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EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

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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 in which evidence may be limited or new and evolving, or in which data are insufficient to fully inform clinical decision making.

In an effort to increase the impact 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 "Expert Consensus Decision Pathways" (ECDPs).

Although ECDPs 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. ECDPs are designed to complement the guidelines and bridge the gaps in clinical guidance that remain. In some cases, topics covered by ECDPs will be addressed subsequently by ACC/American Heart Association 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 apps to accelerate the use of these documents at 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 Expert Consensus Decision Pathways

1. INTRODUCTION

Anticoagulation is the cornerstone of treatment for thrombosis and thromboembolic complications of a variety of disorders. The incidence of the common indications for anticoagulation such as atrial fibrillation (AF) (1) has continued to rise because of advances in early detection and treatment (2,3). It is estimated that over 6 million patients in the United States are treated with anticoagulants (4), and are thus at increased risk of bleeding with substantially increased morbidity and mortality. Secular trends in anticoagulation use have demonstrated a relatively rapid adoption of direct oral anticoagulants (DOACs) for the most common indications for anticoagulation: AF in the absence of a prosthetic valve and venous thromboembolism. Systematic reviews have demonstrated favorable risk-benefit profiles for DOACs when compared with vitamin K antagonists (VKAs) in the management of AF and with low-molecular-weight heparin in the treatment and prevention of venous thromboembolism (5,6). The favorable outcomes with DOACs and the emergence of reversal agents (7) may also further increase the proportionate use of DOACs and influence the management of bleeding that complicates anticoagulant use (8).

This document was informed by the scientific evidence presented and expert opinions considered during the Anticoagulation Consortium Roundtable, and by subsequent review and deliberation on available evidence by the expert consensus writing committee. Although the Roundtable provided valuable insight into the practical issues and gaps in care, this document is a separate and independent activity aimed specifically at addressing the questions raised during the meeting.

The work of the writing committee was supported exclusively by the ACC without commercial support. Writing committee members volunteered their time to this effort. Conference calls of the writing committee were confidential and attended only by committee members and ACC staff. All members of the writing committee, as well as those selected to serve as peer reviewers of this document, were required to disclose relationships with industry and other entities. Writing committee and peer reviewer relationships with industry relevant to this document are included in Appendixes 1 **and** 2, respectively. A formal peer review process was completed consistent with ACC policy, which included expert reviewers nominated by the ACC (see Appendix 2). A public comment period was also held to obtain further feedback. Following reconciliation of all comments, this document was approved for publication by the governing bodies of the ACC.

The guidance in this document is designed to address the clinical problem of bleeding management of patients treated with anticoagulants and will consider both DOACs and VKAs used for any indication. The decision pathway considered the severity of the bleed (major vs. nonmajor), acute medical and surgical management, the need for reversal, the appropriateness and time of restarting anticoagulation, and the impact of pertinent comorbidities and concomitant drug therapy. At each step in the decision pathway algorithms, patient specific factors should be considered.

2. METHODS

This decision pathway focuses on the management of bleeding in patients being treated with DOACs and VKAs for any indication. The role and management of antiplatelet agents is considered in the treatment algorithms. Bleeding classification has been simplified and is categorized as major or nonmajor (9). The former includes bleeding that is associated with hemodynamic compromise, occurs in an anatomically critical site, requires transfusion (≥2 U of packed red blood cells [RBCs]) or results in a hemoglobin drop ≥2 g/dL. All other bleeding is categorized as nonmajor. The recommendations provided by this decision pathway include guidance for temporary or permanent interruption of therapy, general approaches to bleeding management, decision support for treatment with a reversal agent, and indications and timing for reinstituting anticoagulant treatment.

The primary goal of this decision pathway is to guide the management of acute bleeding in patients treated with oral anticoagulants (OACs) and to supplement the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Non-Valvular AF (10), which addresses the management of patients undergoing planned surgical or interventional procedures.

3. ASSUMPTIONS AND DEFINITIONS

Several specific assumptions and definitions were considered by the writing committee during the development of this Decision Pathway.

3.1. General Clinical Assumptions

1. The pathway considers acute bleeding in patients being treated with either DOACs or VKAs.

2. In the setting of bleeding with hemodynamic compromise, standard resuscitative measures should always be performed promptly.
3. All indications for anticoagulation were considered, including AF, venous thromboembolism treatment and prevention, prosthetic cardiac valves, history of prior thromboembolism, intracardiac thrombus, and the presence of a mechanical cardiac support device (e.g., left ventricular assist device).
4. The recommendations for restarting and withholding anticoagulant therapy refers to both DOACs and VKAs.
5. The pathway algorithm assumes that the provider will seek input from the appropriate specialists when indicated and include the patient and/or family in shared decision making when possible.

3.2. Definitions

Definitions of terms used throughout the decision pathway are listed here.

DOACs refer to any direct oral anticoagulant.

Major Bleed(s) are all bleeds associated with hemodynamic compromise, occurring in an anatomically critical site (e.g., intracranial), or associated with a decrease of hemoglobin ≥2 g/dL (when baseline is known) or requiring transfusion of ≥2 U of packed RBCs.

Nonmajor Bleed(s) are all bleeds not classified as major. Some nonmajor bleeds may require intervention or hospitalization.

OACs refer to any oral anticoagulant, including DOACs and VKAs.

Reversal Agents include repletion strategies such as prothrombin complex concentrates (PCCs), plasma, vitamin K, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

Note: Bleeding definitions were modified based on the International Society on Thrombosis and Hemostasis definitions (9).

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.

5. DESCRIPTION AND RATIONALE

The decision pathway algorithms created by the writing committee include guidance on managing bleeds in patients on DOACs and VKAs, which are described in the following text. For ease of clinical use, they are also summarized in Figure 2.

5.1. Assessing Bleed Severity

The assessment of bleed severity in patients treated with OACs and/or antiplatelet therapy is crucial for treatment decisions to achieve hemostasis and preserve organ function. During the initial assessment, a focused history and physical examination, with collection of vital signs and laboratory evaluation, should be obtained, aimed at determining time of onset, location, severity of bleeding, and whether bleeding is ongoing. The assessment of hemodynamic instability should be done promptly and reassessed frequently. Patients with major bleeds, with or without hemodynamic instability, require close monitoring, ideally in the acute or critical care setting. Additional considerations are time of ingestion of last dose of anticoagulant and whether there was an intentional or unintentional overdose. Clinicians should be mindful of comorbidities and concomitant treatments that could also contribute to bleeding or alter its management (e.g., antiplatelet therapy, thrombocytopenia, uremia, or liver disease) and manage them as appropriate.

5.2. Defining Bleed Severity

If ≥1 of the following factors apply, the bleed is classified as major.

Bleeding in a Critical Site

Critical site bleeds are considered bleeds that compromise the organ's function. Intracranial hemorrhage and other central nervous system bleeds (e.g., intraocular, spinal) and thoracic, intra-abdominal, retroperitoneal, intra-articular, and intramuscular bleeds are considered critical as they may cause severe disability and require surgical procedures for hemostasis. Intraluminal gastrointestinal (GI) bleeding is not considered a critical site bleed; however, it can result in hemodynamic compromise. A list of critical bleeding locations can be found in here in Table 1.

Hemodynamic Instability

An increased heart rate may be a first sign of hemodynamic instability due to blood loss. Furthermore, a systolic blood pressure <90 mm Hg, a decrease in systolic blood pressure >40 mm Hg (11), or orthostatic blood pressure changes (systolic blood pressure drop ≥20 mm Hg or diastolic blood pressure drop ≥10 mm Hg upon standing) can indicate hemodynamic instability. However, noninvasively measured blood pressure may not always reflect intra-arterial pressure. Continuous invasive measurement of mean arterial pressure is considered superior for assessment, and a value <65 mm Hg serves as a cut-off for hemodynamic instability (11). In addition to clinical signs, surrogate markers for organ perfusion (including urine output <0.5 mL/kg/h) can be used to evaluate for hemodynamic instability (11).

Overt Bleeding With Hemoglobin Drop ≥2 g/dL or Administration of ≥2 U of Packed RBCs

Bleeding events causing a hemoglobin drop ≥2g/dL or requiring transfusion of ≥2 U of RBCs have been

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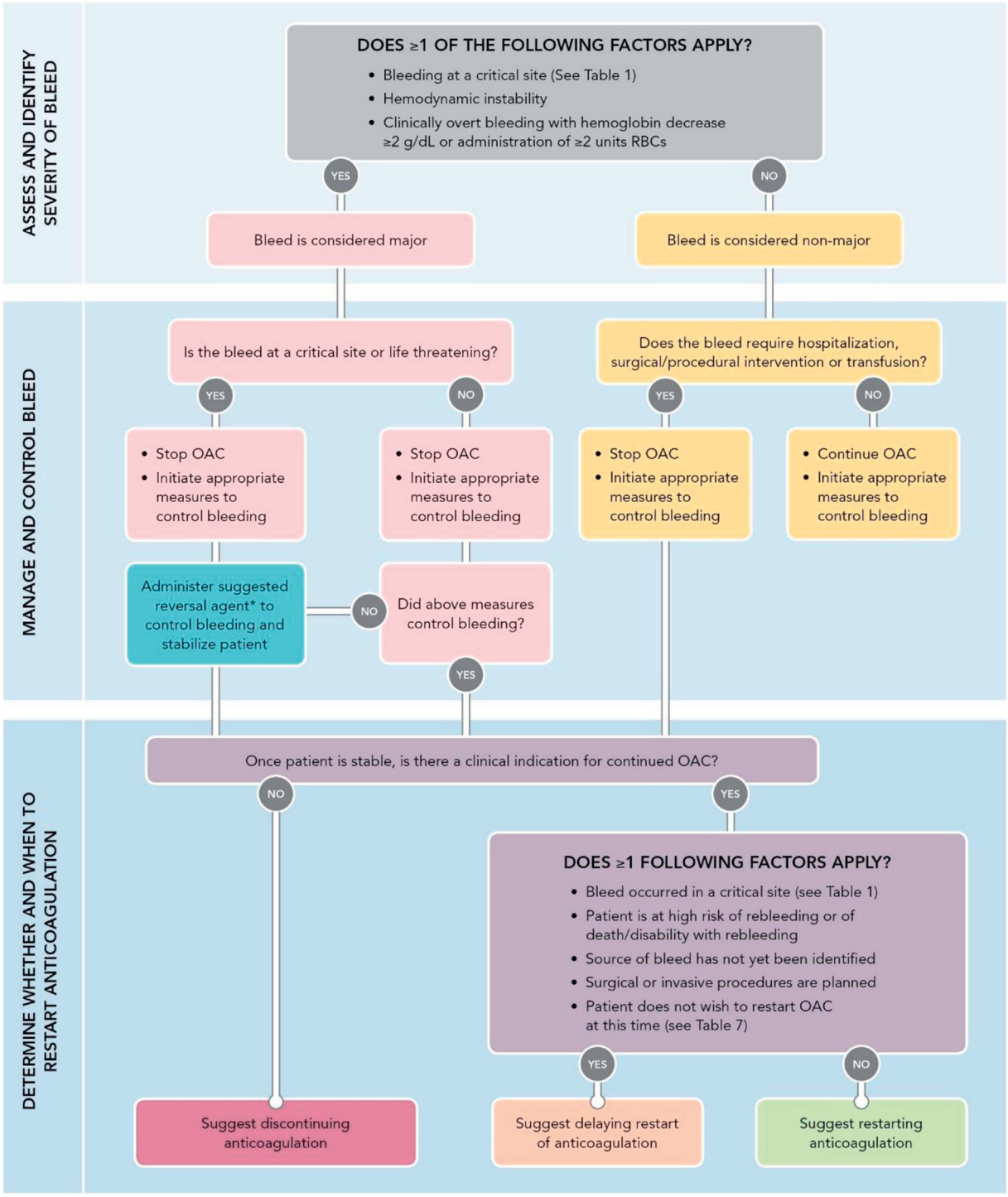
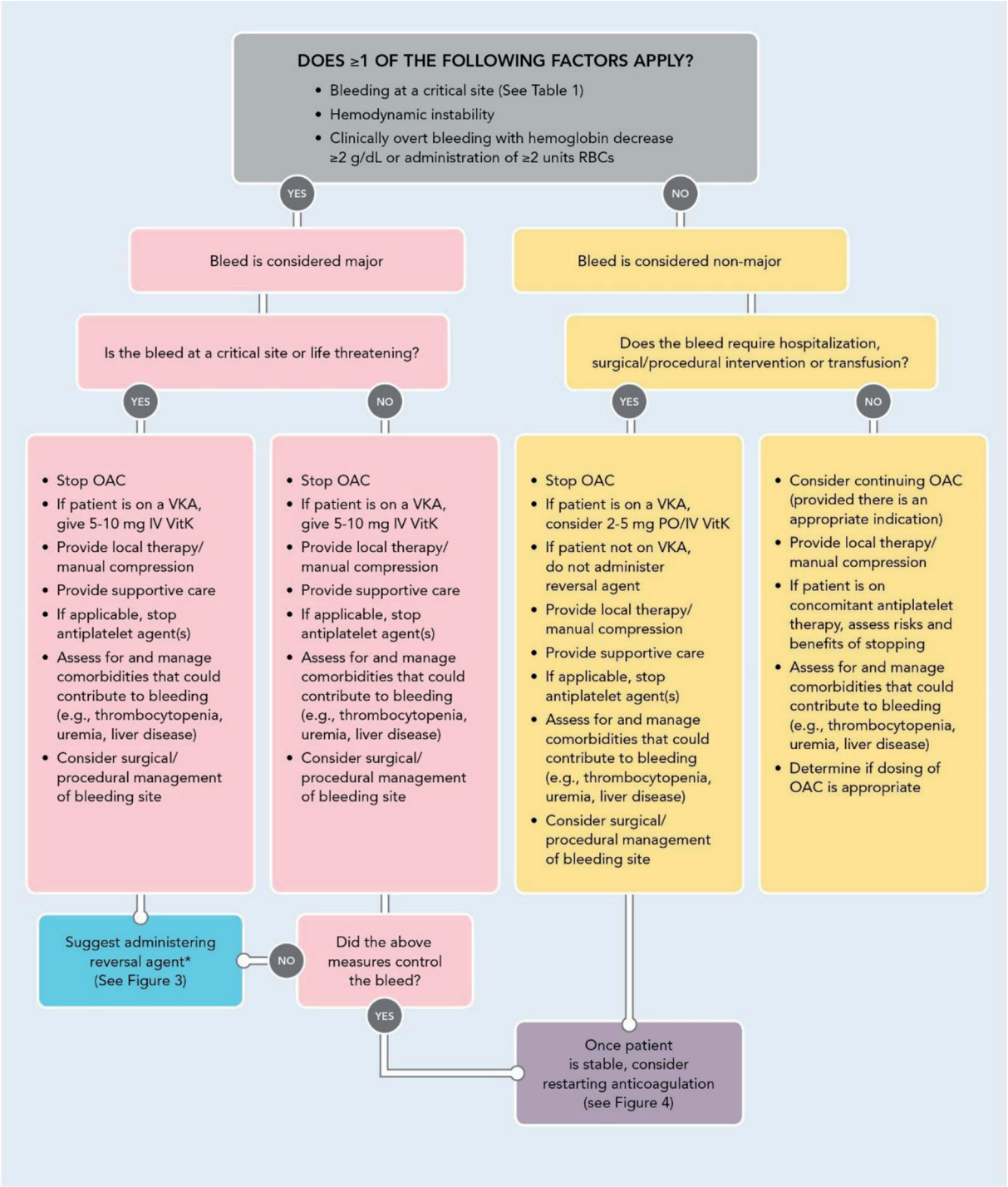
FIGURE 1 **Summary Graphic**



DOAC = direct oral anticoagulant; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; RBCs = red blood cells; VitK = vitamin K; VKA = Vitamin K antagonist
*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

FIGURE 2 Assessing Bleed Severity and Managing Major and Nonmajor Bleeds



DOAC = direct oral anticoagulant; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; PO = per os "by mouth"; RBCs = red blood cells; VitK = vitamin K; VKA = Vitamin K antagonist

*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

TABLE 1 Critical Site Bleeds

Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
Intracranial hemorrhage: Includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	**Unusually intense headache, emesis** **Neurological signs:** e.g., reduced LOC, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	Stupor or coma Permanent neurological deficit Death
Other central nervous system hemorrhage: Includes Intraocular, intra- or extra-axial spinal hemorrhages	**Intraocular:** monocular eye pain, vision changes, blindness **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	**Intraocular:** permanent vision loss **Spinal:** permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	Shortness of breath, tachypnea Hypotension, jugular venous distension Tachycardia, muffled heart sounds, rub	Cardiogenic shock Death
Airway, including posterior epistaxis	**Airway:** hemoptysis, shortness of breath, hypoxia **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	Hypoxemic respiratory failure, Death
Hemothorax, intra-abdominal bleeding, and RPH	**Hemothorax:** tachypnea, tachycardia, hypotension **Intra-abdominal (nongastrointestinal):** abdominal pain, distension, hypotension, tachycardia **RPH:** Back/flank/hip pain, tachycardia, hypotension	**Hemothorax:** respiratory failure **RPH:** femoral neuropathy **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	**Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse **Intra-articular:** joint pain, swelling, decreased range of motion	**Intramuscular:** compartment syndrome, paralysis, limb loss **Intra-articular:** irreversible joint damage

LOC = loss of consciousness; RPH = retroperitoneal hematoma.

associated with a significantly increased mortality risk (12,13). Patients with cardiovascular disease, defined as a history of angina, myocardial infarction, heart failure, or peripheral artery disease, have an increased risk of mortality associated with a hemoglobin drop during their hospitalization (13,14). Patients who present with an acute bleed and no prior records will often have no reference hemoglobin value, and it should be kept in mind that a preresuscitation hemoglobin may be artificially high due to hemoconcentration.

If a patient does not meet criteria for a major bleed (i.e., bleeding is not occurring at a critical site [see **Table 1**], the patient is hemodynamically stable and there is no clinically overt bleeding that has led to a hemoglobin decrease ≥2 g/dL or required ≥2 U of packed RBCs), we have classified this as a nonmajor bleeding event for this decision pathway.

5.3. Laboratory Measurement

In the anticoagulated patient who presents with clinically relevant bleeding or needs an urgent unplanned procedure, measurement of anticoagulant activity is a key step in the evaluation. A prothrombin time (PT) and/or an activated partial thromboplastin time (aPTT) should be requested in all such patients. Interpretation of the PT and aPTT as well as the potential need to request specialized coagulation tests will depend on the clinical situation, the anticoagulant, and test availability.

Unless a concomitant defect in coagulation (e.g., disseminated intravascular coagulation) is suspected, patients taking VKA may be evaluated with the PT/International Normalized Ratio (INR). The INR may be used to guide perioperative or bleeding management.

Laboratory measurement of the anticoagulant activity of the DOACs is more complex. The best assays are specialized and are not widely available. More accessible tests such as the PT and aPTT have important limitations. Suggestions for laboratory measurement of the DOACs based on specialized assay availability are summarized in **Tables 2 and 3** (15,16).

The best tests for assessing the anticoagulant activity of dabigatran include the dilute thrombin time, ecarin clotting time, and ecarin chromogenic assay (see **Table 2**) (18,19). These tests correlate closely with dabigatran levels measured by the reference standard method, liquid chromatography-tandem mass spectrometry. Unfortunately, these assays are not widely available, particularly on an emergent basis (18,19). In their absence, the thrombin time (TT) and aPTT may be used for qualitative assessment (see **Table 3**). The TT is exquisitely sensitive to dabigatran, even at very low drug concentrations. Thus, a normal TT excludes clinically relevant dabigatran levels, but a prolonged TT does not discriminate between clinically important and insignificant drug concentrations. All laboratories that do not offer an around-the-clock assay for dabigatran quantification should be encouraged to offer the TT for rapid exclusion of clinically significant dabigatran levels. A prolonged aPTT suggests the presence of on-therapy or above on-therapy levels of dabigatran. However, a normal aPTT does not exclude the presence of on-therapy levels, especially when a relatively insensitive aPTT reagent is used (16,18,19).

The preferred test for assessing the anticoagulant activity of apixaban, edoxaban, and rivaroxaban is a chromogenic anti-Xa assay (see **Table 2**) (18,19). When the assay is calibrated with the drug of interest, the results

TABLE 2 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are Available

	Clinical Objective		
	Exclude Clinically Relevant* Drug Levels		Measure On-Therapy or Above On-Therapy Drug Levels
Drug	**Suggested Test**	**Interpretation**	**Suggested test**
Dabigatran	Dilute TT ECT ECA	Normal result probably excludes clinically relevant* levels	Dilute TT ECT ECA
Apixaban, edoxaban, or rivaroxaban	Anti-Xa	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant* levels	Anti-Xa†

*The term "clinically relevant" refers to DOAC levels that may contribute to bleeding or surgical bleeding risk. The minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown. The International Society on Thrombosis and Hemostasis recommends consideration of anticoagulant reversal for patients with serious bleeding and a DOAC level >50 ng/mL, and for patients requiring an invasive procedure with high bleeding risk and a DOAC level >30 ng/mL (17). †Useful for quantification of plasma drug levels only when calibrated with the drug of interest.

Anti-Xa = anti-factor Xa; aPTT = activated partial thromboplastin time; DOAC = direct-acting oral anticoagulant; ECA = ecarin chromogenic assay; ECT = ecarin clotting time; PT = prothrombin time; TT = thrombin time.

correlate closely with plasma drug levels measured by liquid chromatography-tandem mass spectrometry. When the assay is calibrated with a low-molecular-weight heparin standard, it can be useful for excluding clinically important levels of drug, but not for quantitation. If an anti-Xa assay is not available, the PT may be useful for qualitative assessment of edoxaban and rivaroxaban. A prolonged PT suggests on-therapy or above on-therapy levels for these agents. However, depending on the sensitivity of the PT reagent, a normal PT may not exclude on-therapy levels (18,19).

The PT and aPTT are insensitive to apixaban. A prolonged PT suggests the presence of clinically important apixaban levels, but a normal PT and aPTT do not exclude on-therapy or even above on-therapy levels of the drug (18–20).

5.4. Managing Major Bleeds

Anticoagulants and antiplatelet agents should be held and airway and large-bore intravenous access secured. Reversal of OAC is recommended if an agent is available for most patients with major bleeding (see section on OAC Reversals), but obtaining and administering the reversal agent must not delay resuscitation and local hemostatic measures. For patients with ongoing bleeding and/or hemodynamic instability, local measures to control bleeding (e.g., pressure, packing) should be combined with volume resuscitation. We recommend aggressive volume resuscitation using intravenous isotonic crystalloids such as 0.9% NaCl or Ringer's lactate (21,22). The goal should be restoration of hemodynamic stability. There does not appear to be a benefit of colloids over crystalloids (23). Hypothermia and acidosis should be corrected, as they

TABLE 3 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are not Available

	Clinical Objective			
	Exclude Clinically Relevant* Drug Levels		Determine Whether On-Therapy or Above On-Therapy Levels Are Present	
Drug	**Suggested Test**	**Interpretation**	**Suggested Test**	**Interpretation**
Dabigatran	TT, aPTT	**Normal TT** excludes clinically relevant* levels **Prolonged TT** does not discriminate between clinically important and insignificant levels **Normal aPTT** usually excludes clinically relevant* levels, if a sensitive reagent is used.	aPTT	**Prolonged aPTT** suggests that on-therapy or above on-therapy levels are present **Normal aPTT** may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used
Apixaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels	PT	**Prolonged PT** suggests that on-therapy or above on-therapy levels are present **Normal PT** may not exclude on-therapy *or above on-therapy levels*, particularly if a relatively insensitive PT reagent is used
Edoxaban or rivaroxaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels	PT	**Prolonged PT** suggests that on-therapy or above on-therapy levels are present **Normal PT** may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used

*The term "clinically relevant" refers to DOAC levels that may contribute to bleeding or surgical bleeding risk. The minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown. The International Society on Thrombosis and Hemostasis recommends consideration of anticoagulant reversal for patients with serious bleeding and a DOAC level >50 ng/mL, and for patients requiring an invasive procedure with high bleeding risk and a DOAC level >30 ng/mL (17).

Anti-Xa = anti-factor Xa; aPTT = activated partial thromboplastin time; DOAC = direct-acting oral anticoagulant; PT = prothrombin time; TT = thrombin time.

may worsen the coagulopathy and perpetuate the bleeding. There is no evidence to support the use of one crystalloid solution over another (24); however, caution should be given to the development of hyperchloremia and hyperchloremic acidosis with administration of large volumes of saline. We recommend early involvement of the appropriate service (e.g., surgery, interventional radiology, gastroenterology) for definitive management of bleeding. This is particularly important for bleeding at critical sites (see **Table 1**).

Supportive measures should include blood product transfusion when appropriate. Randomized trial data suggest that a restrictive compared with liberal transfusion strategy improves survival and reduces the risk of recurrent bleeding in patients presenting with severe acute upper GI bleeding (25). Patients with symptomatic anemia or active bleeding should receive RBC transfusions to maintain hemoglobin ≥7 g/dL (26). In patients with underlying coronary artery disease, particularly those with acute coronary syndromes, a more liberal transfusion strategy is advised. Current guidelines recommend a target hemoglobin ≥8 mg/dL (27). Platelets should be transfused to maintain a platelet count $\geq 50 \times 10^9$/L (28,29) and cryoprecipitate to maintain a fibrinogen >100 mg/dL. For patients requiring ≥3 U of packed RBCs within 1 hour, activation of a massive transfusion protocol should be considered (30). The protocols are variable (31), and currently, many centers use goal-directed transfusion with thromboelastography or rotational thromboelastometry. Ionized calcium levels should be monitored, and if abnormal, administration of calcium is indicated. Early administration of tranexamic acid for trauma patients within the first 3 hours of presentation is associated with decreased bleeding and overall mortality, and should be considered (32). The writing committee recommends further resuscitation using a goal-directed strategy guided by the results of laboratory testing.

Careful attention should be given to comorbidities that could worsen bleeding and subsequent outcome. Because of their dependence on renal function for clearance, all of the DOACs have higher blood levels and longer half lives in patients with renal dysfunction. This is most relevant for patients taking dabigatran, which is 80% to 85% renally excreted (33). In patients with severe renal dysfunction, we recommend laboratory evaluation to detect residual anticoagulant activity (see section on Laboratory Measurement) following administration of a reversal agent and consideration of redosing if bleeding persists or recurs. Patients with renal dysfunction are also at risk for uremia-associated platelet dysfunction and may benefit from administration of desmopressin acetate or cryoprecipitate and optimization of renal status with hemodialysis (34-36). (Dabigatran is the only OAC that can be removed by hemodialysis.) Hepatic dysfunction may be associated with coagulopathy and may also affect bleeding by reducing metabolism of the anticoagulant. Direct factor Xa inhibitors are partially metabolized by the liver and have not been studied in patients with severe hepatic dysfunction. PT, INR, and aPTT may not be reliable measures of hemostatic function in patients with liver disease; in this setting, viscoelastic testing such as thromboelastography or rotational thromboelastometry may be of value for assessment of hemostatic function along with hematology consultation (37-40). Consideration might be given to the use of an antifibrinolytic agent, such as tranexamic acid and epsilon aminocaproic acid. In patients with portal hypertension and esophageal varices, plasma should be used cautiously, because large volumes may increase portal pressure and exacerbate bleeding (41). Patients with inherited bleeding disorders and other acquired hemostatic defects (e.g., use of dual antiplatelet therapy) may be at risk for more severe and prolonged bleeding. This writing committee recommends correction of any underlying hemostatic defects. At this time, there is limited evidence to support routine administration of platelets in the setting of antiplatelet agent use (e.g., aspirin, $P2Y_{12}$ inhibitors). Two systematic reviews of small studies concluded that there was no benefit of such therapy for patients with an intracranial hemorrhage (42,43). Additionally, a more recent trial that randomized patients with intracranial hemorrhage and on antiplatelet therapy to platelet transfusion found higher odds of death or dependence among the platelet transfusion group (44). As such, the writing committee does not recommend routine administration of platelets for patients who are bleeding and on antiplatelet agents, although this can be considered in specific cases, particularly after other measures such as reversal of OAC have failed.

5.5. Managing Nonmajor Bleeds

Irrespective of the severity, local measures should be employed where possible to control any bleeding. For patients with a nonmajor bleed, we do not recommend routine reversal of the OAC, although it is often advisable to temporarily discontinue OAC therapy until the patient is clinically stable and hemostasis has been achieved.

Determining whether the OAC should be temporarily held in a patient with a nonmajor bleed depends upon individual patient characteristics, patient and/or family in shared decision making, the nature of the bleed, and the intensity of anticoagulation. This brings to the forefront the following questions:

- Is the anticoagulation supratherapeutic?
- Is the anticoagulation therapeutic (if target therapeutic goals are known and testable)?
- Is there an invasive procedure needed soon?

- Has the patient's underlying bleeding risk (e.g., new medications, acute deterioration in renal or hepatic function) changed?
- Is continued diagnostic evaluation for the site or clinical impact of bleeding warranted?
- Does the patient have baseline severe anemia requiring transfusion ≥1 U of packed RBCs?
- Does the patient have relevant medical comorbidities, frailty, or other active medical issues (e.g., myocardial infarction or demand ischemia) requiring observation and treatment?
- Is there concern for a slow bleed from a critical site requiring repeat imaging (e.g., head trauma concerning for subdural hematoma development with an early negative scan) (45,46).

For any of these situations, it is recommended that the OAC be discontinued (at least temporarily) and consideration be given to whether concomitant antiplatelet agents could be discontinued safely. If the OAC is stopped, yet an indication for ongoing anticoagulation exists, it is expected that patients should be able to restart the OAC when the concern for additional bleeding complications has resolved. If the patient has undergone a procedure, please refer to the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular AF (10).

If it is determined that the patient does not require hospitalization, a procedure, or a transfusion, and hemostasis has been achieved, the writing committee recommends continuing the OAC. If these patients are on concomitant antiplatelet agents, the risk versus benefit of stopping these drugs should be weighed, although it may be reasonable to continue both. The duration of action of irreversible antiplatelet agents (e.g., aspirin, clopidogrel, and prasugrel) is such that a temporary discontinuation may not have a clinical effect for several days, at which time the bleeding event is not likely an issue. The one exception is ticagrelor, a reversible platelet inhibitor which has a half-life of 7 to 9 hours. Patients should be queried about their use of homeopathic or naturopathic medications such as fish oil or St. John's wort, which may increase the risk of bleeding in patients taking OACs.

5.6. OAC Reversal Strategies

In a life-threatening or critical site bleed, or in situations in which bleeding cannot be controlled, reversal of OACs is required. This section provides information on the options available for reversal of VKAs, dabigatran, and Factor Xa inhibitors. **Figure 3** provides guidance for administering reversal agents based on the OAC prescribed to the patient.

Table 4 summarizes the duration for withholding DOACs based on bleed risk. This table was originally authored by the writing committee responsible for the 2017 Periprocedural Management of Anticoagulation in Patients With Nonvalvular AF: Expert Consensus Decision Pathway (10).

Table 5 summarizes reversal agent indications for each of these OACs.

Vitamin K Antagonists (Warfarin)

Several options exist for reversal of VKAs, including administration of Vitamin K, PCCs, and plasma.

Vitamin K is a specific reversal agent for VKA because it restores intrinsic hepatic carboxylation of vitamin K-dependent clotting factors by overcoming VKA in a dose-dependent manner (1 to 10 mg). It can be given orally, subcutaneously, or intravenously. Slow intravenous administration (in 25 to 50 mL normal saline over 15 to 30 min) effects a more predictable and rapid reduction in the INR (4 to 6 h) compared with oral (18 to 24 h) or subcutaneous (unpredictable and not recommended) administration. Anaphylactic reactions reported in the past with intravenous administration are not encountered with current preparations (57). The administration of vitamin K does not result in immediate correction of coagulopathy, and for the patient with a major bleed as defined herein, administration must be accompanied by a repletion strategy (PCCs or plasma only if 4-factor prothrombin complex concentrate [4F-PCC] is unavailable).

PCCs contain purified vitamin K-dependent clotting factors obtained from pooled human plasma and are free of viral contaminants. Nonactivated 3-factor PCCs contain FII, FIX, and FX with negligible FVII, protein C, and S, whereas nonactivated 4F-PCCs contain FII, FVII, FIX, FX, and protein C and S. The amount of each vitamin K-dependent factor varies and is listed on every vial. Only 4F-PCCs are licensed for rapid VKA reversal. They do not require ABO compatibility and can be stored at room temperature as a lyophilized powder; therefore, they can be rapidly reconstituted and infused. They are dosed based on INR and body weight (INR 2 to 4 at 25 U/kg, INR 4 to 6 at 35 U/kg, and INR >6 at 50 U/kg; max dose 5,000 U capped at 100 kg body weight) for VKA reversal. Per unit volume, 4F-PCCs contain approximately 25× (25 U/mL) the concentration of vitamin K-dependent factors as compared with plasma (1 U/mL). Therefore, PCC can be given in a much smaller volume at a much faster infusion rate (8×) compared with plasma and is preferred (58).

There are concerns about thromboembolic events (TEs) with both nonactivated and activated PCCs. These concerns stem from anecdotal reports of TEs associated with the extended use of 3F/4F-PCCs in patients with hemophilia. Recent randomized clinical trials comparing 4F-PCC with plasma for VKA reversal showed similar TE incidence in both groups (56,59).

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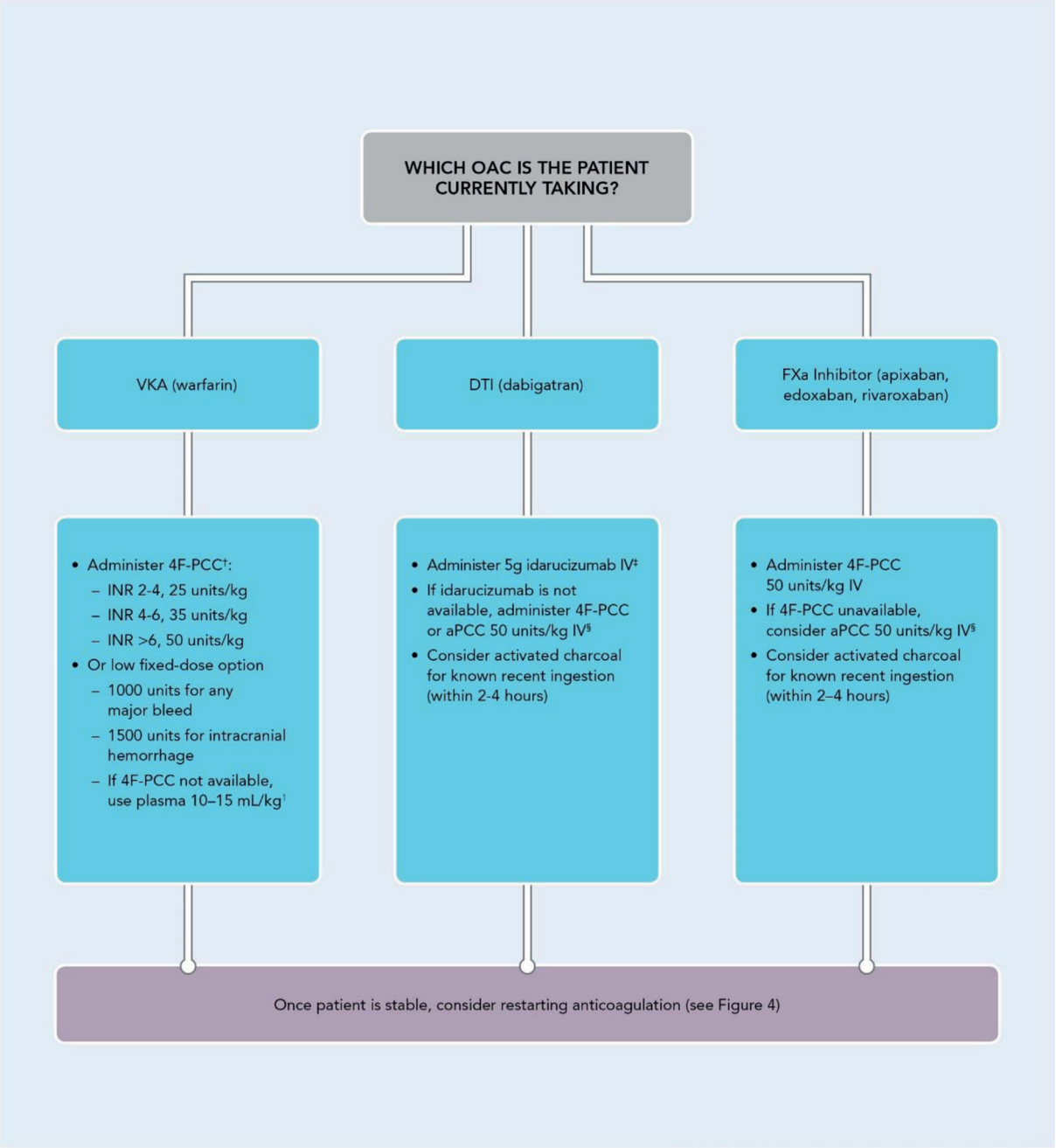
FIGURE 3 Guidance for Administering Reversal Agents*



4F-PCC = four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; DOAC = direct oral anticoagulant; DTI = direct thrombin inhibitor; FXa = Factor Xa; INR = international normalized ratio; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; VitK = vitamin K; VKA = Vitamin K antagonist.

*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

† When PCCs are used to reverse VKAs, VitK should also always be given (see Figure 2 for dosing guidance).

‡ If bleeding persists after reversal and there is laboratory evidence of a persistent dabigatran effect, or if there is concern for a persistent anticoagulant effect before a second invasive procedure, a second dose of idarucizumab may be reasonable.

§ Refer to prescribing information for max units.

1. Sarode R, Milling TJ, Jr., Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013; 128:1234-43.

TABLE 4 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 (47–55).

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

A unit of plasma (225 to 300 mL, fresh frozen, frozen, or thawed plasma) is usually obtained from a whole blood donation. Vitamin K-dependent clotting factors are not affected by storage temperature of plasma. A unit of plasma contains not only vitamin K-dependent clotting factors, but also other coagulations factors and proteins, and is hence considered a nonspecific reversal agent. Plasma transfusion requires ABO blood type matching and thawing of frozen plasma. Thus, generally from the time of the order to transfusion, actual administration of the first unit of plasma may take up to 90 minutes. Because 1 unit of any given factor is present in 1 mL of normal pooled plasma, an adequate dose of plasma for VKA reversal would be 15 to 30 mL/kg; however, this plasma dose is not practical (70 kg × 30 mL = 2,100 mL = 8 plasma U) for rapid VKA reversal, and so the plasma dose used in daily practice was used (amounting to 10 to 15 mL/kg [see **Figure 3**]) (58). The adverse effects of plasma transfusion include circulatory volume overload (58), allergic reactions, and risk of transfusion-related acute lung injury, these effects are not observed with PCC, which should hence be preferred, especially in volume-sensitive patients.

TABLE 5 Available Reversal Agents and Suggested Use

Reversal Agent	Vitamin K Antagonists (Warfarin)	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban)
4F-PCC (56)	First line	Second line	First line
aPCC	Not indicated	Second line	Second line
Idarucizumab	Not indicated	First line	Not indicated
Plasma	If 4-PCC is unavailable	Not indicated	Not indicated

4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate.

Factor IIa Inhibitors (Dabigatran)

Most bleeding complications associated with dabigatran therapy can be managed with conservative measures and withholding the anticoagulant; most nonurgent invasive procedures can be temporarily delayed for normal offset of anticoagulant effect (47). In rare situations, hemorrhage may be so profound, or the need for a procedure in a dabigatran-treated patient so acute, that immediate reversal of anticoagulation is indicated. These vexing clinical situations have been studied in an open-label study of the Fab fragment idarucizumab, which is directed specifically at dabigatran (60). The affinity of idarucizumab for dabigatran is approximately 350× that of dabigatran for thrombin (61).

In the RE-VERSE AD (Reversal of Dabigatran Anticoagulant Effect with Idarucizumab) study, dabigatran-treated patients with anticoagulation emergencies (either ongoing severe or life-threatening hemorrhage, or emergency procedures on therapy) were given 5 grams of idarucizumab as a fixed-dose intravenous infusion of two 2.5-gram aliquots (62). The study's primary endpoint of maximum reversal of the anticoagulant effect of dabigatran within 4 hours was 100% as assessed by dilute thrombin or ecarin clotting time and was achieved in all patients. Among patients with bleeding, cessation was achieved within a median time of 3.5 to 4.5 hours, depending on the location of the bleed (63). In patients undergoing procedures or surgery, the attending surgeon judged hemostasis to be normal in 92% of patients during their procedure. Treatment with idarucizumab was safe with no significant adverse effects and a 6% rate of thrombotic complications, with approximately two-thirds of those events occurring in patients not receiving anticoagulation post-reversal (62). Idarucizumab has not been studied outside of these emergency reversal scenarios (64).

Idarucizumab is widely, but not universally, available in the United States. If idarucizumab is unavailable, then either PCC or activated prothrombin complex concentrate (aPCC) at 50 U/kg (max dose 4,000 U) may be used; these measurements are based on some limited animal, *ex vivo,* and human studies showing variable efficacy of either agent in improving hemostatic parameters in vitro (65-71). Since dabigatran is mostly not bound to proteins in the serum (>85%), hemodialysis has been suggested if the drug level is very high, especially in patients with impaired renal function (72,73). Activated charcoal (50 g) may also be used if the drug was ingested within last 2 to 4 hours (61).

Factor Xa Inhibitors (Apixaban, Edoxaban, and Rivaroxaban)

There are currently no specific antidotes clinically available for reversal of direct factor Xa (FXa) inhibitor anticoagulant effect. Coagulation factor supplementation with PCC or aPCC has been suggested as a potential nonspecific reversal strategy for the direct FXa inhibitors, primarily based on data from in vitro studies, animal models, ex vivo human samples spiked with FXa inhibitors, and healthy volunteer subjects receiving FXa inhibitors; all of these studies have important limitations. None of these agents has demonstrated efficacy or safety in FXa inhibitor-treated patients with bleeding or a requirement for urgent surgery (74,75). 4F-PCC is the most extensively studied nonspecific reversal strategy for factor Xa inhibitors and is the only agent studied in vivo in humans. Three randomized studies evaluated the effect of 4F-PCC or comparator (placebo or 3-factor PCC) in human volunteer subjects administered an oral direct FXa inhibitor (65,76,77). All 3 trials evaluated the effect of 4F-PCC on coagulation laboratory parameters (coagulation tests and thrombin generation), and 1 study evaluated bleeding following punch biopsy. The results demonstrated correction of anticoagulant-induced laboratory abnormalities, but results were not consistent across all parameters and all studies. Bleeding duration following punch biopsy was fully corrected with the highest dose of 4F-PCC evaluated (50 U/kg), and was partially corrected with a lower dose of 4F-PCC (25 U/kg). Based on these limited data, 4F-PCC (50 U/kg maximum dose as per product monograph) is a reasonable option for emergency reversal such as severe or life-threatening bleeding in patients anticoagulated with oral direct FXa inhibitors.

aPCC has variable effects on FXa inhibitor-induced abnormalities in coagulation tests, thrombin generation in vitro, and bleeding in an animal model. When added ex vivo to samples from healthy volunteers who received 1 dose of rivaroxaban, aPCC corrected abnormal thrombin generation indices (66). To control bleeding in hemophilia patients with inhibitors, aPCC is typically administered intravenously in doses ranging from 50 U/kg to 100 U/kg, with a daily maximum of 200 U/kg (78). There are no randomized data regarding dosing in patients with FXa inhibitor-related major bleeding. Based on preclinical evidence, case reports, and case series data, an initial intravenous dose of 50 U/kg is suggested for patients with FXa inhibitor major bleeding and who are known or likely to have clinically significant anticoagulant levels (79).

OAC Reversal Agents in Development

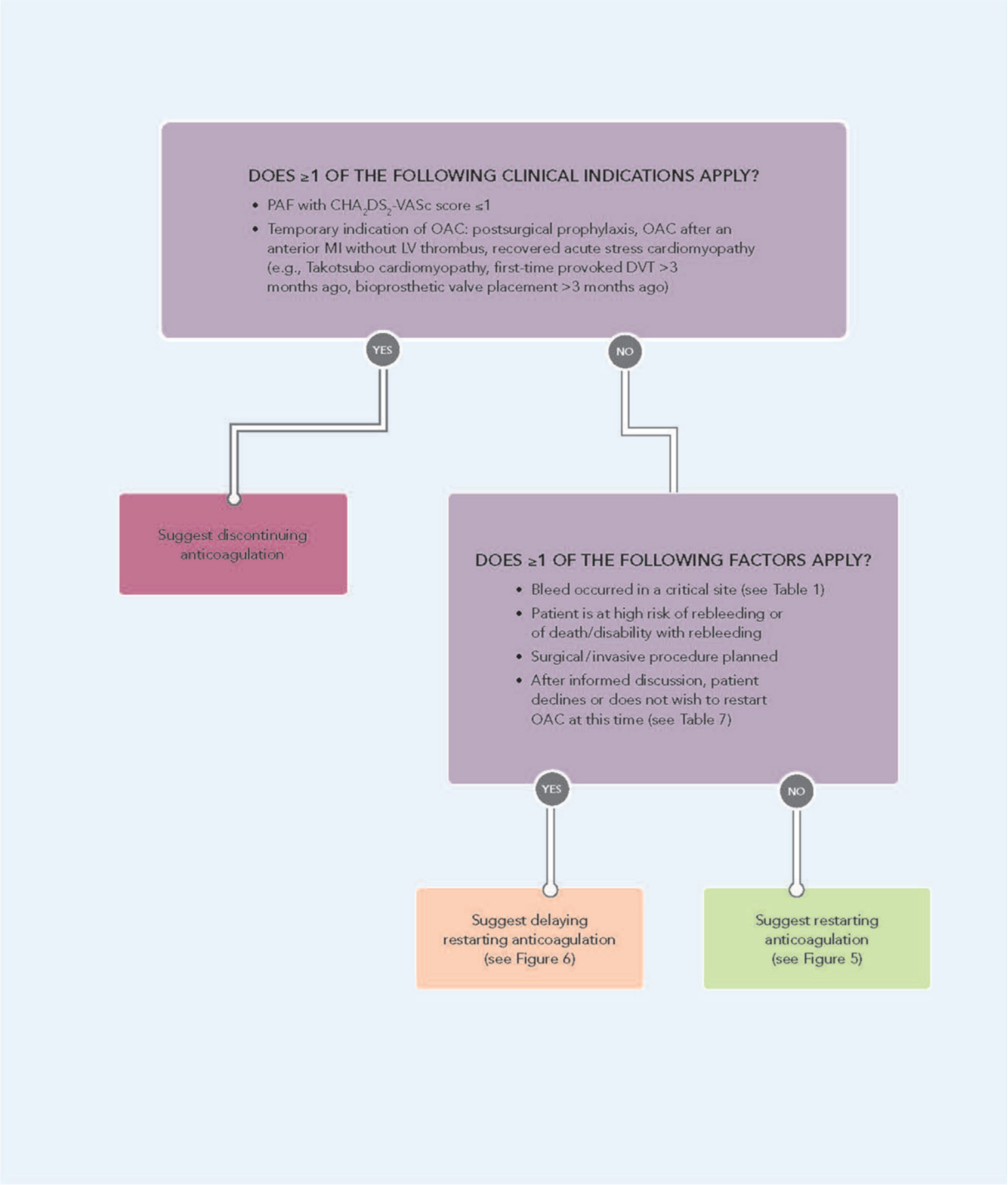
Andexanet alfa (andexanet) is a specific reversal agent for FXa inhibitors currently under clinical development. It is a recombinant protein with a similar structure to endogenous FXa that binds FXa inhibitors but is not enzymatically active (80). A bolus and 2-hour infusion of andexanet alfa rapidly reversed the anticoagulant effects of apixaban and rivaroxaban in older healthy volunteers (81). Andexanet is being evaluated in FXa inhibitor-treated patients with major bleeding who had taken an Fxa inhibitor within 18 hours in the ANNEXA-4 (Andexanet Alfa in Patients Receiving a FXa Inhibitor Who Have Acute Major Bleeding) trial. In a preliminary analysis of the trial (n=67), andexanet reduced anti-FXa activity and active drug levels by over 90%, and clinical hemostasis was adjudicated to be good/excellent in 79% of patients (82). Due to the short half-life of andexanet alfa, some anticoagulant effects of the direct FXa inhibitor return within 1 to 3 hours of stopping the infusion, raising concerns regarding the optimal duration of infusion and/or need for repeat administration (81,82). In healthy volunteers, andexanet increased biomarkers of thrombin generation with no clinical thrombosis. Although further data regarding thrombotic risk with andexanet in patients with major bleeding is being collected, interim results show 18% of patients experienced thrombotic events within 30 days of andexanet infusion, the majority of whom (92%) had not restarted anticoagulant therapy. It is unclear whether this rate of thrombosis is higher than would be expected in bleeding patients who are at increased baseline thrombotic risk in whom anticoagulation was discontinued. Andexanet does bind to the natural anticoagulant tissue factor pathway inhibitor, which could produce a procoagulant effect (80).

Ciraparantag (PER977) is a small, synthetic, water-soluble molecule that binds to direct and indirect inhibitors of FXa and thrombin via a noncovalent charge-charge interaction. Once ciraparantag is bound, it prevents the anticoagulant from binding to its endogenous target. Ciraparantag is still in the early stages of development, with 1 study demonstrating rapid and maintained (24 hours) reversal of whole-blood clotting times in volunteer subjects receiving edoxaban (83,84).

5.7. Considerations for Restarting Anticoagulation

Figure 4 includes guidance for considering when and whether a patient should resume anticoagulation therapy.

FIGURE 4 Considerations for Restarting Anticoagulation



AF = atrial fibrillation; CHA2DS2-VASc = clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; LV = left ventricular; MI = myocardial infarction; OAC = oral anticoagulant, including VKAs and DOACs; PAF = paroxysmal atrial fibrillation; VKA = vitamin K antagonist

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Should Anticoagulation be restarted?

In most cases, there is net clinical benefit to restarting OAC after a bleeding event (85). After a patient has a bleeding event on OAC, the indication for OAC should be reassessed to determine whether continued therapy is warranted based on established clinical practice guidelines. The following are possible conditions for which OAC may no longer be indicated:

- Paroxysmal atrial fibrillation with CHA_2DS_2-VASc score ≤1
- Temporary indication for OAC (e.g., postsurgical prophylaxis, OAC after an anterior myocardial infarction without left ventricular thrombus, recovered acute stress cardiomyopathy [e.g., Takotsubo cardiomyopathy], first time provoked venous thromboembolism >3 months ago, or bioprosthetic valve placement >3 months ago) (86)

If there is an ongoing indication for OAC, the clinician must evaluate the net clinical benefit of OAC in the context of a recent bleed to decide whether the risk of bleeding temporarily or permanently outweighs the benefit of treatment or thromboprophylaxis with OAC. This risk-benefit assessment should be conducted in consultation with other practitioners (e.g., surgeons, interventionalists, and neurologists) and in discussion with patients or caregivers.

There are many factors that contribute to the risk-benefit assessment of restarting anticoagulation. Reversible factors that may have contributed to the bleed, such as a high INR in a patient on a VKA, concomitant antiplatelet therapy, acute or worsening renal insufficiency leading to elevated OAC levels, or significant drug interactions that could increase DOAC levels, can be addressed prior to restarting therapy. Determining the appropriateness of the drug and dose for individual patients based on indication, age, weight, and renal function is important to minimize the potential for adverse events. If the patient is on antiplatelet therapy, re-evaluating whether dual antiplatelet therapy is needed or whether aspirin can be discontinued is reasonable (47). Bleed characteristics that contribute substantially to the risk of restarting anticoagulation include, but are not limited to: 1) the location of the bleed (i.e., critical or noncritical site); 2) the source of bleeding and whether it was definitively identified and treated; 3) the mechanism of the bleed (i.e., traumatic or spontaneous); and 4) whether further surgical or procedural interventions are planned. Finally, the indication for anticoagulation must be considered, as patients who are at high thrombotic risk will likely benefit from restarting anticoagulation, even if the risk of rebleeding is high. **Table 6** provides indications for anticoagulation with high thrombotic risk.

TABLE 6 Indications for Anticoagulation With High Thrombotic Risk

Indication	Patient Characteristics
Mechanical valve prosthesis	■ Mechanical valve + additional thrombotic considerations: AF, CHF, prior stroke/TIA ■ Caged-ball or tilting disc aortic valve prosthesis ■ Stroke/TIA within 6 months
AF	■ AF with $CHADS_2$ score ≥4 (or CHA_2DS_2-VASc score ≥6) (84) ■ Stroke/TIA within 3 months ■ Stroke risk ≥10% per year ■ Rheumatic valve disease or mitral stenosis
VTE	■ VTE within 3 months ■ History of unprovoked or recurrent VTE ■ Active cancer and history of cancer-associated VTE
Prior thromboembolism with interruption of anticoagulation	
Left ventricular or left atrial thrombus	
Left ventricular assist device (LVAD)	

AF = atrial fibrillation; CHF = congestive heart failure; TIA = transient ischemic attack; VTE = venous thromboembolism.

Timing of Anticoagulation Reinitiation

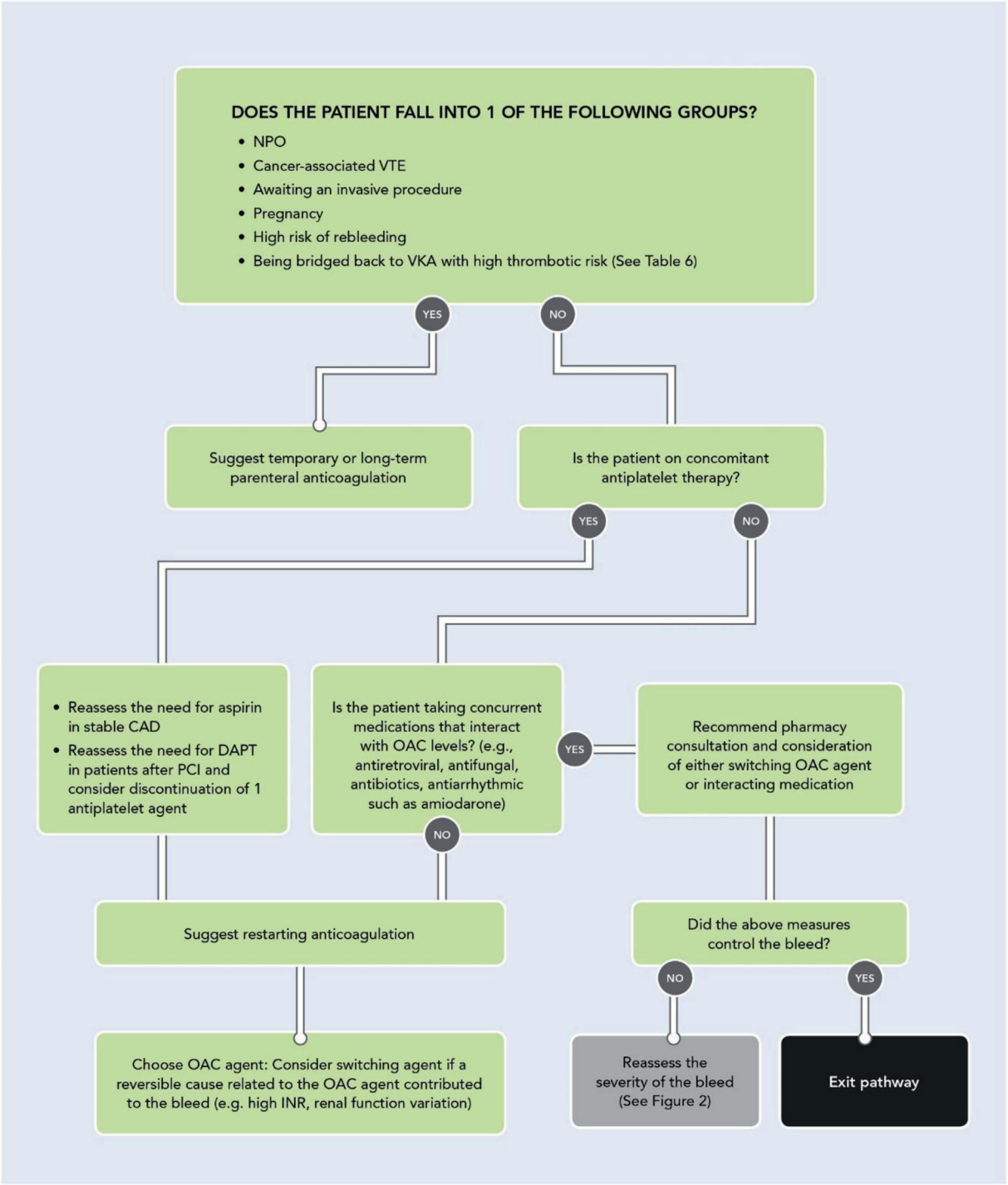
Figure 5 provides clinical guidance for situations in which it is recommended that the patient restart anticoagulation.

Figure 6 provides clinical guidance for situations where it is recommended that the patient delay restart of anticoagulation.

Determining the optimal timing for reinitiation of OAC has the dual therapeutic aim of preventing thrombotic events while minimizing rebleeding. In general, conditions with high thrombotic risk (see **Table 6**) favor early reinitiation of anticoagulation once hemostasis is achieved and the patient is clinically stable. OAC may be reinitiated with close monitoring in patients with high thrombotic risk; for patients with moderate or high rebleeding risk, individualized strategies are appropriate. For example, parenteral anticoagulants can often be started with close monitoring within 1 to 3 days in most patients. For patients at high rebleeding risk for whom the thrombotic risk is unacceptably high and therapeutic anticoagulation is deemed necessary, it is suggested that unfractionated heparin be administered by intravenous infusion, due to its short half-life and an available reversal agent (protamine sulfate) that can rapidly stop and/or reverse anticoagulation in the event of rebleeding.

Prophylactic doses of parenteral anticoagulants (e.g., subcutaneous unfractionated or low-molecular-weight heparin) may reduce the risk of further bleeding compared with therapeutic doses. However, temporary

FIGURE 5 **Restarting Anticoagulation**



CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; INR = international normalized ratio; NPO = nil per os "nothing by mouth"; OAC = any oral anticoagulant, including VKAs and DOACs; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist; VTE = venous thromboembolism.

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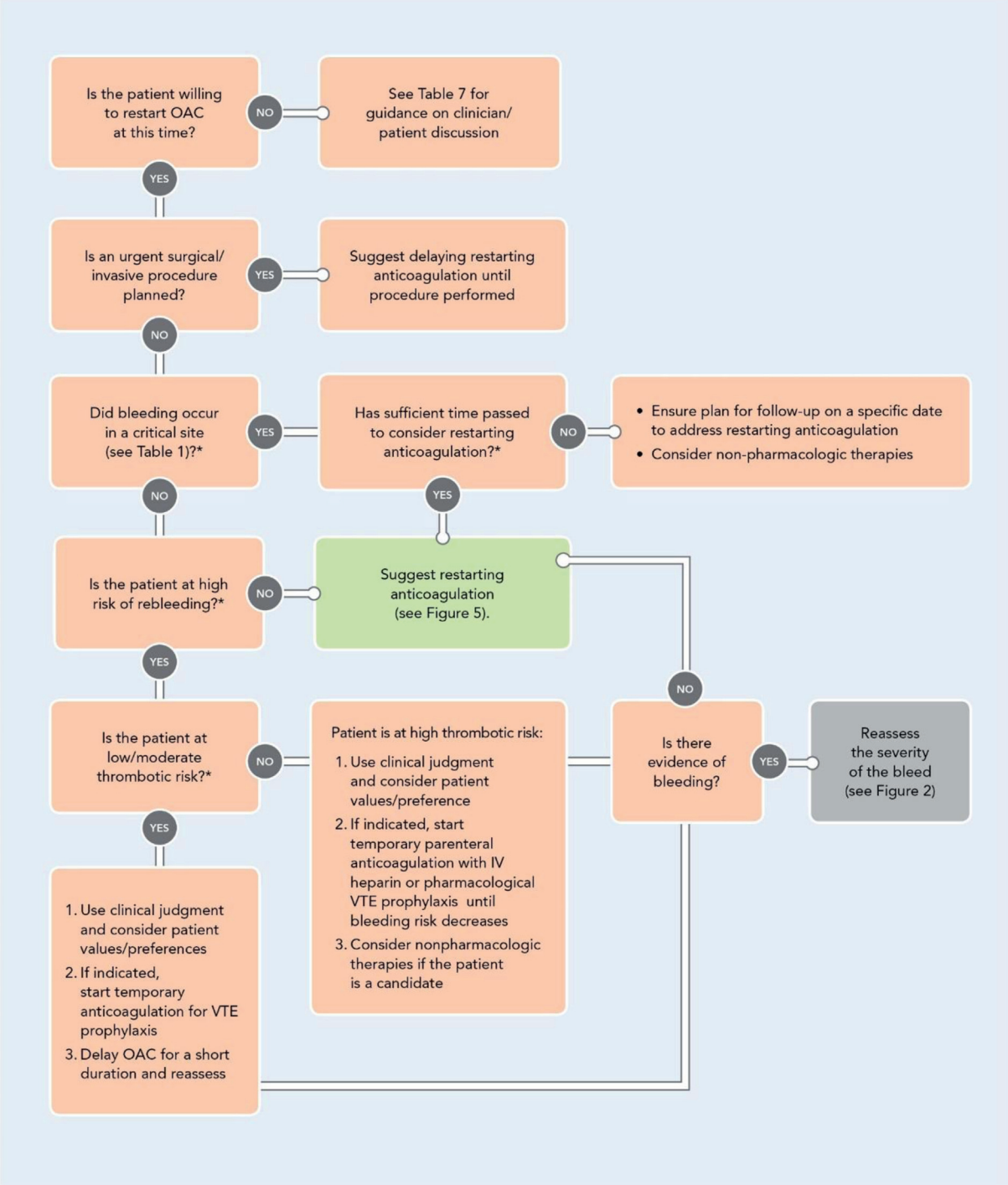
FIGURE 6 Factors to Consider in Delaying Restart of Anticoagulation



IV = intravenous; DOAC = direct oral anticoagulant; OAC = oral anticoagulant, including VKAs and DOACs; VKA = vitamin K antagonist; VTE = venous thromboembolism

*Discuss risk of rebleeding and thrombosis with specialists involved in patient's care (e.g., neurologist, neurosurgeon, gastroenterologist). See text or general guidance on when to restart anticoagulation in common situations.

use of prophylactic doses with close clinical monitoring and titration to therapeutic doses is a reasonable strategy to balance bleeding and thrombotic risk in this setting.

In patients with both a high thrombotic risk and high bleeding risk resulting in a relative or absolute contraindication to restarting anticoagulation, non-pharmacological therapies may be considered. Devices such as a left atrial appendage occlusion device to mitigate thrombotic risk in AF or a temporary retrievable inferior vena cava filter for acute DVT may be considered in consultation with the appropriate specialists. For left atrial appendage closure, there are several minimally invasive options that carry different procedural and bleeding risks. For instance, an endocardial device requires therapeutic anticoagulation for at least 45 days following insertion. An epicardial device, however, does not require anticoagulation. Consultation with a specialist familiar with the options for left atrial appendage closure is advised. Judicious use of inferior vena cava filters is crucial, because randomized trials have demonstrated that their use may be complicated by adverse procedural events and an increased risk of DVT with no benefit demonstrated with regard to pulmonary embolism or mortality (87,88). One trial showed a numerically (but not statistically significant) increase in pulmonary embolism. Inferior vena cava filters are considered temporary adjuncts indicated only for patients with recent proximal DVT and an absolute contraindication to therapeutic anticoagulation. If used, inferior vena cava filters should be removed as soon as therapeutic anticoagulation is achieved, preferably prior to hospital discharge (89).

In general, temporary interruption of OAC for a short duration is likely appropriate for most patients *without* high thrombotic risk as rebleeding may lead to further prolonged anticoagulant interruption and exposure to thrombotic risk. Changing the anticoagulant used may also be considered when restarting anticoagulation after a bleeding event. In cases where identifiable risk factors (e.g., impaired renal function) were associated with a bleeding event, it may be appropriate to consider alternative anticoagulants. For instance, a patient on warfarin with a history of labile INR values who had a hemorrhagic complication with an elevated INR may benefit from a DOAC, or a patient with a decrement in renal function who had a bleeding complication on a DOAC may benefit from a change to warfarin. However, it is beyond the scope of this document to recommend specific agents for individual patients. The particular situations of GI bleeding, intracranial hemorrhage, and postprocedural anticoagulation are outlined in the following text.

Patient Engagement in Restarting Anticoagulation

Optimal patient engagement in the decision to restart anticoagulation involves shared decision making with patients and care providers. Discussions should outline the risks of bleeding that come with resuming anticoagulation, including clinical signs of bleeding (e.g., monitoring for melena after GI bleeding), implications for thrombotic events, and death without anticoagulation. For example, the 30-day mortality may be as high as ~25% after an ischemic stroke from AF without OAC (90,91), and it is important for patients to understand such a risk. Discussions should be initiated early to allow patients to ask questions or raise concerns, and should involve their primary care providers when possible. Important topics to discuss with patients prior to restarting anticoagulation are listed in **Table 7**.

TABLE 7 Components of the Clinician-Patient Discussion

Factors to Consider	Discussion Points
Timing	Discussion of reinitiation of anticoagulation should be done in advance of restarting to give the patient time to formulate questions
Associated risks	Clinical and site-specific signs of bleeding for which the patient should remain vigilant (e.g., melena after a GI bleed) Recurrent bleeding thrombotic event (personalized risk assessment if possible, e.g., CHA_2DS_2-VASc prediction of thromboembolism risk) Discussion of the sequelae of a thromboembolic event (e.g., higher mortality for ischemic strokes with AF)
Associated benefits	Improved mortality with no increase in bleeding after certain types of bleeds on anticoagulant (e.g., GI bleeding)

AF = atrial fibrillation; GI = gastrointestinal.

Concurrent Medications

A comprehensive medication review should identify medications that can increase anticoagulant drug levels and potentially increase the risk for a bleeding event. Drugs that inhibit the activity of P-glycoprotein and/or cytochrome P450 3A4, such as antiarrhythmics (e.g., amiodarone, diltiazem, verapamil), antiretrovirals, antifungals and immunosuppressives, can increase OAC levels (47). Other medications that affect hemostasis such as antiplatelet therapy (aspirin, clopidogrel, prasugrel, ticagrelor, cangrelor) or nonsteroidal anti-inflammatory drugs administered in combination with OAC will increase the risk of rebleeding. In particular, the use of an anticoagulant in the presence of single- or dual-antiplatelet therapy is a significant risk factor for bleeding and a rapidly evolving area in terms of clinical trials to guide the management of such patients. The necessity and duration for single- or dual-antiplatelet therapy should therefore be reviewed to determine appropriate treatment for the patient (92–94). For patients receiving VKA therapy, a review of nutritional recommendations may help prevent lability in INR values and improve the time in therapeutic range.

Gastrointestinal Bleeding (GI Bleeding)

GI bleeding is a relatively common hemorrhagic complication of chronic OAC therapy. Anticoagulant therapy is permanently discontinued in a substantial proportion of patients despite evidence of benefit with reinitiating the OAC. In a systematic review of observational studies, patients with OAC-associated GI bleeding who resumed anticoagulation had a lower risk of thromboembolism (9.9% vs. 16.4%; hazard ratio [HR]: 0.68; 95% CI: 0.52 to 0.88) and death (24.6% vs. 39.2%; HR: 0.76; 95% CI: 0.66 to 0.88) compared with those who did not restart, with a nonsignificant increase in the risk of recurrent bleeding (10.1% vs. 5.5%; HR: 1.20; 95% CI: 0.97 to 1.48) (95). A recent retrospective study showed a reduced risk of thromboembolism (HR: 0.19; 95% CI: 0.07 to 0.55) and death (HR: 0.61; 95% CI: 0.39 to 0.94) and increased risk of recurrent GI bleeding (HR: 2.5; 95% CI: 1.4 to 4.5) in patients who restarted VKA compared with those who did not restart (96). The timing of anticoagulation reinitiation has not been systematically studied and is highly variable, although a prospective study in which anticoagulation was restarted at the time of discharge in patients with a median length of stay of 5 days (including patients in whom no source of bleeding was found) demonstrated fewer TEs at 90 days with no increase in bleeding events; in AF patients, restarting warfarin >7 days after a bleed was associated with improved survival and decreased thromboembolism without an increased risk of recurrent GI bleeding (97,98). Therefore, in most cases of GI bleeding, the writing committee favors reinitiation of anticoagulation in patients with an indication for OAC once bleeding has been controlled (including patients in whom no discrete source of bleeding was identified).

Intracranial Hemorrhage

Intracranial hemorrhage is the most feared complication of anticoagulant therapy. Although rare, intracranial hemorrhage while on OAC can be catastrophic, with 30-day mortality rates approaching 50% (99). Approximately 20% of spontaneous intracranial hemorrhage is related to anticoagulation therapy. Therefore, a cautious, individualized approach to restarting OAC after intracranial hemorrhage is warranted. Factors associated with a higher risk of recurrence include the mechanism of intracranial hemorrhage (i.e., spontaneous vs. traumatic), lobar location of the initial bleed (suggesting amyloid angiopathy), the presence and number of microbleeds on magnetic resonance imaging, and ongoing anticoagulation (100).

Limited data exist on the reinitiation of OAC after an intracranial hemorrhage. Depending on bleed characteristics, risk factor modification, and the indication for anticoagulation, restarting OAC after a nonlobar intracranial hemorrhage may be considered (100). In observational studies of patients with warfarin-associated intracranial hemorrhage, resumption of anticoagulation appears to confer a 50% to 70% lower risk of thrombosis and 50% to 70% lower risk of death without a significant increased risk of recurrent bleeding compared with discontinuation (101-108). Optimization of modifiable cardiovascular risk factors (such as hypertension) is important prior to OAC reinitiation. Lobar intracranial hemorrhage secondary to amyloid angiopathy (either spontaneous or related to warfarin use) and spontaneous subdural hematomas are associated with a particularly high risk of rebleeding. Restarting anticoagulation in these settings should be approached with significant caution in consultation with either neurology or neurosurgical expertise. DOACs are associated with a lower risk of intracranial hemorrhage than warfarin, but the safety of switching a patient with an intracranial hemorrhage to a DOAC has not been evaluated (100,109).

The timing of anticoagulation reinitiation following an intracranial hemorrhage has not been systematically studied and varies widely in observational studies (72 h to 30 weeks), reflecting a lack of consensus. However, in patients without mechanical heart valves, guidelines recommend avoiding anticoagulation for at least 4 weeks, and if indicated, aspirin monotherapy may be restarted in the days after an intracranial hemorrhage (100). In a large, retrospective study that demonstrated benefit associated with OAC reinitiation, the median time to restart OAC was approximately 1 month after the bleeding event (101). Therefore, the writing committee favors delaying the resumption of anticoagulation for at least 4 weeks in patients without high thrombotic risk.

Restarting Anticoagulation After a Surgery/Procedure

If anticoagulation was discontinued and/or reversed for an urgent or emergent surgery/procedure without a preceding bleeding event and adequate postprocedural hemostasis was achieved, anticoagulation should likely be restarted expeditiously. For procedures that carry a low postprocedural bleeding risk, anticoagulation can likely be restarted 24 hours after the procedure. If the postprocedural bleeding risk is higher, therapeutic dose anticoagulation should be delayed for 48 to 72 hours (10). Of note, the use of parenteral anticoagulation while restarting VKA therapy (so-called bridging anticoagulation) after temporary discontinuation for procedures/surgeries is associated with an increased risk of bleeding and no decrease in thrombotic events in nonvalvular AF patients (110). Limited data is available regarding the efficacy and safety of bridging anticoagulation in the subset of patients with a high thrombotic risk who will be restarting VKA therapy. In these patients, bridging anticoagulation with parenteral

anticoagulants may be considered once hemostasis is achieved, in consultation with the surgeon or proceduralist. If a DOAC is used postprocedurally, bridging anticoagulation should not be used.

For surgeries/procedures performed to control bleeding, restarting anticoagulation after the procedure may carry a higher bleeding risk. This depends on the characteristics of the bleed and the surgical management. If the source of bleeding was identified and completely corrected with adequate hemostasis, restarting anticoagulation in a similar fashion as discussed in the previous text may be reasonable. Individualized strategies with close clinical monitoring apply for patients in whom bleeding was not successfully controlled by surgical/procedural management.

6. DISCUSSION AND IMPLICATION OF PATHWAY

The primary objective of this decision pathway is to provide a clinically applicable, easily referenced conceptual framework to support clinician decision making while caring for patients with bleeding complications during OAC therapy. The writing committee considered patients taking anticoagulant therapy for any indication to broaden the potential clinical use and impact of the decision pathway. Whenever possible, recommendations are based on quantitative evidence from clinical research. However, large gaps in knowledge exist, and therefore, so much of what clinicians do to care for these patients is based on limited information. It is anticipated that as the population continues to age, more people will be treated with OACs. As more evidence is generated from ongoing research and clinical practice, further refinement to this decision pathway will be needed. For now, the writing committee hopes that this decision pathway helps the multidisciplinary team of clinicians that care for patients treated with OACs who have bleeding.

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KEY WORDS ACC Expert Consensus Decision Pathway, atrial fibrillation, deep vein thrombosis, factor II, factor X, gastrointestinal bleeding, intracranial hemorrhage, vitamin K

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2017 ACC EXPERT CONSENSUS DECISION PATHWAY ON MANAGEMENT OF BLEEDING IN PATIENTS ON ORAL ANTICOAGULANTS

To avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. The ACC Task Force on Clinical Expert Consensus Decision Pathways reviews these disclosures to determine what companies make products (on market or in development) that pertain to the document under development. Based on this information, a writing committee is formed to include a majority of members with no relevant relationships with industry (RWI), led by a chair with no relevant RWI. RWI is reviewed on all conference calls and updated as changes occur. Author RWI pertinent to this document is disclosed in the following table, and peer reviewer information is disclosed in Appendix 2. Additionally, to ensure complete transparency, authors' comprehensive disclosure information—including RWI not pertinent to this document—is available online (See Online Appendix 1). Disclosure information for the ACC Task Force on Clinical Expert Consensus Decision Pathways is also available online, as is the ACC disclosure policy for document development.

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Gordon F. Tomaselli, Chair	Johns Hopkins School of Medicine—Chief of Cardiology	None	None	None	None	None	None
Kenneth W. Mahaffey, Vice Chair	Stanford Center for Clinical Research—Director; Stanford Department of Medicine—Vice-Chair of Clinical Research, Department of Medicine Stanford Center for Clinical Research	■ Ablynx ■ AstraZeneca* ■ Boehringer Ingelheim Pharmaceuticals* ■ GlaxoSmithKline ■ Janssen Pharmaceuticals ■ Portola	None	None	None	■ AstraZeneca ■ Verily (Google)	None
Adam Cuker	University of Pennsylvania—Assistant Professor and Pathology & Laboratory Medicine	None	None	None	None	None	None
Paul P. Dobesh	University of Nebraska Medical Center—AQ Cardiology Professor of Pharmacy Practice, College of Pharmacy	■ AstraZeneca ■ Boehringer Ingelheim ■ Daiichi Sankyo ■ Janssen Pharmaceuticals ■ Pfizer	None	None	None	None	None
John U. Doherty	Jefferson Medical College of Thomas Jefferson University—Professor of Medicine	None	None	None	None	None	None
John W. Eikelboom	McMaster University—Associate Director, Department of Medicine	■ AstraZeneca* ■ Boehringer Ingelheim* ■ Bristol Myers Squibb† ■ Daiichi Sankyo ■ GlaxoSmithKline ■ Pfizer†	None	None	■ Boehringer Ingelheim*	None	None
Roberta Florido	Johns Hopkins School of Medicine—Fellow in Cardiovascular Medicine	None	None	None	None	None	None

(continued on the next page)

APPENDIX 1. CONTINUED

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Roxana Mehran	Mount Sinai Medical Center—Professor of Medicine	■ Janssen Pharmaceuticals	None	None	■ AstraZeneca† ■ Bristol Myers Squibb† ■ CSL Behring*	None	None
Steven R. Messé	University of Pennsylvania—Associate Professor of Neurology	None	None	None	None	None	None
Charles V. Pollack, Jr.	Thomas Jefferson University Hospital—Professor of Emergency Medicine and Associate Provost	■ AstraZeneca† ■ Boehringer Ingelheim* ■ Daiichi Sankyo ■ Janssen Pharmaceuticals* ■ Pfizer†	None	None	■ AstraZeneca* ■ Boehringer Ingelheim* ■ Daiichi Sankyo* ■ Janssen Pharmaceuticals* ■ Portola* ■ CSL Behring*	None	None
Fatima Rodriguez	Stanford University Medical Center-Fellow in Cardiovascular Medicine	None	None	None	None	None	None
Ravindra Sarode	University of Texas Southwestern—Professor of Pathology, Chief of Pathology and Medical Director of Clinical Laboratory Services, UT Southwestern Medical Center, and Director, Transfusion Medicine and Hemostasis	■ CSL Behring ■ Portola	None	None	None	None	None
Deborah Siegal	McMaster University—Clinical Scholar, Division of Hematology and Thromboembolism	■ Bristol-Myers Squibb/Pfizer	None	None	None	■ Portola	None
Barbara S. Wiggins	Medical University of South Carolina—Clinical Pharmacy Specialist, Cardiology Department of Pharmacy Services	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. 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.

According to the ACC, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Significant relationship.

†No financial benefit.

ACC = American College of Cardiology; SCAI = Society for Cardiac Angiography and Interventions.

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APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2017 ACC EXPERT CONSENSUS DECISION PATHWAY ON MANAGEMENT OF BLEEDING IN PATIENTS ON ORAL ANTICOAGULANTS

This table represents the individuals, organizations, and groups that peer reviewed this document. A list of corresponding comprehensive healthcare-related disclosures for each reviewer is available as Online Appendix 2.

Reviewer	Representation	Employment
Timothy A. Dewhurst	Official Reviewer—Board of Governors	Kaiser Permanente, Washington—Seattle Cardiology Operations Chief
Joseph E. Marine	Official Reviewer—ACC Task Force on Clinical Expert Consensus Decision Pathways	Johns Hopkins University School of Medicine—Associate Professor of Medicine
Linda A. Briggs	Organizational Reviewer—AANP	The George Washington University School of Nursing—Assistant Professor
Mark A. Crowther	Organizational Reviewer—Anticoagulation Forum	McMaster University—Chair of Department of Medicine
Eileen Mary Handberg	Organizational Reviewer—ACC and PCNA	University of Florida—Research Professor of Medicine; Director, Clinical Trials Program; Florida CARES & CAP—Program Director
Jeffrey Kline	Organizational Reviewer—SAEM	Indiana University School of Medicine—Vice Chair of Research, Department of Emergency Medicine; Professor, Department of Cellular and Integrative Physiology
Geno J. Merli	Organizational Reviewer—ACP	Thomas Jefferson University Hospital—Professor; Co-Director, Jefferson Vascular Center
Edith A. Nutescu	Organizational Reviewer—ACCP	The University of Illinois at Chicago—Associate Professor; Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research, College of Pharmacy; University of Illinois Hospital and Health Sciences System—Co-Director, Personalized Medicine Program
Andrea M. Russo	Organizational Reviewer—HRS	Cooper Medical School of Rowan University—Professor of Medicine; Director, Cardiac Electrophysiology and Arrhythmia Services; Director; CCEP Fellowship
Kim K. Birtcher	Content Reviewer—Individual	University of Houston College of Pharmacy—Clinical Professor
Michael S. Firstenberg	Content Reviewer—Surgeons' Section Leadership Council	Northeast Ohio Medical Universities—Associate Professor of Surgery and Integrative Medicine; Summa Akron City Hospital—Cardiothoracic Surgeon
Ty J. Gluckman	Content Reviewer—ACC Roundtable Participant	Providence Heart and Vascular Institute—Medical Director
Bulent Gorenek	Content Reviewer—EP Section Leadership Council	Eskisehir Osmangazi University—Professor, Cardiology Department; Vice Director
Christopher B. Granger	Content Reviewer—ACC Roundtable Participant	Duke Clinical Research Institute—Professor of Medicine; Director, Cardiac Care Unit
Kousik Krishnan	Content Reviewer—EP Section Leadership Council	Rush University Medical Center—Associate Professor of Medicine & Pediatrics; Director, Clinical Cardiac Electrophysiology Fellowship Program; Director, Arrhythmia Device Clinic; Associate Director, Electrophysiology Lab
Pamela B. Morris	Content Reviewer—Task Force on Expert Consensus Decision Pathways	Medical University of South Carolina—Director, Seinsheimer Cardiovascular Health Program; Co-Director, Women's Heart Care
Win-Kuang Shen	Content Reviewer—Individual	Mayo Clinic Arizona-Phoenix Campus—Professor of Medicine; Consultant
Sarah A. Spinler	Content Reviewer—ACC Roundtable Participant	University of the Sciences Philadelphia College of Pharmacy—Professor of Clinical Pharmacy
Karol E. Watson	Content Reviewer—Task Force on Expert Consensus Decision Pathways	UCLA Medical School—Co-Director, UCLA Program in Preventive Cardiology

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It 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. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

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AANP = American Association of Nurse Practitioners; ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; ACP = American College of Physicians; CCEP = Clinical Cardiac Electrophysiology; EP = Electrophysiology; HRS = Heart Rhythm Society; NIH = National Institutes of Health; PCNA = Preventative Cardiovascular Nurses Association; SAEM = Society for Academic Emergency Medicine; UCLA = University of Southern California at Los Angeles.

APPENDIX 3. ABBREVIATIONS

AF = atrial fibrillation

aPCC = activated prothrombin complex concentrate

aPTT = activated partial thromboplastin time

CI = confidence interval

DOAC = direct oral anticoagulant

4F-PCC = 4-factor prothrombin complex concentrate

GI = gastrointestinal

HR = hazard ratio

INR = international normalized ratio

OAC = any oral anticoagulant, including vitamin K antagonists and direct oral anticoagulants

PCC = prothrombin complex concentrates

PT = prothrombin time

RBC = red blood cell

VKA = vitamin K antagonist