. Witt	Content Reviewer—Individual	University of Utah College of Pharmacy—Professor (Clinical), Vice Chair, and Assistant Dean for Clinical Affairs, Department of Pharmacotherapy	None	None	None	None	None	■ Plaintiff, reversal of anticoagulation, 2016 ■ Defendant, fatal GI bleeding, 2015 ■ Defendant, anticoagulation therapy management, 2015*

This table represents ALL healthcare relationships with industry and other entities by peer reviewers, including those not deemed to be relevant, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC Disclosure Policy.

*Significant relationship.

†No financial benefit.

ABIM = American Board of Internal Medicine; ACC = American College of Cardiology; AG-ACNP = adult gerontology acute care nurse practitioner; CCEP = clinical cardiac electrophysiology; DSMB = Data Safety Monitoring Board; LIJ = Long Island Jewish; NHLBI = National Heart, Lung, and Blood Institute.

APPENDIX 3. ABBREVIATIONS

AF = atrial fibrillation

COR = Class of Recommendation

CrCl = creatinine clearance

DOAC = direct-acting oral anticoagulant

INR = international normalized ratio

LMWH = low molecular weight heparin

LOE = Level of Evidence

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulant

TI = temporary interruption

TIA = transient ischemic attack

UFH = unfractionated heparin

VKA = vitamin K antagonists

VTE = venous thromboembolism