AMERICAN COLLEGE of CARDIOLOGY

2017 ACC EXPERT CONSENSUS DECISION PATHWAY

Management of Bleeding in Patients on Oral Anticoagulants

ALGORITHMS FOR CONSIDERATION

ANTICOAGULATION: BLEED MANAGEMENT

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

A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY TASK FORCE ON EXPERT CONSENSUS DECISION PATHWAYS

WRITING COMMITTEE:

Gordon F. Tomaselli, MD, FACC, Chair
Kenneth W. Mahaffey, MD, FACC, Vice Chair
Adam Cuker, MD, MS
Paul P. Dobesh, PharmD
John U. Doherty, MD, FACC
John W. Eikelboom, MBBS
Roberta Florido, MD
William Hucker, MD, PhD
Roxana Mehran, MD, FACC
Steven R. Messé, MD
Charles V. Pollack, Jr, MA, MD
Fatima Rodriguez, MD
Ravindra Sarode, MD
Deborah Siegal, MD, MSC
Barbara S. Wiggins, PharmD, FACC

The ACC convened this writing committee 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. non-major), 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.

The following resource contains Figures and Tables from the 2017 Decision Pathway which focuses on the management of bleeding in patients being treated with DOACs and VKAs for any indication. This resource is only an excerpt from the Decision Pathway published in the *Journal of the American College of Cardiology* and the full publication should be reviewed for important context and additional information.

CITATION: J Am Coll Cardiol 2017 Dec 1 [E-pub ahead of print]; 10.1016/j.jacc.2017.09.1085

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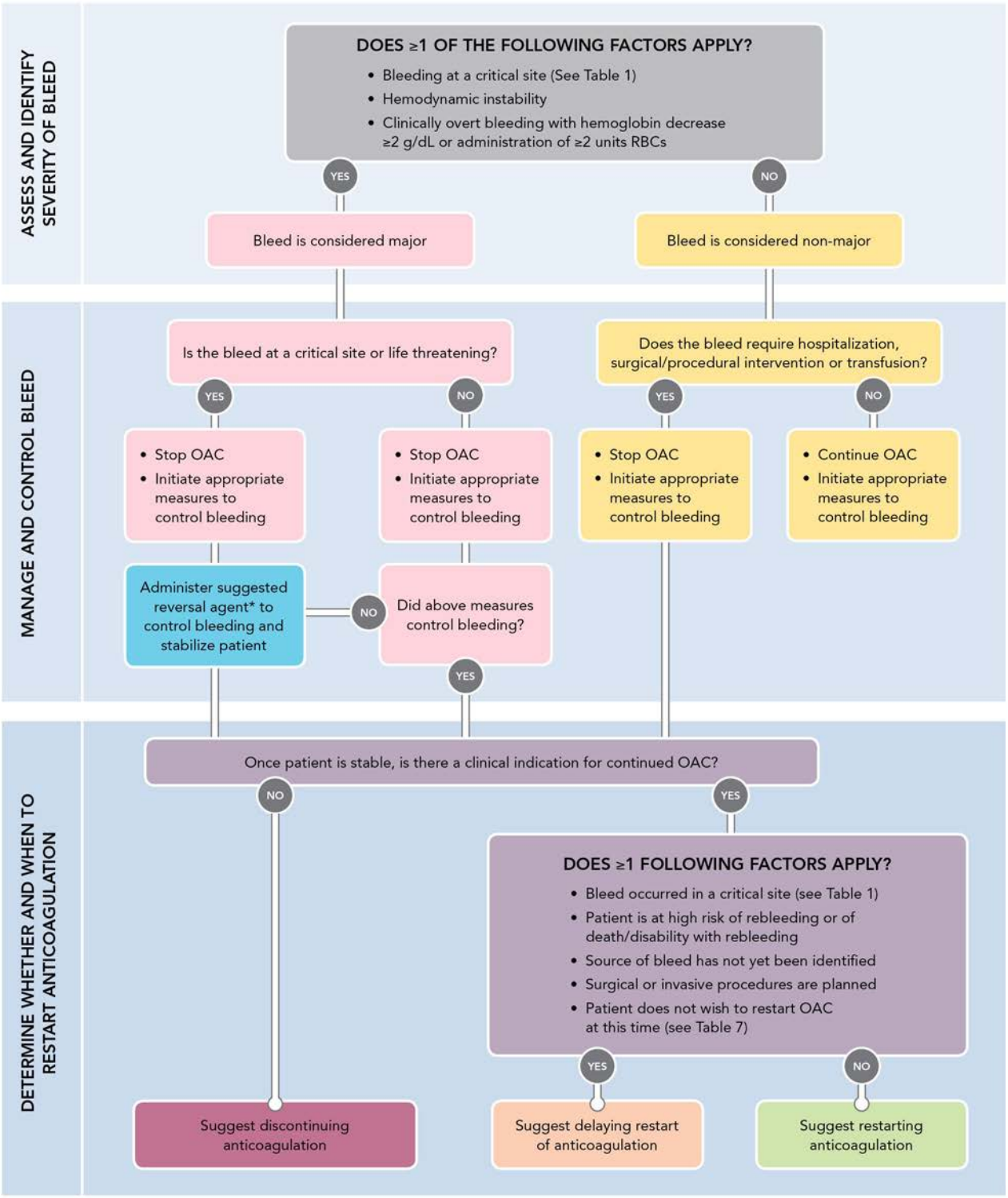
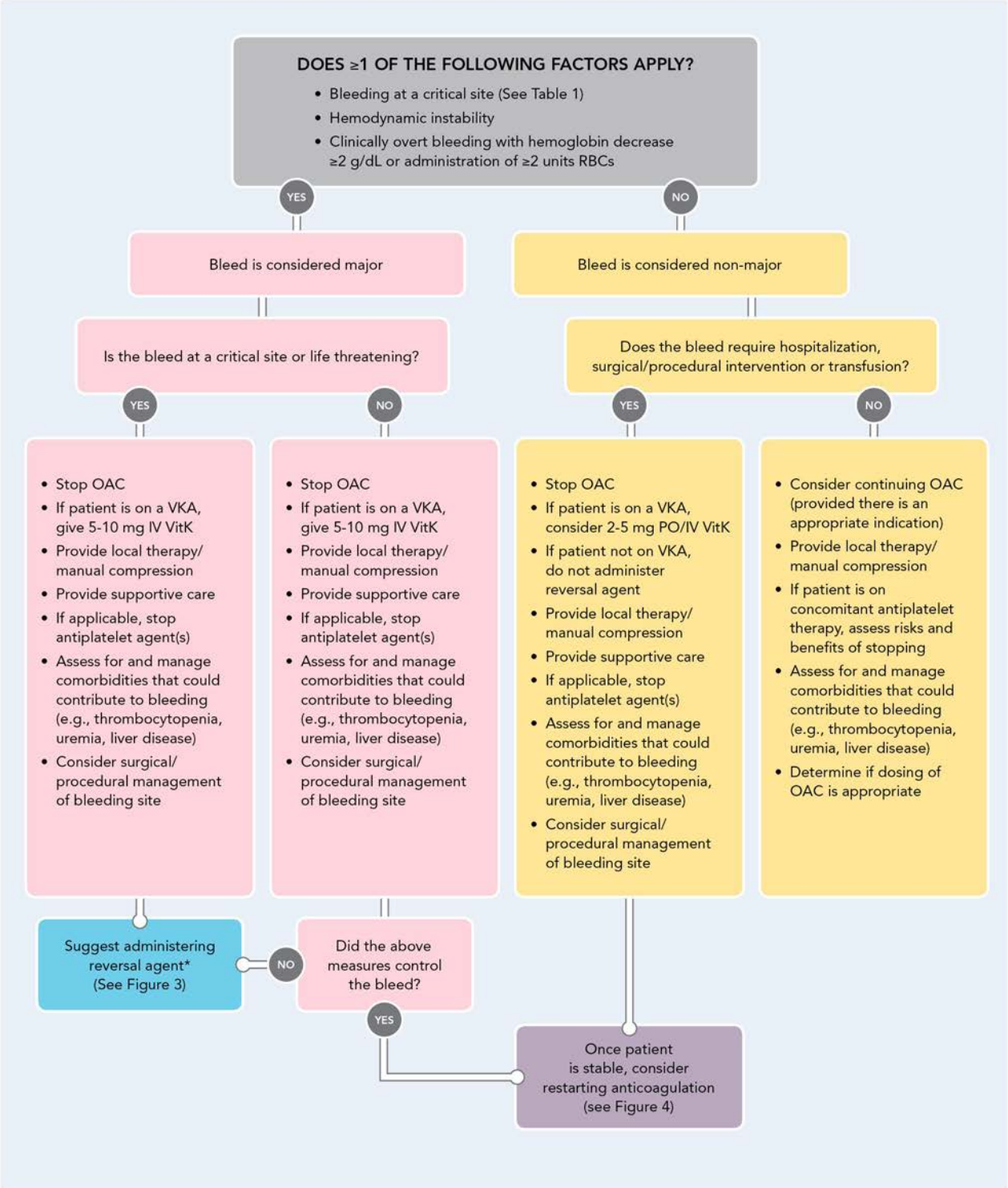
FIGURE 1.
Summary Graphic



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).

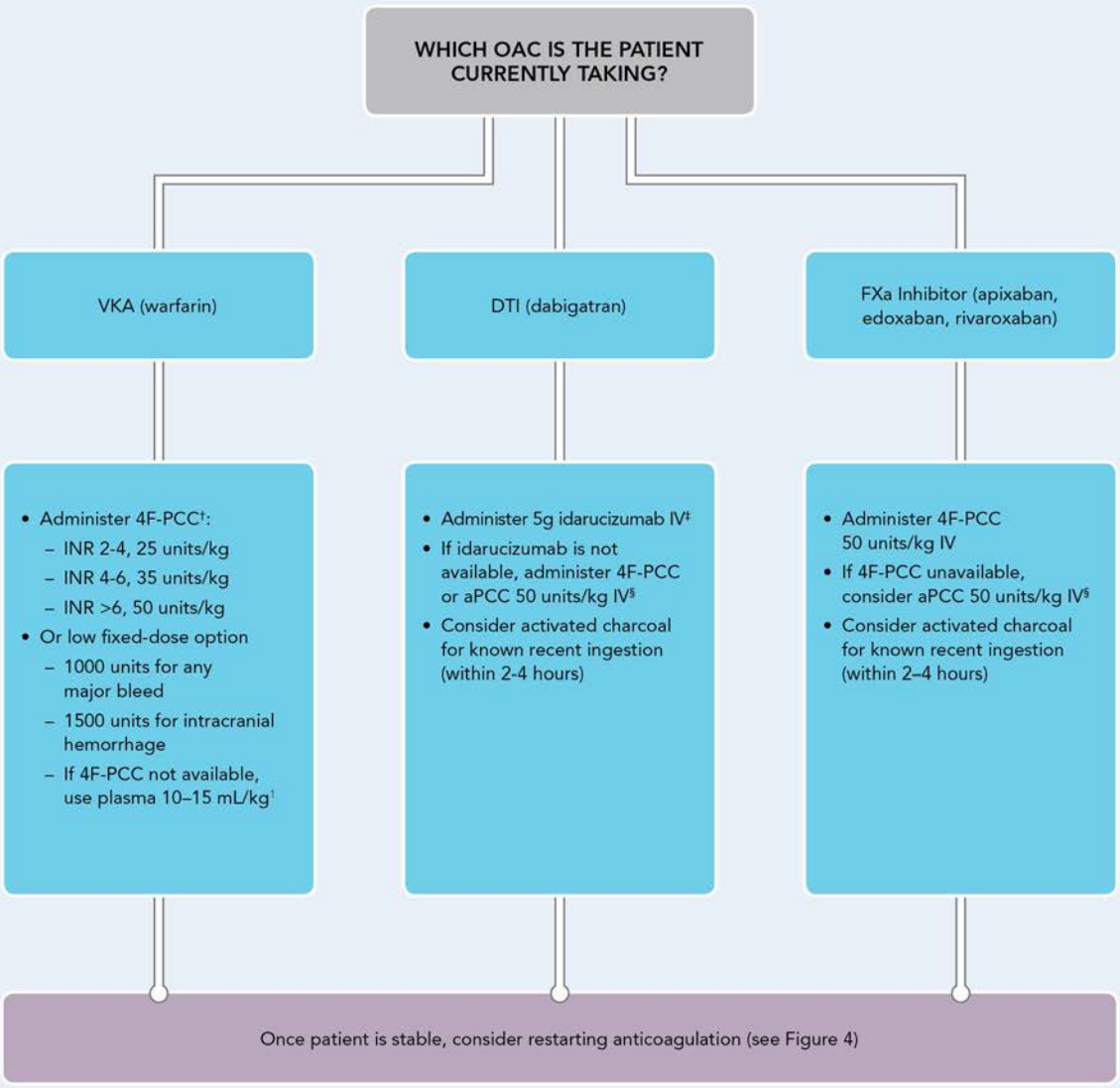
FIGURE 2.
Assessing Bleed Severity and Managing Major and Non-Major Bleeds



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).

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).

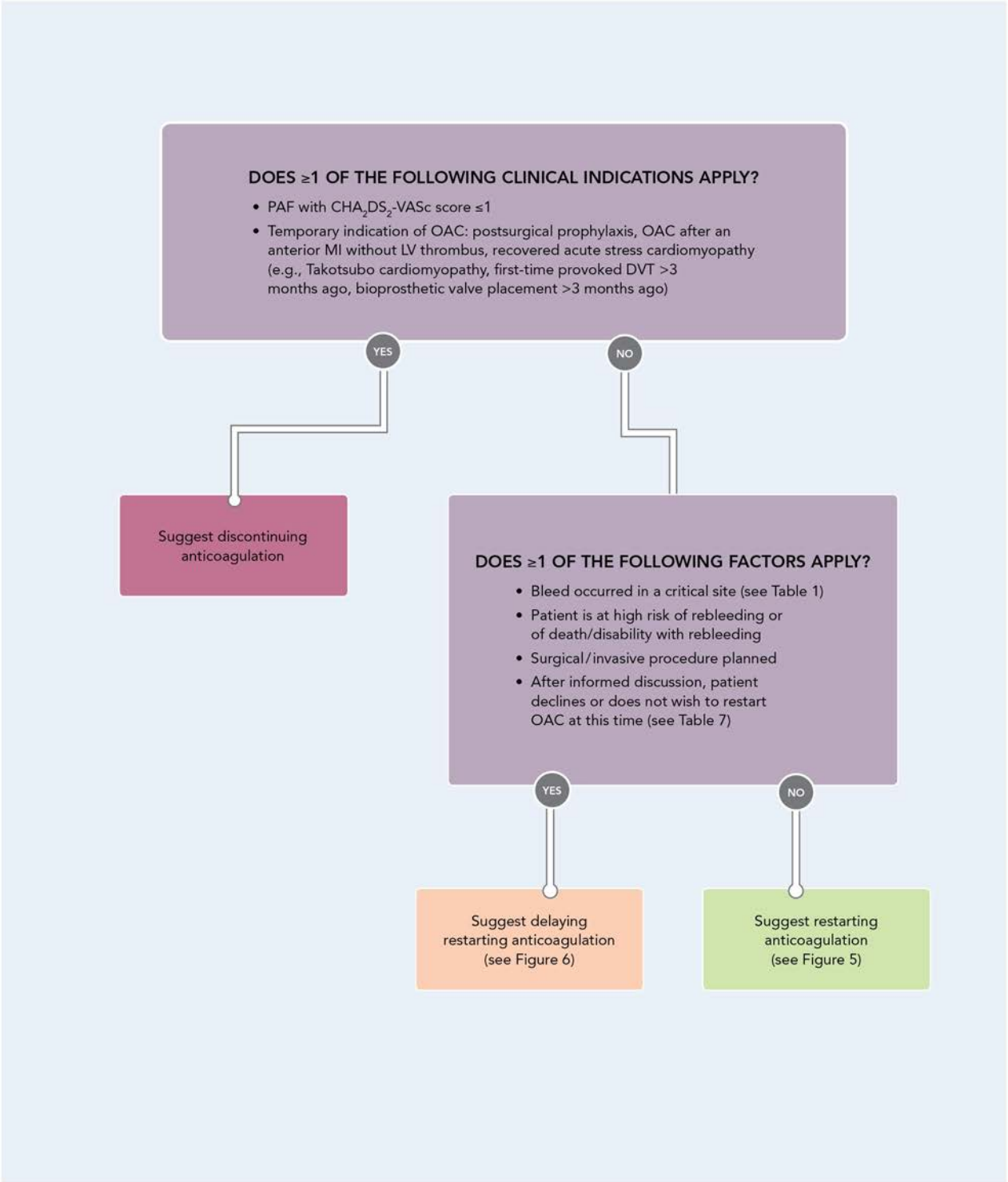
† When PCCs are used to reverse VKAs, VitK should also always be given (see Figure 2 for dosing guidance).

‡ 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.

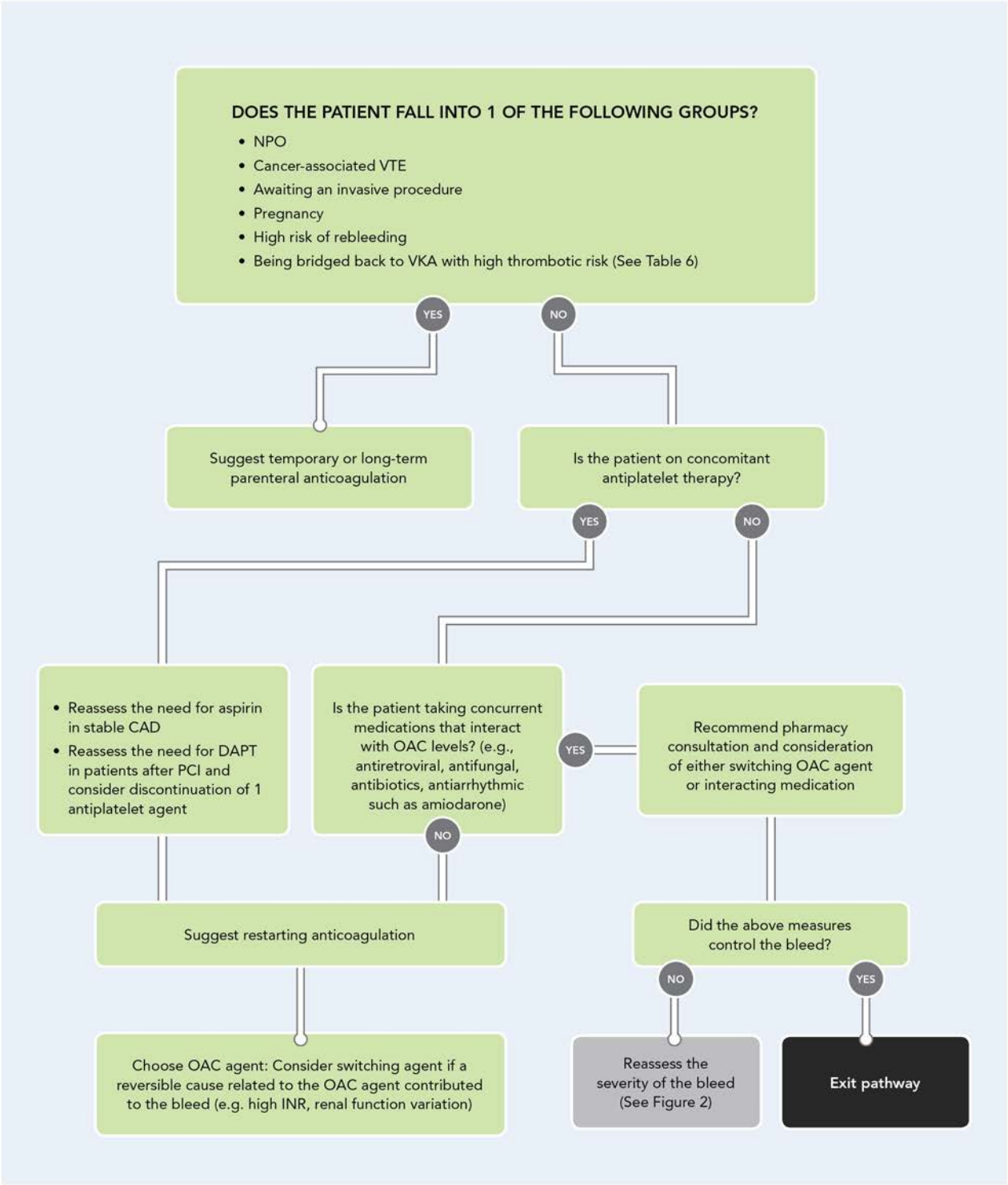
1. Sarode R, Milling TJ, Jr., Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013; 128:1234-43.

FIGURE 4.
Considerations for Restarting Anticoagulation



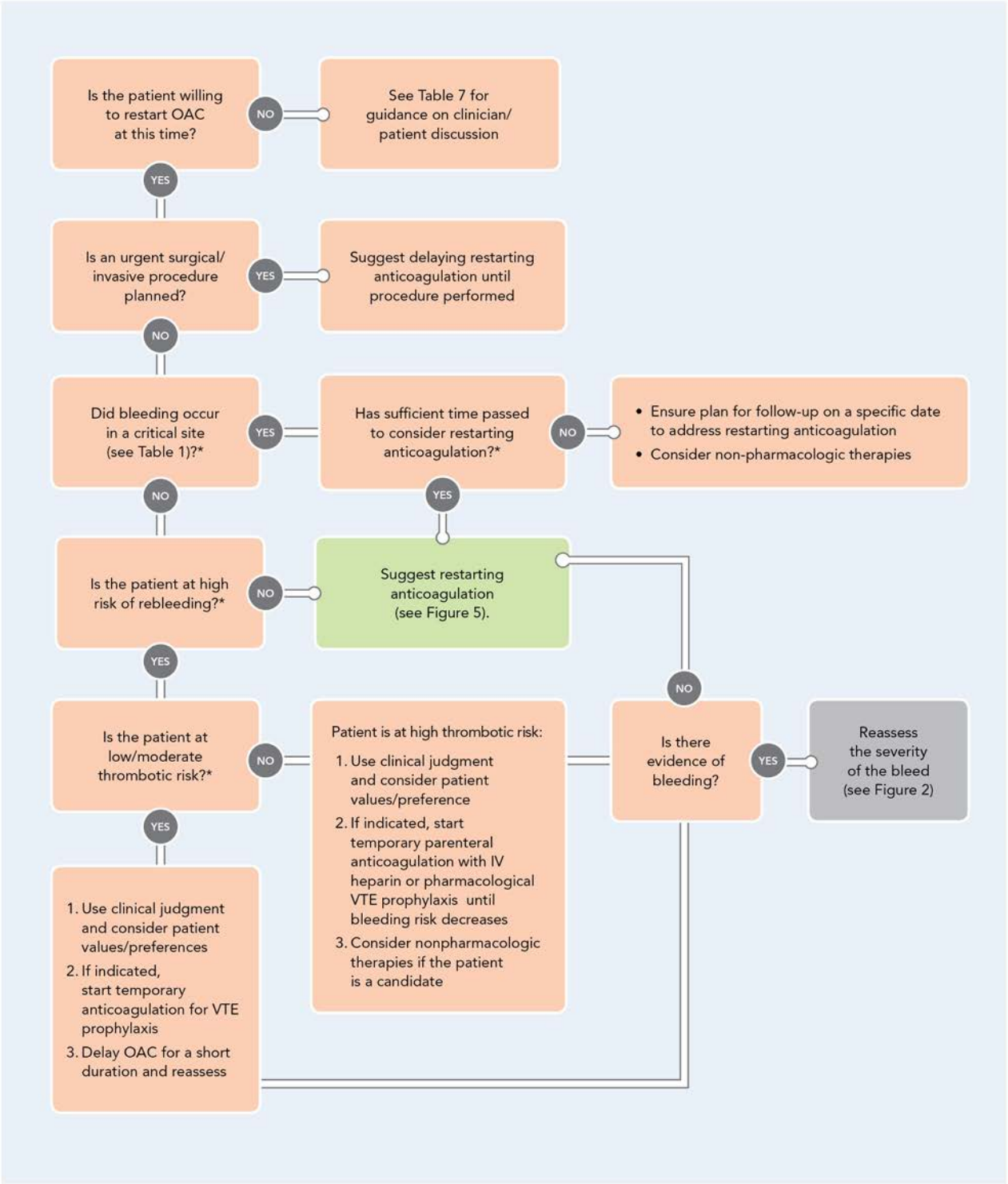
AF = atrial fibrillation; CHA2DS2-VASc = clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; LV = left ventricular; MI = myocardial infarction; OAC = oral anticoagulant, including VKAs and DOACs; PAF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

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.

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.

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.

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.

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.

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.

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.

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.

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.

Expert Consensus Decision Pathways

ACC has modernized Expert Consensus Documents to target key points of care with concise decision pathways rather than the traditional longer documents. These newly rebranded Expert Consensus Decision Pathways (ECDPs) leverage the expert insights drawn from a multidisciplinary group of experts and relevant stakeholders who are convened for Roundtables and Think Tanks often held as part of ACC quality programs.

ECDPs are intended to provide guidance for clinicians in areas where evidence may be limited, new and evolving, or lack sufficient data to fully inform clinical decision making. They include algorithms that are more actionable and can be translated into tools or apps to further accelerate the use of ACC clinical policy at point of care.

Translated Into Clinical Apps

While an app for bleed management is currently in development, the ACC offers a suite of clinical apps dedicated to improving quality of anticoagulation care.

AnticoagEvaluator App

This app helps clinicians make informed decisions on antithrombotic therapy for their non-valvular AFib patients. The app calculates a patient's CHA_2DS_2-VASc and HAS-BLED scores to provide an assessment of stroke and bleed risk associated with therapeutic options vs. no therapy, and calculates creatinine clearance to provide accurate dosing.

BridgeAnticoag App

This app supports clinicians across specialties in safely managing anticoagulation around an invasive procedure for NVAF patients. The app calculates patient and procedural risk to provide individualized advice that balances bleed and stroke risk. Clinicians can use the app to assess whether and when to interrupt, whether and how to bridge, and how to restart anticoagulation.

To access other relevant ACC mobile tools and apps, visit ***ACC.org/Apps***