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EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Solution Set Oversight Committee

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PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (e.g., decision pathways, health policy statements, appropriate use criteria) to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular (CV) care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence may be new and evolving or where sufficient data may be more limited. In spite of this, numerous care gaps continue to exist, highlighting the need for more streamlined and efficient

processes to implement best practices in service to improved patient care.

Central to the ACC's strategic plan is the generation of "actionable knowledge"—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has evolved from developing isolated documents to the development of integrated "solution sets." Solution sets are groups of closely related activities, policy, mobile applications, decision support, and other tools necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for CV conditions and their related management. The success of solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated tools will be refined over time to best match member needs.

Expert consensus decision pathways (ECDPs) represent a key component of solution sets. The methodology for ECDPs is grounded in assembling a group of clinical experts to develop content that addresses key questions facing our members across a range of high-value clinical topics (1). This content is used to inform the development of various tools that accelerate real time use of clinical policy at the point of care. They are not intended to provide a single correct answer; rather, they encourage clinicians to ask questions and consider important factors as they define a treatment plan for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as standalone policy.

Ty J. Gluckman, MD, FACC
Chair, ACC Solution Set Oversight Committee

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) (2) has continued to rise because of an aging population; rising age-adjusted incidence due to higher burdens of chronic illness; and advances in early detection, prevention, and treatment (3,4). It is estimated that over 6 million patients in the United States are treated with anticoagulants (5) 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-acting oral anticoagulants (DOACs) for the most common indications for anticoagulation. There has been particularly rapid adoption of DOACs in venous thromboembolism (VTE) and AF in the absence of mechanical valves or mitral stenosis. Systematic reviews have demonstrated favorable risk-benefit profiles for DOACs when compared with vitamin K antagonists (VKAs) in the management of AF and when compared with low-molecular-weight heparin followed by a VKA in the treatment and prevention of VTE (6,7). Additionally, the emergence of reversal agents (8) may also further increase the proportionate use of DOACs and influence the management of bleeding that complicates anticoagulant use (9).

This ECDP 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 (10). The former includes bleeding that is associated with hemodynamic compromise, occurs in an anatomically critical site, requires transfusion (≥2 units of packed red blood cells [RBCs]), or results in a hemoglobin drop ≥2 g/dL (10). All other bleeding is categorized as nonmajor. The recommendations provided by this ECDP 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 ECDP 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 Nonvalvular Atrial Fibrillation" (11), which addresses the management of patients undergoing planned surgical or interventional procedures.

Given the emergence of new OACs for use in the prevention of VTE as well as the introduction of new reversal strategies for factor Xa (FXa) inhibitors, it was determined that an update of the original ECDP, published in 2017, was needed to include guidance for use of those therapeutic options in addition to those previously included (12).

Of important note, the boxes within the ECDP algorithms were delegated certain colors to align with specific guidance found throughout each of the figures.

- Pink = considerations for major bleeds
- Yellow = considerations for nonmajor bleeds
- Blue = considerations for administering reversal/hemostatic agents
- Purple = considerations for timing of reinitiation of anticoagulation

- Orange = considerations for delaying the restart of anticoagulation
- Green = considerations for restarting anticoagulation

2. METHODS

This ECDP 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 writing committee. Although the Roundtable provided valuable insight into the practical issues and gaps in care, this ECDP 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. Committee conference calls were confidential and attended only by committee members and ACC staff. Following reconciliation of all comments, this ECDP was approved for publication by the governing bodies of the ACC. The guidance in this ECDP 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 ECDP considered the severity of the bleed (major versus 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 ECDP algorithms, patient-specific factors should be considered.

The ACC and the Solution Set Oversight Committee (SSOC) recognize the importance of avoiding real or perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI Policy in determining what constitutes a relevant relationship, with additional vetting by the SSOC.

ECDP writing groups must be chaired or co-chaired by an individual with no relevant RWI. While vice chairs and writing group members may have relevant RWI, this must constitute less than 50% of the writing group. Relevant disclosures for the writing group, external reviewers, and SSOC members can be found in Appendix 1. To ensure complete transparency, a full list of disclosure information, including relationships not pertinent to this document, is available in an online appendix. Participants are discouraged from acquiring relevant RWI throughout the writing process.

3. ASSUMPTIONS AND DEFINITIONS

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

3.1. General Clinical Assumptions

1. The ECDP 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, VTE treatment and prevention, prosthetic cardiac valves, history of prior thromboembolism, intracardiac thrombus, and the presence of a mechanical circulatory support device (e.g., a left ventricular assist device).
4. The recommendations for restarting and withholding anticoagulant therapy refer to both DOACs and VKAs.
5. The ECDP algorithms assume that the provider will seek input from the appropriate specialists when indicated and involve the patient and/or family in shared decision making when possible.

3.2. Definitions

Definitions of terms used throughout the ECDP are listed here.

ABO: The three basic blood groups.

DOAC: Any direct-acting oral anticoagulant (e.g., apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban).

OAC: Any oral anticoagulant, including DOACs and VKAs.

Reversal/hemostatic agents: Repletion strategies such as prothrombin complex concentrates (PCCs), plasma, vitamin K, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran, andexanet alfa for apixaban or rivaroxaban).

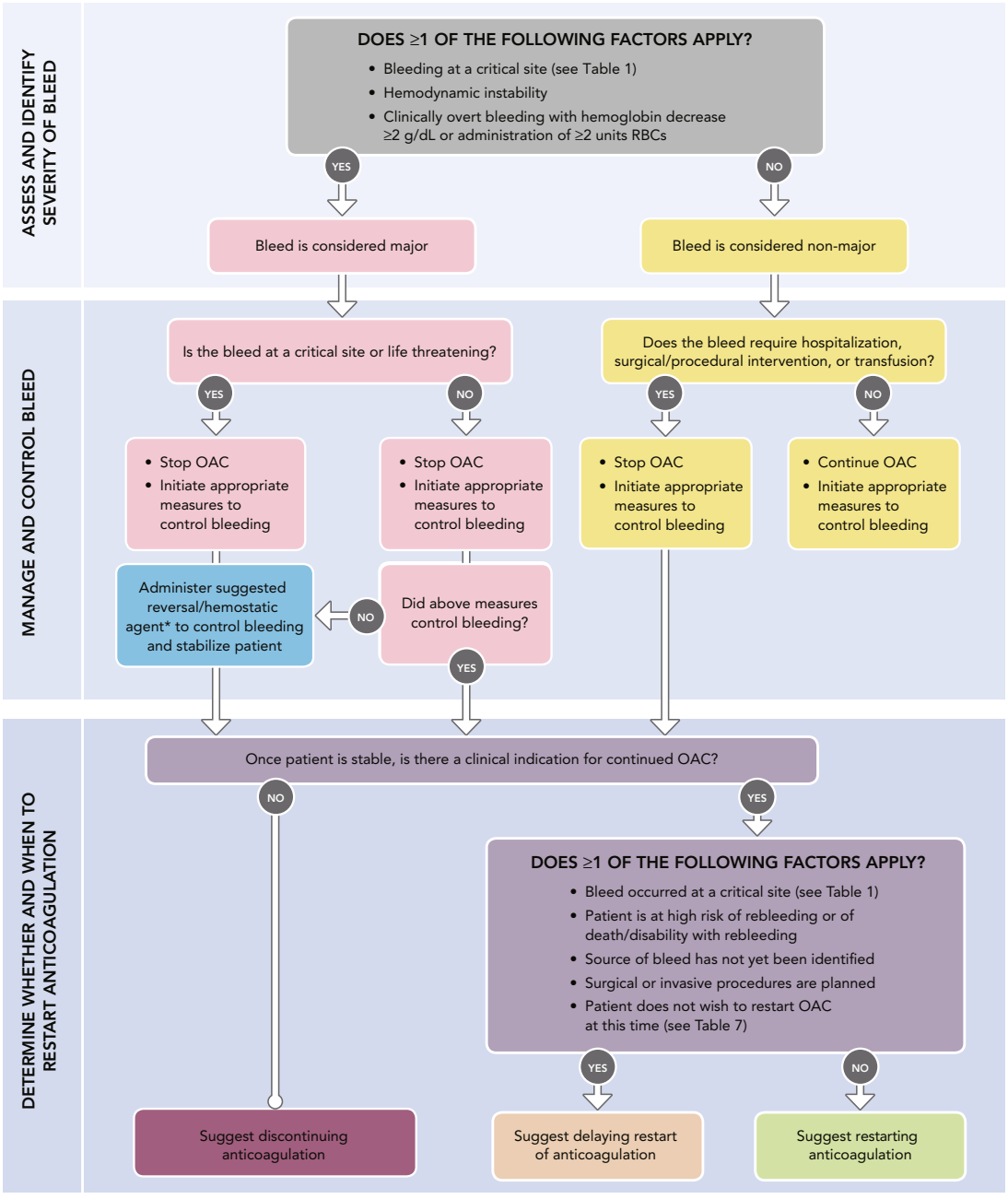
VKAs: Vitamin K antagonists (e.g., warfarin and other coumarins)

Note: The definitions of major and nonmajor bleeds were modified on the basis of the International Society on Thrombosis and Hemostasis definitions and criteria (10).

4. PATHWAY SUMMARY GRAPHIC

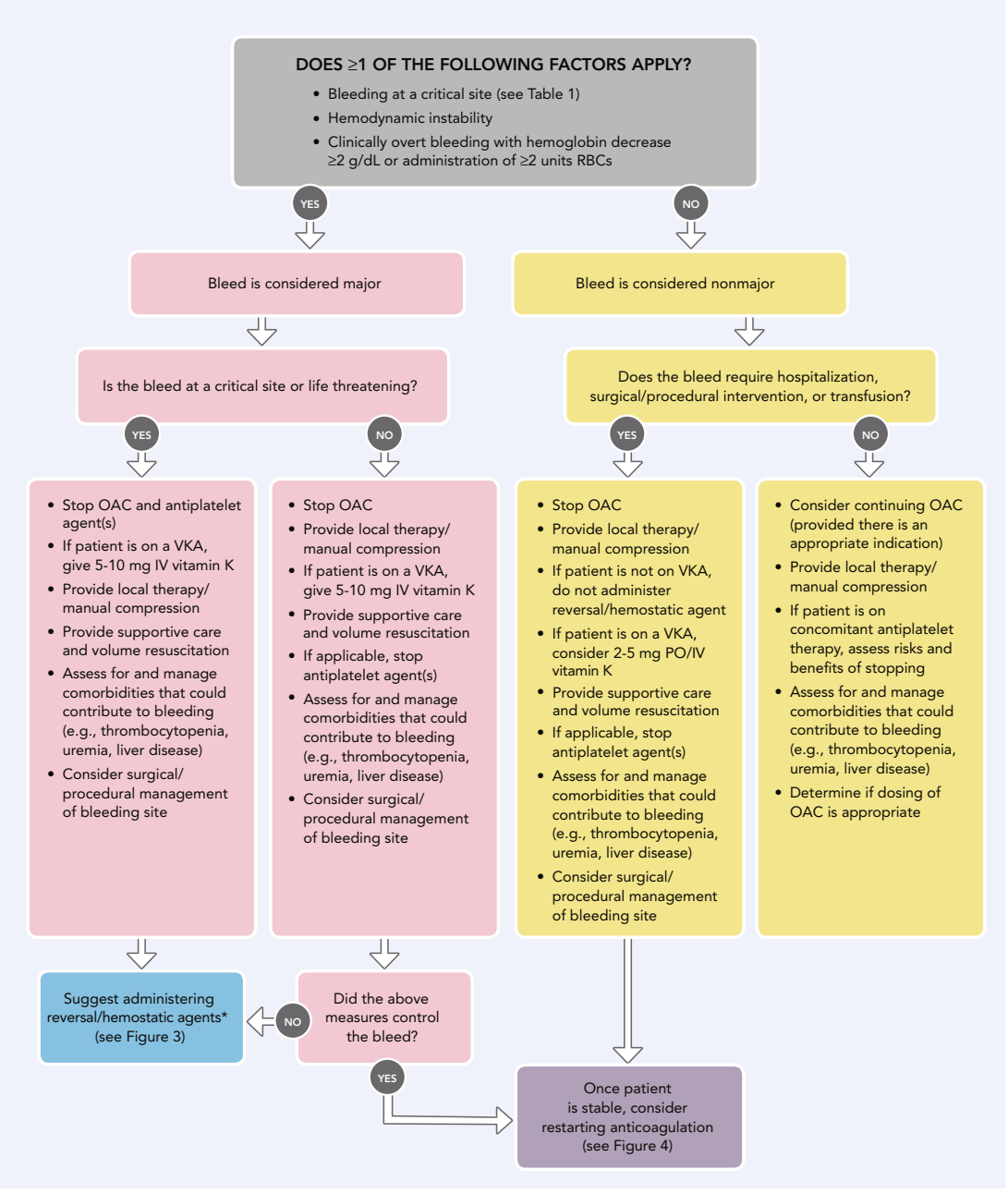
Figure 1 provides an overview of what is covered in this ECDP. See each section for more detailed considerations and guidance.

FIGURE 1 Summary Graphic



DOAC = direct-acting oral anticoagulant; OAC = oral anticoagulant, including DOACs and VKAs; PCC = prothrombin complex concentrate; RBC = red blood cell; VKA = vitamin K antagonist *Reversal/hemostatic agents include repletion strategies such as PCCs, plasma, vitamin K, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran; andexanet alfa for apixaban or rivaroxaban).

FIGURE 2 **Assessing Bleed Severity and Managing Major and Non-Major Bleeds**



DOAC = direct-acting oral anticoagulant; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCC = prothrombin complex concentrate; PO = per os "by mouth"; RBCs = red blood cells; VKA = vitamin K antagonist *Reversal/hemostatic agents include repletion strategies such as PCCs, plasma, vitamin K, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran; andexanet alfa for apixaban or rivaroxaban).

5. DESCRIPTION AND RATIONALE

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

5.1. Assessing Bleed Severity

The assessment of bleed severity in patients treated with OACs 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, with the aim of determining time of onset, location, severity of bleeding, and whether bleeding is ongoing. The assessment of hemodynamic instability should be done promptly and repeated 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, liver disease) and manage them as appropriate.

5.2. Defining Bleed Severity

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

5.2.1. Bleeding in a Critical Site

Bleeds that compromise the organ's function such as intracranial hemorrhage (ICH) and other central nervous system bleeds (e.g., intraocular, spinal) are considered to be critical site bleeds. Thoracic, airway, pericardial, intra-abdominal, retroperitoneal, intra-articular, and intramuscular bleeds are considered critical as they may cause severe disability and necessitate 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 **Table 1**.

5.2.2. Hemodynamic Instability

An increased heart rate may be the 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 (13), 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 (13). 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 (13).

TABLE 1 Critical Site Bleeds

Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
ICH: includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	• Unusually intense headache, emesis, reduced or loss of consciousness, 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, paradoxical pulse, jugular venous distension, tachycardia, muffled heart sounds, rub	• Cardiogenic shock • Death
Airway: includes 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 retroperitoneal hemorrhage	• **Hemothorax:** tachypnea, tachycardia, hypotension, decreased breath sounds • **Intra-abdominal (non-GI):** abdominal pain, distension, hypotension, tachycardia • **Retroperitoneal hemorrhage:** back/flank/hip pain, tachycardia, hypotension	• **Hemothorax:** respiratory failure • **Retroperitoneal hemorrhage:** 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

GI = gastrointestinal; ICH = intracranial hemorrhage.

5.2.3. Overt Bleeding With Hemoglobin Drop ≥2 g/dL or Administration of ≥2 Units of Packed RBCs

Bleeding events causing a hemoglobin drop ≥2 g/dL or requiring transfusion of ≥2 units of RBCs have been associated with a significantly increased mortality risk (14,15). Patients with CV disease—defined as a history of angina, myocardial infarction, heart failure, or peripheral artery disease—are more likely to die of hemoglobin drops than patients without CV disease during their hospitalization (15,16). 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 pre-resuscitation hemoglobin may be artificially high due owing to hemoconcentration.

Patients who do not meet criteria for a major bleed are classified as experiencing a nonmajor bleeding event for this ECDP.

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 a 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 minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown. The International Society on Thrombosis and Haemostasis 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). Assays suitable for quantitation 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 assay availability are summarized in **Tables 2 and 3** (17,18).

Tests suitable for dabigatran quantitation include the dilute thrombin time, ecarin clotting time, and ecarin chromogenic assay (see **Table 2**) (19,20). 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 (19,20). 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. 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 (18–20).

TABLE 2 Assays Suitable for Quantitation of DOACs

Drug	Suggested Test
Dabigatran	• Liquid chromatography-tandem mass spectrometry • Dilute thrombin time • Ecarin clotting time • Ecarin chromogenic assay
Apixaban, betrixaban, edoxaban, or rivaroxaban	• Liquid chromatography-tandem mass spectrometry • Anti-FXa*

*Useful for quantitation of plasma drug levels only when calibrated with the drug of interest.

DOAC = direct-acting oral anticoagulant; FXa = factor-Xa.

The preferred test for quantitation of apixaban, edoxaban, and rivaroxaban is a chromogenic anti-FXa assay calibrated with the drug of interest (see **Table 2**) (19,20). Anti-FXa assays may also be useful for quantitation of betrixaban, but modification of current methods is necessary to achieve suitable sensitivity (21). When an anti-FXa assay is calibrated with a low-molecular-weight heparin or unfractionated heparin standard, it can be useful for excluding clinically important levels of drug, but not for quantitation (see **Table 3**). If an anti-FXa assay is not available, the PT may be useful for qualitative assessment of betrixaban, 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 (19,20,22). 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 (19,20,23). Whole-blood viscoelastic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) exhibit dose-dependent changes in response to DOACs. However, thresholds that are sufficiently sensitive and specific for guiding decisions about use of reversal agents have not been established (19).

5.4. Managing Major Bleeds

Anticoagulants and antiplatelet agents should be discontinued, 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 5.6.) but obtaining and administering the reversal agent must not delay resuscitation and local hemostatic

TABLE 3 Suggestions for Qualitative Assessment of DOACs When Assays Suitable for Quantitation Are Not Available

	Clinical Objectives			
	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 significant 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	UFH or LMWH anti-FXa	• **Normal PT and aPTT** do not exclude clinically relevant* levels. • **UFH or LMWH anti-FXa below the lower limit of quantitation** probably excludes 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.
Betrixaban, edoxaban, or rivaroxaban	UFH or LMWH anti-FXa	• **Normal PT and aPTT** does not exclude clinically relevant* levels. • **UFH or LMWH anti-FXa below the lower limit of quantitation** probably excludes 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 (10).

aPTT = activated partial thromboplastin time; DOAC = direct-acting oral anticoagulant; FXa= factor Xa; LMWH = low-molecular-weight heparin; PT = prothrombin time; TT = thrombin time; UFH = unfractionated heparin.

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. Aggressive volume resuscitation using intravenous isotonic crystalloids such as 0.9% NaCl or Ringer's lactate (24,25) is also recommended. The goal should be restoration of hemodynamic stability. There does not appear to be a benefit for colloids over crystalloids (26). Hypothermia and acidosis should be corrected, as they may worsen the coagulopathy and perpetuate the bleeding. There is no evidence to support the use of one crystalloid solution over another (27); however, caution should be given to the development of hyperchloremia and hyperchloremic acidosis with administration of large volumes of saline. Early involvement of the appropriate service (e.g., surgery, interventional radiology, gastroenterology) for definitive management of bleeding is recommended. 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 (rather than liberal) transfusion strategy improves survival and reduces the risk of recurrent bleeding in patients presenting with severe acute upper GI bleeding (28). Patients with symptomatic anemia or active bleeding should receive RBC transfusions to maintain a hemoglobin ≥7 g/dL (29). In patients with underlying coronary artery disease, particularly those with acute coronary syndromes, the current guidelines recommend a target hemoglobin ≥8 g/dL (30). Platelets should be transfused to maintain a platelet count ≥50 X 10^9/L (31,32) and cryoprecipitate to maintain a fibrinogen >100 mg/dL. For patients requiring ≥3 units of packed RBCs within 1 hour, activation of a massive transfusion protocol should be considered (33). The protocols are variable (34), and currently, many centers use goal-directed transfusion with TEG or ROTEM. Ionized calcium levels should be monitored; if abnormal, administration of calcium is indicated. Early administration of tranexamic acid for trauma patients within the first 3 hours is associated with decreased bleeding and overall mortality and should be considered (35). 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 and potential complications of aggressive fluid resuscitation, which could worsen bleeding and subsequent outcome. Because of their dependence on renal function for clearance, all 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 (36). In patients with severe renal dysfunction, laboratory evaluation to detect residual anticoagulant activity is recommended (see Section 5.3.). 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 (37–39). Importantly, however, 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 FXa 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 TEG or ROTEM may be of value for assessment of hemostatic function along with hematology consultation (40-43). Consideration might be given to the use of an antifibrinolytic agent, such as tranexamic acid or 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 (44). Patients with inherited bleeding disorders and other acquired hemostatic defects (e.g., those necessitating the use of dual antiplatelet therapy) may be at risk for more severe and prolonged bleeding. The writing committee supports correction of any underlying hemostatic defects. Currently, there is limited evidence to support routine administration of platelets in the setting of antiplatelet agent use (e.g., aspirin, P2Y12 inhibitors). Two systematic reviews of small studies concluded that there was no benefit of such therapy for patients with an ICH (45,46). Additionally, a more recent phase 3 trial, PATCH (Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Hemorrhage Associated With Antiplatelet Therapy), randomized patients with ICH and on antiplatelet therapy to platelet transfusion and found higher odds of death or dependence among the platelet transfusion group (47). Therefore, the writing committee does not support 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 severity, local measures should be employed where possible to control any bleeding. For patients with a nonmajor bleed, the writing committee does not support 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, the nature of the bleed, and the intensity of anticoagulation; should follow discussion with the patient and/or family as part of shared decision making; and brings to the forefront the following questions:

- Is the anticoagulation supratherapeutic?
- Is the anticoagulation therapeutic (if target therapeutic goals are known and testable)?
- Is an invasive procedure needed soon?
- Has the patient's underlying bleeding risk changed (e.g., as a result of new medications, acute deterioration in renal or hepatic function)?
- Is continued diagnostic evaluation to determine the site or clinical impact of bleeding warranted?
- Does the patient have baseline severe anemia requiring transfusion of ≥1 units of RBCs?
- Does the patient have relevant medical comorbidities, frailty, or other active medical issues (e.g., myocardial infarction, 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)? (48,49).

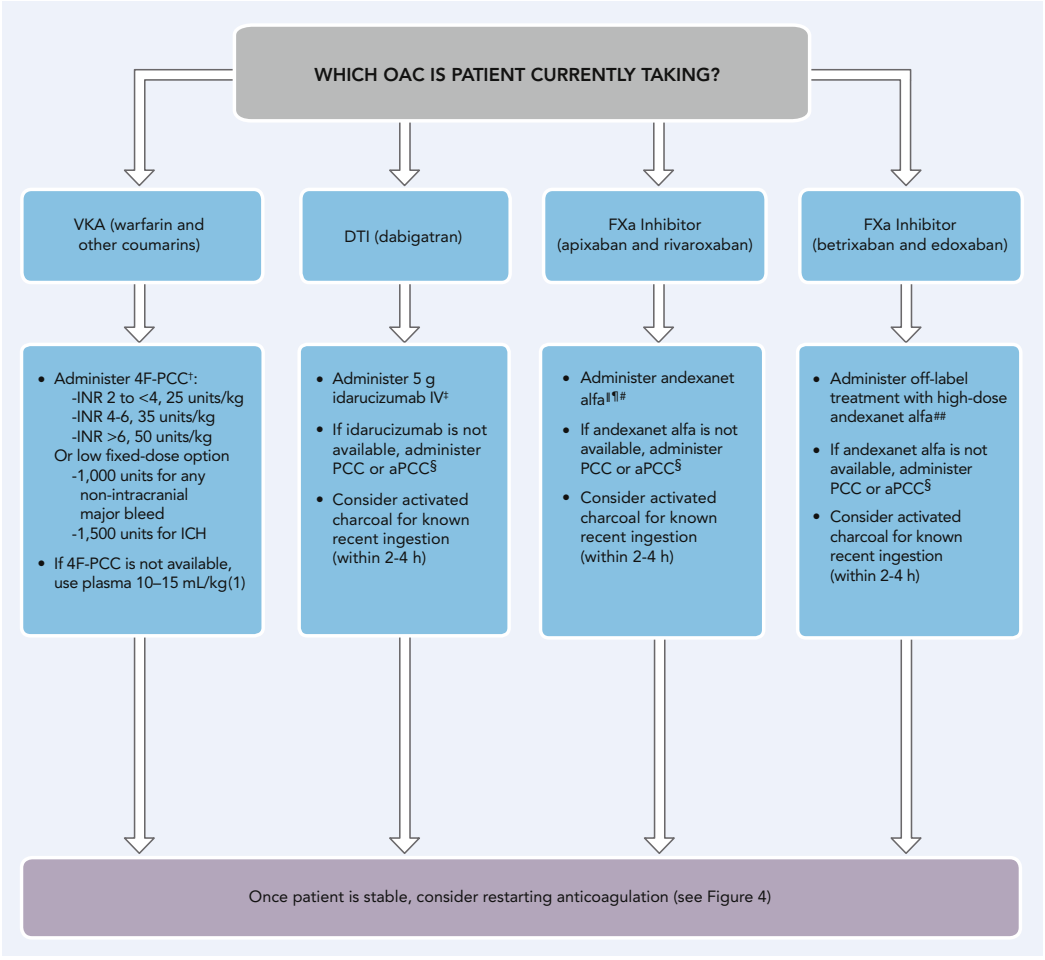
For any of these situations, the writing committee advises that the OAC be discontinued (at least temporarily) and consideration be given to whether concomitant antiplatelet agents could be discontinued safely. If the OAC is stopped, yet an indication for ongoing anticoagulation exists, it is expected 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 Atrial Fibrillation" (11).

If it is determined that the patient does not require hospitalization, a procedure, or a transfusion, and hemostasis has been achieved, the writing committee supports 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, 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 1 exception is ticagrelor, a reversible platelet inhibitor with a half-life of 7 to 9 hours.

5.6. OAC Reversal/Hemostatic Strategies

Reversal/hemostatic strategies for OAC should be considered if an agent is available for patients with major bleeding. Relevant clinical trials are summarized in an online supplement. This section provides information on the options available for reversal of VKAs, dabigatran, and FXa inhibitors. **Figure 3** provides guidance for administering reversal/hemostatic agents based on the OAC prescribed to the patient.

FIGURE 3 Considerations for Reversal/Hemostatic Agents*



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

*Reversal/hemostatic agents include repletion strategies such as PCCs, plasma, vitamin K, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran; andexanet alfa for apixaban or rivaroxaban). †When PCCs are used to reverse VKAs, vitamin K 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 maximum units. ‖ In patients taking ≤5 mg apixaban or ≤10 mg rivaroxaban, administer low dose andexanet alfa = initial IV bolus 400 mg at a target rate of 30 mg/min, followed by IV infusion 4 mg/min for up to 120 minutes. ¶In patients taking >5 mg apixaban or >10 mg rivaroxaban, administer high dose andexanet alfa = initial IV Bolus 800 mg at a target rate of 30 mg/min, followed by IV infusion 8 mg/min for up to 120 minutes. #ANNEXA-4 full report excluded patients with DOAC levels <75 ng/ml because those patients were considered to have clinically insufficient levels for reversal agent. If drug effect/level can be assessed without compromising urgent clinical care decisions, then assessment should be performed before andexanet alfa is administered ## In patients taking betrixaban or edoxaban, administer high dose andexanet alfa = initial IV Bolus 800 mg at a target rate of 30 mg/min, followed by IV infusion 8 mg/min for up to 120 minutes.

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 4A Estimated Drug Half-Life Based on CrCl

	Dabigatran					Apixaban, Betrixaban, 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)	• Apixaban, edoxaban, rivaroxaban: 6–15 • Betrixaban: 19–27	• Apixaban: 17 • Edoxaban: 17 • Rivaroxaban: 9	• Apixaban: 17 (off dialysis) • Edoxaban: 10–17 (off dialysis) • Rivaroxaban: 13 (off dialysis)

CrCl = creatinine clearance.

Table 4a summarizes the drug half-life based on creatinine clearance. Table 4b summarizes the duration for withholding DOACs based on bleed risk. Table 5 summarizes reversal/hemostatic agents' indications for each of these OACs. While there are currently no randomized trials comparing PCC or activated prothrombin complex concentrate (aPCC) with reversal agents indicated for use in patients taking dabigatran, apixaban, betrixaban, edoxaban or rivaroxaban, it is reasonable to consider idarucizumab or andexanet alfa in situations in which reversal is required, if these agents are available at your institution (see **Figure 3 and** Section 5.6.2. and Section 5.6.3.).

5.6.1. 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 VKAs because it restores intrinsic hepatic carboxylation of vitamin K-dependent clotting factors by overcoming VKAs 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 minutes) effects a more predictable and rapid reduction in the INR (4 to 6 hours) compared with oral (18 to 24 hours) or subcutaneous (unpredictable and not recommended) administration. Anaphylactic reactions reported in the past with intravenous administration are not encountered with current preparations (62). The administration of vitamin K does not result in immediate correction of coagulopathy, and for the patient with a major bleed (as defined herein) warranting reversal, administration must be accompanied by a repletion strategy (If 4-factor prothrombin complex concentrate [4F-PCC] is unavailable, PCCs or plasma may be used).

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 proteins 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 blood group compatibility and can be stored at room temperature as a lyophilized powder; therefore, they can be rapidly reconstituted and infused. They are dosed on the basis of 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 units capped at 100 kg body weight) for VKA reversal. Per unit volume, 4F-PCCs contain approximately 25 times (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 (63).

There are concerns about thromboembolic events with both nonactivated and activated PCCs. These concerns stem from anecdotal reports of thromboembolic events associated with the extended use of 3F/4F-PCCs in patients with hemophilia. Recent randomized clinical trials

TABLE 4B Suggested Duration for Withholding DOAC Based on Bleed Risk

	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	**≥80**	**50–79**	**30–49**	**15–29**	**<15**	**≥30**	**15–29**	**<15**
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 (50–58).

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

TABLE 5 Suggested Reversal/Hemostatic Strategy for OACs*

OAC	Suggested Reversal Strategy
VKA	• Administer 4F-PCC (59).† • If 4F-PCC is not available, administer plasma.
Factor IIa inhibitor (dabigatran)	• Administer idarucizumab (60). • If idarucizumab is not available, administer either PCC or aPCC. • Consider activated charcoal for known recent ingestion (within 2–4 h).
FXa inhibitor (apixaban, betrixaban, edoxaban, and rivaroxaban)	• Administer andexanet alfa (61). • If andexanet alfa is not available, administer either PCC or aPCC. • Consider activated charcoal for known recent ingestion (within 2–4 hours).

*See Figure 3 for specific guidance for administering reversal/hemostatic agents.
†When PCCs are used to reverse VKAs, vitamin K should also always be given.

4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; DOAC = direct-acting anticoagulant; FXa = factor Xa; OAC = oral anticoagulant, including DOACs and VKAs; PCC = prothrombin complex concentrate.; VKA = vitamin K antagonists.

comparing 4F-PCC with plasma for VKA reversal showed a similar thromboembolic event incidence in both groups (59,64).

A unit of plasma (225 to 300 mL, fresh frozen, frozen, or thawed) is usually obtained from a whole-blood donation. It contains not only vitamin-K-dependent clotting factors, but also other coagulation factors and proteins, and hence is considered a nonspecific reversal agent. Vitamin K-dependent clotting factors are not affected by freezing; however, significant time is required to ABO blood group type match and thaw plasma. In general, it may take up to 90 minutes from the time of the transfusion order to administration of the first unit of plasma volume. Because 1 unit of any given factor is present in 1 mL of normal pooled plasma, adequate plasma for VKA reversal is 15 to 30 mL/kg. This volume of plasma at this dose, however, is not practical for rapid VKA reversal (e.g., 70 kg × 30 ml = 2,100 mL or approximately 8 units of plasma), and so a plasma concentration of 10 to 15 mL/kg is used more commonly (see **Figure 3**) (63). Potential adverse effects of plasma transfusion include circulatory volume overload (63), allergic reactions, and risk of transfusion-related acute lung injury. Because these effects are not observed with PCC, it is used preferentially, particularly in volume-sensitive patients.

5.6.2. Factor IIa Inhibitors (Dabigatran)

Most bleeding complications associated with dabigatran can be managed with conservative measures and withholding of the anticoagulant. In addition, most nonurgent invasive procedures can be temporarily delayed for normal offset of the anticoagulant effect (50). In rare situations, however, 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 clinical situations have been analyzed in an open-label study of the Fab fragment idarucizumab (65)—a reversal agent with an affinity for dabigatran that is approximately 350 times that of dabigatran for thrombin (66). In the REVERSE 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 2 2.5-gram aliquots (67). The study's primary endpoint of maximum reversal of the anticoagulant effect of dabigatran within 4 hours as assessed by dilute thrombin or ecarin clotting time 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 (60). In patients undergoing procedures or surgery, hemostasis was judged to be normal in 92% of patients during their procedure. Treatment with idarucizumab was safe, with no significant adverse effects. The rate of postreversal thrombotic complications was 6%, with approximately two-thirds of those events occurring in patients who had not reinitiated any antithrombotic therapy (67). Accordingly, in the "2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation," idarucizumab has been given a Class I, Level of Evidence: B recommendation for the reversal of dabigatran in the event of life-threatening or uncontrolled bleeding (68). Idarucizumab has not, however, been studied outside of these emergency reversal scenarios (69).

Idarucizumab is widely, but not universally, available in the United States. If idarucizumab is unavailable, then either PCC or aPCC may be used at 50 U/kg (maximum dose 4,000 units). This advice is based on limited animal, ex vivo, and human studies showing variable improvement in hemostatic parameters of either agent in vitro (70–76). Because dabigatran is mostly not protein-bound in the plasma (>85%), hemodialysis may be considered if the drug level is very high, especially in patients with impaired renal function (77,78). Activated charcoal (50 g) may also be used in patients with drug ingestion that has occurred within the last 2 to 4 hours (66).

5.6.3. Factor Xa Inhibitors (Apixaban, Betrixaban, Edoxaban, and Rivaroxaban)

Andexanet alfa is the first reversal agent approved by the U.S. Food and Drug Administration (FDA) to treat life-

threatening bleeding in patients on apixaban and rivaroxaban (79). It is a recombinant protein with a similar structure to endogenous FXa that binds FXa inhibitors but is not enzymatically active. Andexanet alfa has been studied in 352 patients with major bleeding (primarily intracranial or GI) who had taken an FXa inhibitor within 18 hours in the ANNEXA-4 (Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding) trial (80). Hemostatic efficacy was evaluated in patients who were adjudicated to have acute major bleeding and who had drug levels >75 ng/mL (28% patients who received andexanet alfa were excluded from the hemostatic efficacy assessment). All patients who received andexanet alfa were included in the safety analysis. Andexanet alfa decreased the median anti-FXa activity by 92% for both apixaban and rivaroxaban, with excellent or good hemostasis 12 hours after infusion (80), although the drug levels had increased postinfusion to almost half (>75 ng/ml) of the baseline. Notably, there was no correlation between nadir FXa activity and bleeding. At 30-day follow-up, 14% of patients had died and 10% had had a thrombotic event, the majority of which occurred in participants not restarted on anticoagulation (80). In patients with rivaroxaban- or apixaban-associated critical site (see **Table 1**) or life-threatening major bleeding, it is reasonable to use andexanet alfa for reversal in concordance with the Class of Recommendation IIa; Level of Evidence: B-NR recommendation in the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation (68). If andexanet alfa is not available, it is reasonable to use hemostatic agents such as PCC or aPCC (see **Figure 3**).

Although patients receiving edoxaban were included in the ANNEXA-4 trial, the number of patients enrolled was limited. In healthy volunteers receiving edoxaban, a bolus of andexanet alfa (600 or 800 mg) followed by an infusion (8 mg/min for 2 hours) reduced FXa activity by 52% and 73%, respectively (81). Reversal of betrixaban with andexanet alfa has only been evaluated in healthy volunteers. A bolus dose of andexanet alfa (800 mg) followed by a 2-hour infusion (8 mg/min) reduced anti-FXa activity by 78% and lowered unbound betrixaban plasma concentrations from 12.3 ± 5.6 ng/mL to 3.6 ± 2.7 ng/mL. Thrombin generation was also restored in most subjects (11 of 12) following andexanet alfa (82). Andexanet alfa continues to be studied in ongoing trials in patients on a DOAC with major bleeding (NCT02329327) and ICH (NCT03661528).

Evidence supporting the use of coagulation factor supplementation with PCC as hemostatic therapy in FXa inhibitor-treated patients with major bleeding is limited. 4F-PCC is the most extensively studied. Three randomized studies evaluated its effect on laboratory indices of anticoagulation compared with placebo or 3-factor PCC in human volunteer subjects administered an oral direct FXa inhibitor (70,83,84). All 3 trials evaluated the effect of 4F-PCC on coagulation laboratory parameters (coagulation tests and thrombin generation), and one study evaluated bleeding following punch biopsy of the skin. The results demonstrated modest correction of some anticoagulant-induced laboratory abnormalities, but the results were not consistent across all parameters and all studies. Prolonged 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) (79).

Two single-cohort observational studies evaluated the use of 4F-PCC as part of institutional protocols for FXa inhibitor-treated patients with major bleeding. In 1 study, 66 patients received a fixed dose of 4F-PCC (2,000 units), and hemostatic efficacy was achieved in 85% of patients (85). In the other study, 84 patients received 4F-PCC dosed by body weight (1,500 units <65 kg; 2,000 units >65 kg), and hemostatic efficacy was achieved in 69% of patients (86). The mean times from the last dose of FXa inhibitor to 4F-PCC were 18 and 12 hours, respectively. Although these results bear some similarities to those from the ANNEXA-4 trial, there are important differences, including a lack of standardized prospective data collection for all patients such as repeat imaging for those with an ICH in these studies. Further, hemostatic efficacy was evaluated at 24 hours in these studies, as opposed to 12 hours in ANNEXA-4, at which point drug levels would be expected to be lower owing to drug clearance (80). Like ANNEXA-4, the incremental benefit of 4F-PCC in addition to supportive measures, definitive treatments, and drug clearance is uncertain owing to the absence of a control group. On the basis of these limited data, it is reasonable to administer 4F-PCC at a fixed dose of 2,000 units for severe or life-threatening bleeding in patients anticoagulated with oral direct factor Xa inhibitors (80). A systematic review of 10 case series and 340 patients with major bleeding who received 4F-PCC showed low rates of bleeding, thromboembolic events, and mortality (87).

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 hemophiliac patients with inhibitors, aPCC is typically administered intravenously in doses ranging from 50 to 100 U/kg, with a daily maximum of 200 U/kg (88). There are no randomized

data regarding dosing in patients with FXa inhibitor-related major bleeding. On the basis of 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 who are known or likely to have clinically significant anticoagulant levels (89).

On the basis of currently available data, the writing committee suggests andexanet alfa is preferable to 4F-PCC for treatment of patients with major bleeding on oral direct FXa inhibitors. In coming to this preference, the writing committee considered the following:

1. The approval of andexanet alfa was based on the results of the ANNEXA-4 trial, a protocolized prospective observational study that demonstrated both reversal of anticoagulant effect and evidence of clinical hemostasis determined by blind outcome adjudication after andexanet alfa administration (80);
2. Data supporting the use of 4F-PCC in such patients are derived primarily from assessments of clinical efficacy based on review of medical records in small observational studies; and
3. Andexanet alfa is the only treatment approved by the FDA for apixaban- and rivaroxaban-associated major bleeding. Several other groups have also published guidance statements in accordance to FDA approval of andexanet alfa within this consideration (90,91).

5.6.4. OAC Reversal Agents in Development

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-hour) reversal of whole-blood clotting times in volunteer subjects receiving edoxaban (92,93).

5.7. Considerations for Restarting Anticoagulation

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

5.7.1. Should Anticoagulation Be Restarted?

In most cases, restarting OAC after a bleeding event provides net clinical benefit (94). After a patient has a bleeding event on OAC, the indication for OAC should be reassessed to determine whether continued therapy is warranted on the basis of established clinical practice guidelines.

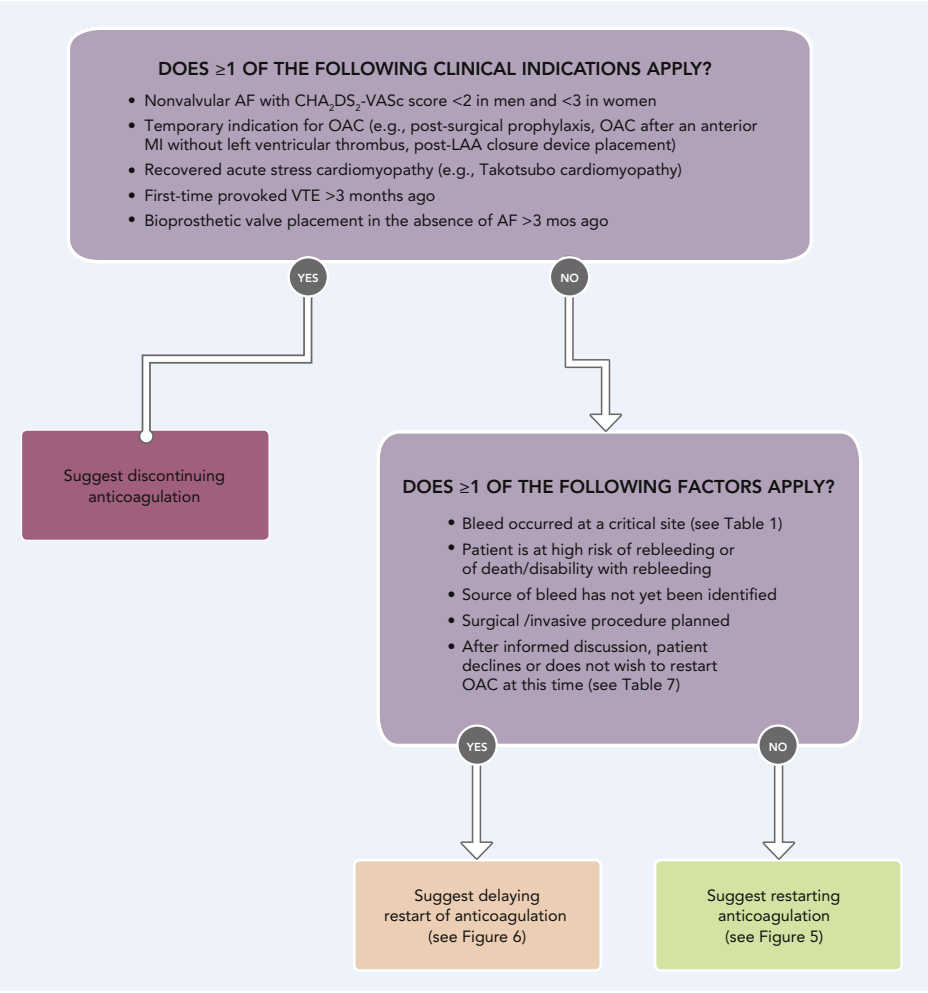
The following are possible conditions for which OAC may no longer be indicated:

- Nonvalvular AF with CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age [>65 = 1 point, ≥ 75 = 2 points], Diabetes, previous Stroke/transient ischemic attack [2 points]) score <2 in men and <3 in women (68)
- Temporary indication for OAC (e.g., postsurgical prophylaxis, OAC after an anterior MI without left ventricular thrombus, post-LAA closure device placement)
- Recovered acute stress cardiomyopathy (e.g., Takotsubo cardiomyopathy)
- First time provoked VTE >3 months ago
- Bioprosthetic valve placement in the absence of AF >3 months ago (95).

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, neurologists) and in discussion with patients or caregivers. Several validated bleeding assessment tools are available, but none has been studied in the specific situation of active or very recent bleeding.

There are many patient characteristics (e.g. age, sex) and other 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, should be addressed prior to restarting therapy. Determining the appropriateness of the drug and dose for individual patients on the basis of indication, age, weight, and renal function is important to minimize the potential for adverse events. If the patient is on dual antiplatelet therapy, re-evaluating whether such therapy is needed or whether aspirin can be discontinued is reasonable (50). Bleed characteristics that contribute substantially to the risks associated with restarting anticoagulation include: 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.

FIGURE 4 **Considerations for Restarting Anticoagulation**



AF = atrial fibrillation; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age (>65 = 1 point, ≥75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); LAA = left atrial appendage; MI = myocardial infarction; mos = months; OAC = oral anticoagulant, including VKAs and DOACs; VKA = vitamin K antagonist; VTE = venous thromboembolism.

5.7.2. Timing of Anticoagulation Reinitiation

In general, all such decisions should be made by a multidisciplinary care team. **Figure 5** provides clinical guidance for situations in which it is suggested that the patient restart anticoagulation.

Figure 6 provides clinical guidance for situations in which it is suggested 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 owing to its short half-life and the availability of a reversal agent (protamine sulfate) that can rapidly stop and/or reverse anticoagulation in the event of rebleeding.

TABLE 6 Original Indications for Anticoagulation With High Thrombotic Risk

Indication	Patient Characteristics That May Further Increase Thrombotic Risk
Mechanical valve prosthesis with or without AF*	• Mechanical valve (mitral > aortic) + additional thrombotic considerations: AF, HF, prior stroke/TIA • Caged ball or tilting disc valve prosthesis • Stroke/TIA within 6 months
Nonvalvular AF†	• AF with CHA_2DS_2-VASc score of ≥4 (84)‡ • Ischemic stroke/TIA within 3 months • Stroke risk ≥10% per year
Valvular AF (with moderate or greater mitral stenosis or a mechanical valve prosthesis)*	
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 thrombus§	• >3 months post-MI, if recovery of LV function
Left atrial thrombus	
Left ventricular assist device§	

*Currently, only warfarin is indicated for patients ready to restart their anticoagulation.
†Patients can resume any OAC when ready to restart their anticoagulation.
‡For patients with CHA_2DS_2-VASc scores of 4, the annual rate of thromboembolism is 4% (2.8%–5.4%) (96).
§Currently, only conventional-intensity warfarin therapy is indicated for patients ready to restart their anticoagulation.

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age (>65 = 1 point, ≥75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); HF = heart failure; LV = left ventricular; MI = myocardial infarction; TIA = transient ischemic attack; VTE = venous thromboembolism.

Prophylactic doses of parenteral anticoagulants (e.g., subcutaneous unfractionated or low-molecular-weight heparin) may reduce the risk of further bleeding more than therapeutic doses. In addition, temporary use of prophylactic doses with close clinical monitoring is a reasonable strategy to balance bleeding and thrombotic risk in this setting.

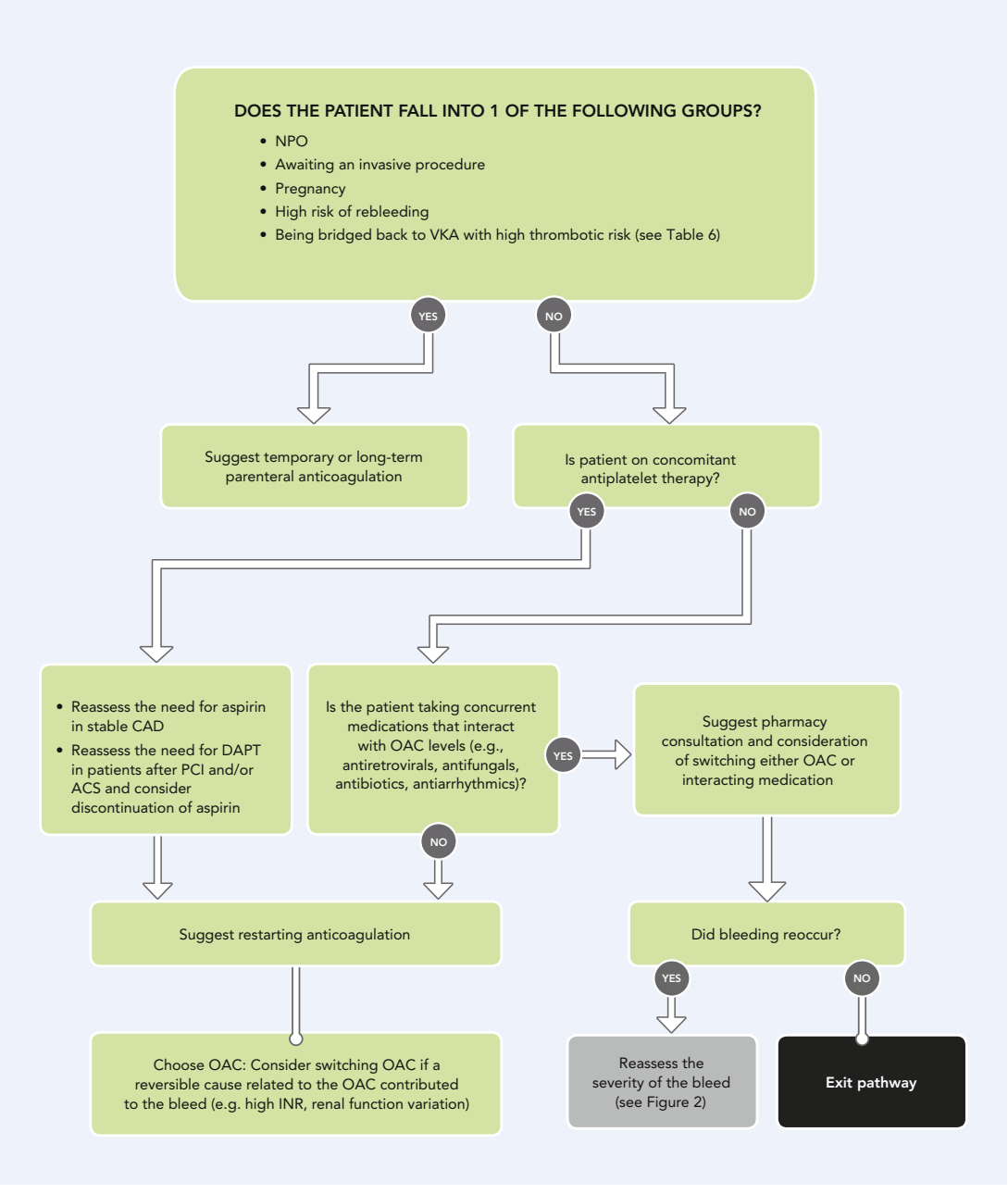
In patients with both high bleeding risk (with relative or absolute contraindication to restarting anticoagulation) and high thrombotic risk, nonpharmacological therapies may be considered. Devices such as left atrial appendage closure/occlusion devices to mitigate thrombotic risk in AF or retrievable inferior vena cava (IVC) filters for acute deep vein thrombosis and/or pulmonary embolism may be considered in consultation with the appropriate specialists. For left atrial appendage closure/occlusion, several minimally invasive options exist that carry different procedural and bleeding risks. Of note, an endocardial device may require therapeutic anticoagulation for at least 45 days following insertion; in contrast, an epicardial device generally does not. Consultation with a specialist familiar with the options for left atrial appendage closure/occlusion is advised. Although IVC filters are considered temporary adjuncts for patients with recent proximal deep vein thrombosis and an absolute contraindication to therapeutic anticoagulation, their judicious use is crucial. Randomized trials have demonstrated the potential for procedural complications and increased risk of deep vein thrombosis, with no benefit in preventing pulmonary embolism or reducing mortality (97,98). When used, IVC filters should be removed as soon as therapeutic anticoagulation is achieved, preferably prior to hospital discharge (99).

In general, temporary interruption of OAC for limited periods is likely appropriate for most patients without high thrombotic risk as determined by the care team. Rebleeding in these patients may lead to further interruption of anticoagulant therapy, thus exposing the patient to greater thrombotic risk. Switching to an alternate OAC should also be considered after a bleeding event, particularly in cases in which a specific cause is identified. For instance, when patients experience a bleeding event in the setting of a supratherapeutic INR, switching to a DOAC should be considered. Likewise, a decrease in renal function may increase DOAC drug levels and prompt switching to a VKA. While it is beyond the scope of this document to make suggestions about specific anticoagulants, management in the setting of GI bleeding, ICH, and postprocedural anticoagulation is outlined in the following sections (Section 5.7.4. and Section 5.7.6.).

5.7.2. 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), as well as implications for thrombotic events and death without anticoagulation. For example, the 30-day mortality rate from AF without OAC may be as high as ~25% after an ischemic stroke AF (100,101). Discussions should be initiated early

FIGURE 5 Restart of Anticoagulation



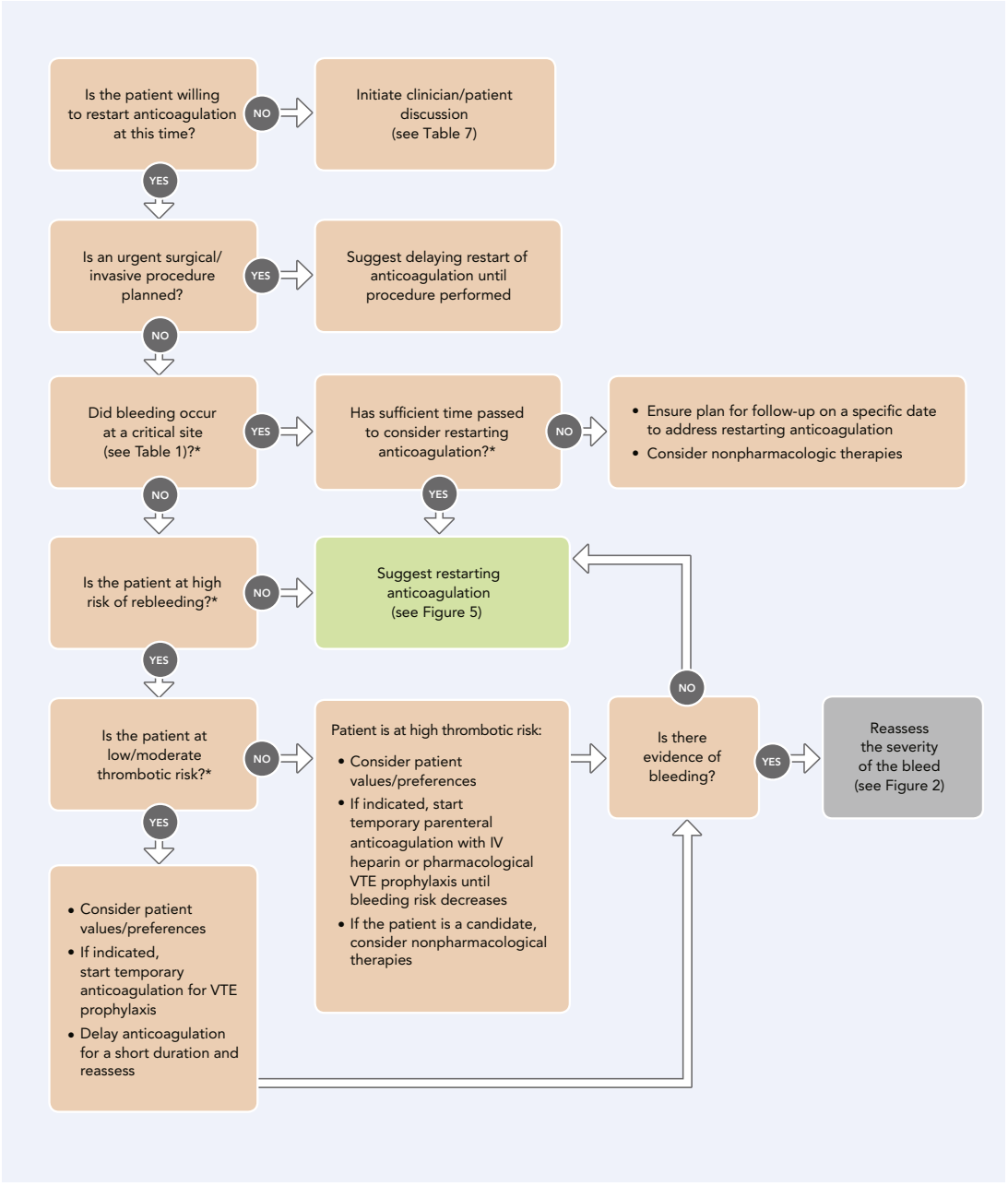
ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DOAC = direct-acting oral anticoagulant; INR = international normalized ratio; NPO = nil per os "nothing by mouth"; OAC = any oral anticoagulant, including VKAs and DOACs; PCI = percutaneous coronary intervention;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

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.

5.7.3. Concurrent Medications

A comprehensive medication review that includes dietary supplements should be performed with all bleeds to identify medications that can increase anticoagulant drug

FIGURE 6 Delaying Restart of Anticoagulation



IV = intravenous; 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.

levels (e.g., antiretrovirals, antifungals, immunosuppressives) (50) or potentiate bleeding when coadministered with an OAC (e.g., antiplatelets and nonsteroidal anti-inflammatory drugs). For example, patients taking medications that inhibit cytochrome P450 3A4 (e.g., verapamil, diltiazem, antifungals) or inhibitors of P-glycoprotein (e.g., digitalis, proton pump inhibitors) may exhibit an increase in levels of rivaroxaban, which is a 3A4 substrate (102). For patients on combination antithrombotic therapy, it is important to re-evaluate the

TABLE 7 Components of the Clinician-Patient Discussion

Factors to Consider	Discussion Points
Timing	• The clinician-patient discussion should be carried out prior to reinitiation of anticoagulation to provide sufficient time for patients to formulate questions.
Associated risks	• Review clinical and site-specific signs of bleeding for which the patient should remain vigilant (e.g., melena after a GI bleed). • Assess the risk of a thrombotic event, ideally by performing personalized risk assessment (e.g., CHA_2DS_2-VASc prediction of thromboembolism risk). • Discuss the sequelae associated with thromboembolic events (e.g., higher mortality for ischemic strokes with AF).
Associated benefits	• Reinforce the net benefit from anticoagulation reinitiation in certain types of bleeds on an anticoagulant (e.g., GI bleeding).

AF = atrial fibrillation; CHA_2DS_2-VASc= Congestive heart failure, Hypertension, Age (>65 = 1 point, ≥75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); GI = gastrointestinal.

necessity for single or dual antiplatelet therapy (103-105). For patients receiving a VKA, it is also important to provide nutritional recommendations to minimize time spent outside the therapeutic range.

5.7.4. GI Bleeding

GI bleeding is a relatively common hemorrhagic complication of chronic OAC therapy, often leading to its permanent discontinuation. In a systematic review of 12 observational studies (3,098 patients), patients with OAC-associated GI bleeding who resumed anticoagulation had a lower risk of thromboembolism (relative risk [RR]: 0.30, 95% confidence interval [CI]: 0.13-0.68; 9 studies) and death (RR: 0.51, 95% CI: 0.38-0.70; 8 studies) than those who did not restart but an increased risk of recurrent bleeding (RR: 1.91, 95% CI: 1.47-2.48; 11 studies) (106). Similar findings were noted in a recent retrospective study among those restarting a VKA (107). The timing of anticoagulation reinitiation has not been systematically studied. In 1 study that restarted anticoagulation at the time of discharge (after median length of stay of 5 days), fewer thromboembolic events were noted at 90 days, with a greater rate of bleeding events (108). In a separate study of patients with AF who restarted warfarin >7 days after a bleed, improved survival and lower rates of thromboembolism were observed without increased risk of recurrent GI bleeding (109). Accordingly, for most cases of GI bleeding, it is reasonable to reinitiate OAC once hemostasis has been achieved.

5.7.5. Intracranial Hemorrhage

Although rare, ICH is the most feared complication of anticoagulation therapy. Approximately 20% of cases of spontaneous ICH are related to anticoagulation, with 30-day mortality rates approaching 50% (110). Accordingly, a cautious, individualized approach to restarting OAC after ICH is warranted. Factors associated with a higher risk of recurrence include the mechanism of ICH (i.e., spontaneous versus traumatic), lobar location of the initial bleed (suggesting amyloid angiopathy), the presence and number of microbleeds on magnetic resonance imaging, and ongoing anticoagulation (111).

Limited data exist on the reinitiation of OAC after an ICH. Depending on bleed characteristics, risk factor modification, and the indication for anticoagulation, restarting OAC after a nonlobar ICH may be considered (111). In observational studies of patients with warfarin-associated ICH, resumption of anticoagulation appears to confer a 50% to 70% lower risk of thrombosis and 50% to 70% lower risk of death without a significantly increased risk of recurrent bleeding compared with discontinuation (112-119). Optimization of modifiable CV risk factors (such as hypertension) prior to OAC reinitiation is important. Lobar ICH secondary to amyloid angiopathy, whether spontaneous or related to warfarin use, and spontaneous subdural hematomas carry a particularly high risk of rebleeding. As such, restarting anticoagulation in these settings should be approached with extreme caution and with neurologic and/or neurosurgical guidance. Although DOACs are associated with a lower risk of ICH than warfarin, the safety of switching a patient with an ICH to a DOAC has not been evaluated (111,120). The timing of anticoagulation reinitiation following an ICH has not been systematically studied and varies widely in observational studies (72 hours to 30 weeks). Current guidelines recommend avoiding anticoagulation for at least 4 weeks in patients without mechanical heart valves, and, if indicated, using aspirin monotherapy initially after an ICH (111). An open-label blinded-endpoint randomized trial of 537 patients evaluated the risk of restarting aspirin after ICH and surprisingly demonstrated a strong trend toward less risk of recurrent ICH (adjusted hazard ratio: 0.51, 95% CI: 0.25-1.03; p = 0.060), although no reduction in risk of ischemic events was observed in those assigned to aspirin therapy (adjusted hazard ratio: 1.02, 95% CI: 0.65-1.60; p = 0.92) (121). 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 (112). For these reasons, we favor delaying the resumption of anticoagulation for at least 4 weeks in patients without high thrombotic risk.

5.7.6. 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 (11). Limited data are 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. 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 (122). 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 fashion similar to that discussed in the previous paragraph 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 ECDP is to provide a clinically applicable, easily referenced, conceptual framework to support clinical decision making while caring for patients with bleeding complications during OAC therapy. The writing committee considered patients taking anticoagulant therapy for any indication in order to broaden the potential clinical use and impact of the ECDP. 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 ECDP will be needed.

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KEY WORDS ACC Expert Consensus Decision Pathway, apixaban, atrial fibrillation, betrixaban, dabigatran, edoxaban, rivaroxaban, venous thromboembolism, warfarin

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2020 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 Solution Set Oversight Committee reviews these disclosures to determine what companies make products (on market or in development) that pertain to the document under development. On the basis of 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 table below 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. Disclosure information for the ACC Solution Set Oversight Committee is also available online, as is the ACC disclosure policy for document development.

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APPENDIX 1. CONTINUED

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This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, 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/AHA Disclosure Policy for Writing Committees.

*No financial benefit

†Significant relationship

‡Contributions to the development of the 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants were also provided by Charles V. Pollack, Jr, MA, MD, FACC.

ACC = American College of Cardiology.

APPENDIX 2. PEER REVIEWER INFORMATION—2020 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 comprehensive list of corresponding healthcare-related disclosures for each reviewer is available online.

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CCEP = Clinical Cardiology Electrophysiology; UCLA = University of California-Los Angeles.

APPENDIX 3. ABBREVIATIONS

4F-PCC = 4-factor prothrombin complex concentrate

AF = atrial fibrillation

aPCC = activated prothrombin complex concentrate

aPTT = activated partial thromboplastin time

CI = confidence interval

CV = cardiovascular

DOAC = direct-acting oral anticoagulant

ECDP = Expert Consensus Decision Pathway

GI = gastrointestinal

FXa = factor Xa

HR = hazard ratio

ICH = intracranial hemorrhage

INR = international normalized ratio

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

PCC = prothrombin complex concentrates

PT = prothrombin time

RBC = red blood cell

ROTEM = rotational thromboelastometry

TEG = thromboelastography

VKA = vitamin K antagonist

VTE = venous thromboembolism