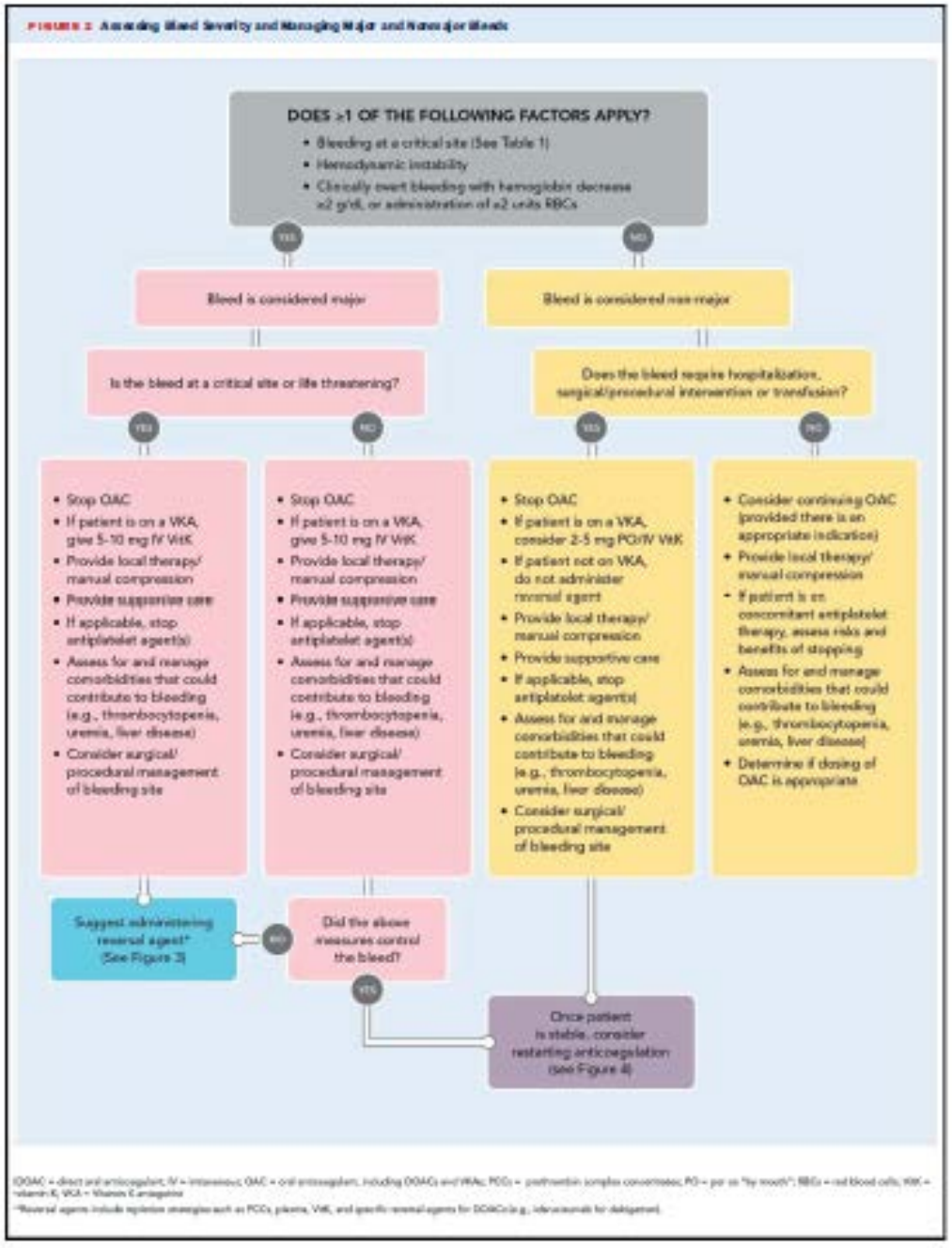


No-majorでなければ
全て中止する必要はないようです
しかし十分な管理、精査が必要となります。

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.

消化管出血は重大な部位とはなっていませんので直ぐに中止のではなく、十分な管理体制下の範疇です。

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.

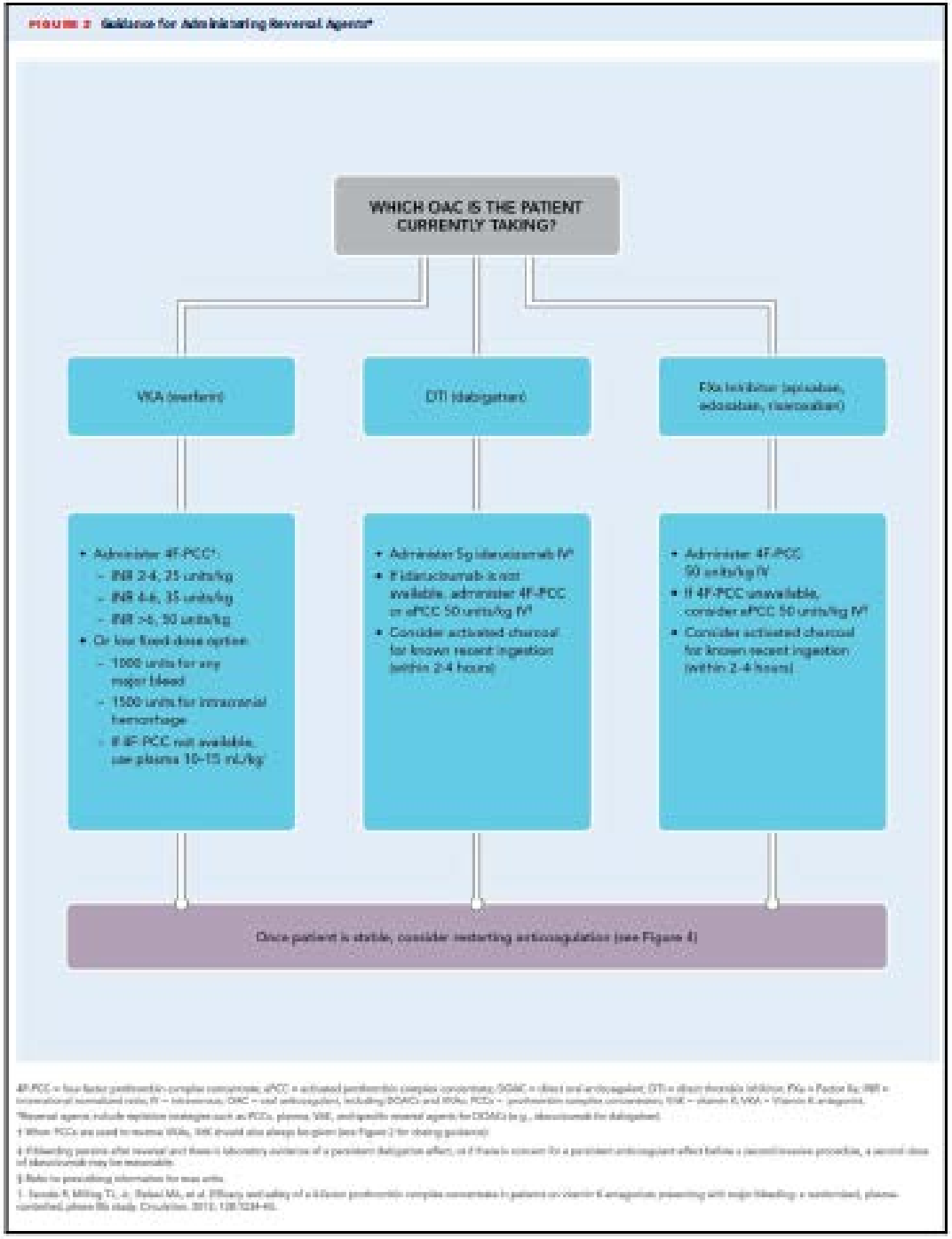
TABLE 3 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are not Available

	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.

プラザキサはaPTTで正常なら出血を誘発する事はないかもしれません。
　延長している場合は治療域か減量すべきか判断できません。
他のDOACはPTが正常でも延長の場合でも判断ができません。
　経過観察して前回の値との比較が有効かもしれません。


WHICH OAC IS THE PATIENT CURRENTLY TAKING?
VKA (warfarin)
DTI (dabigatran)
FXa inhibitor (apixaban, edoxaban, rivaroxaban)
• Administer 4F-PCC†:
– INR 2-4; 25 units/kg
– INR 4-6; 35 units/kg
– INR >6; 50 units/kg
• Or low fixed-dose option
– 1000 units for any major bleed
– 1500 units for intracranial hemorrhage
– If 4F-PCC not available, use plasma 10–15 mL/kg‡
• Administer 5g idarucizumab IV§
• If idarucizumab is not available, administer 4F-PCC or aPCC 50 units/kg IV‖
• Consider activated charcoal for known recent ingestion (within 2-4 hours)
• Administer 4F-PCC 50 units/kg IV
• If 4F-PCC unavailable, consider aPCC 50 units/kg IV‖
• Consider activated charcoal for known recent ingestion (within 2-4 hours)
Once patient is stable, consider restarting anticoagulation (see Figure 4)

中和剤の薬剤一覧表

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.

手術や処置で中断をする場合、その期間は出血のリスクの程度と腎機能により決定される。

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.

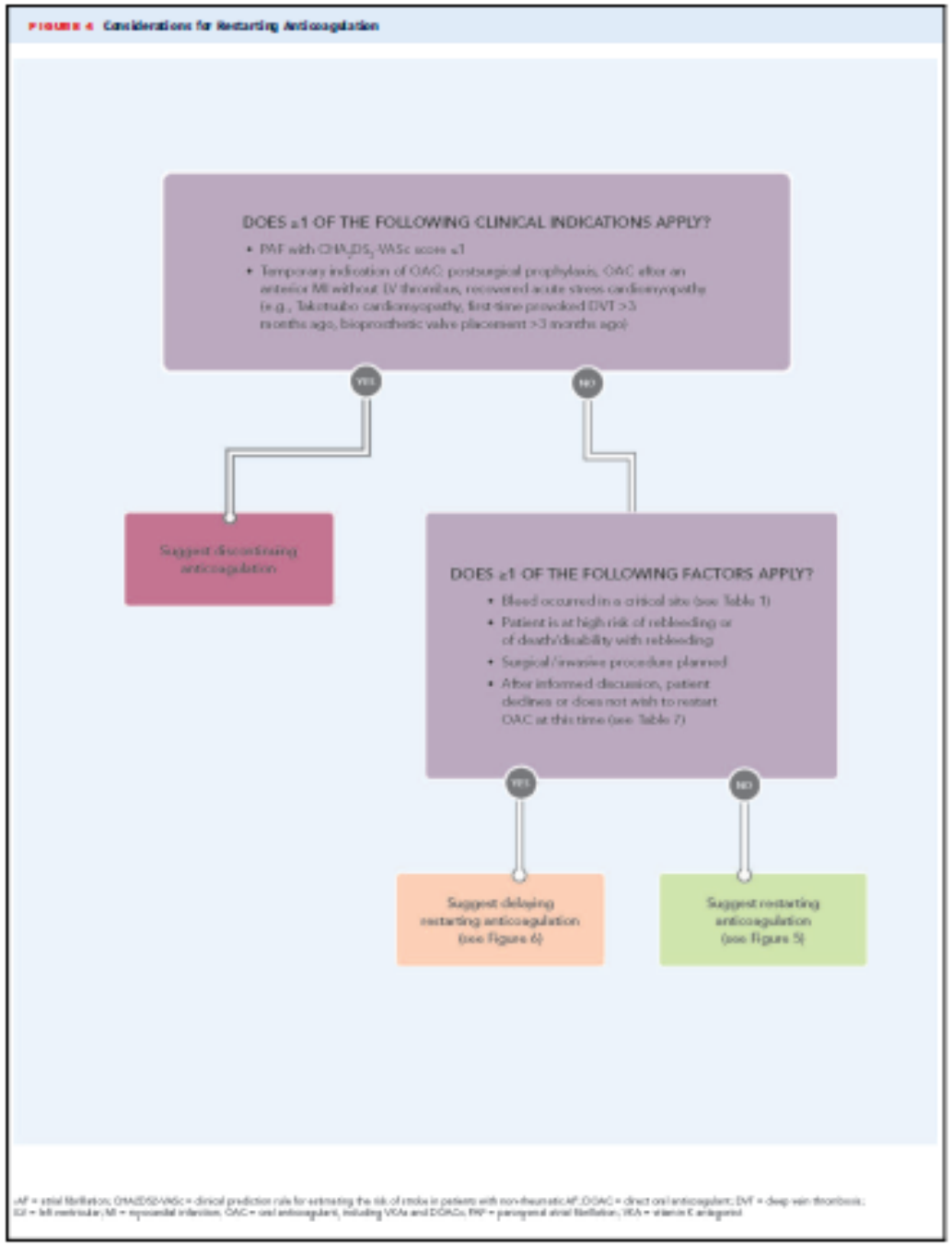


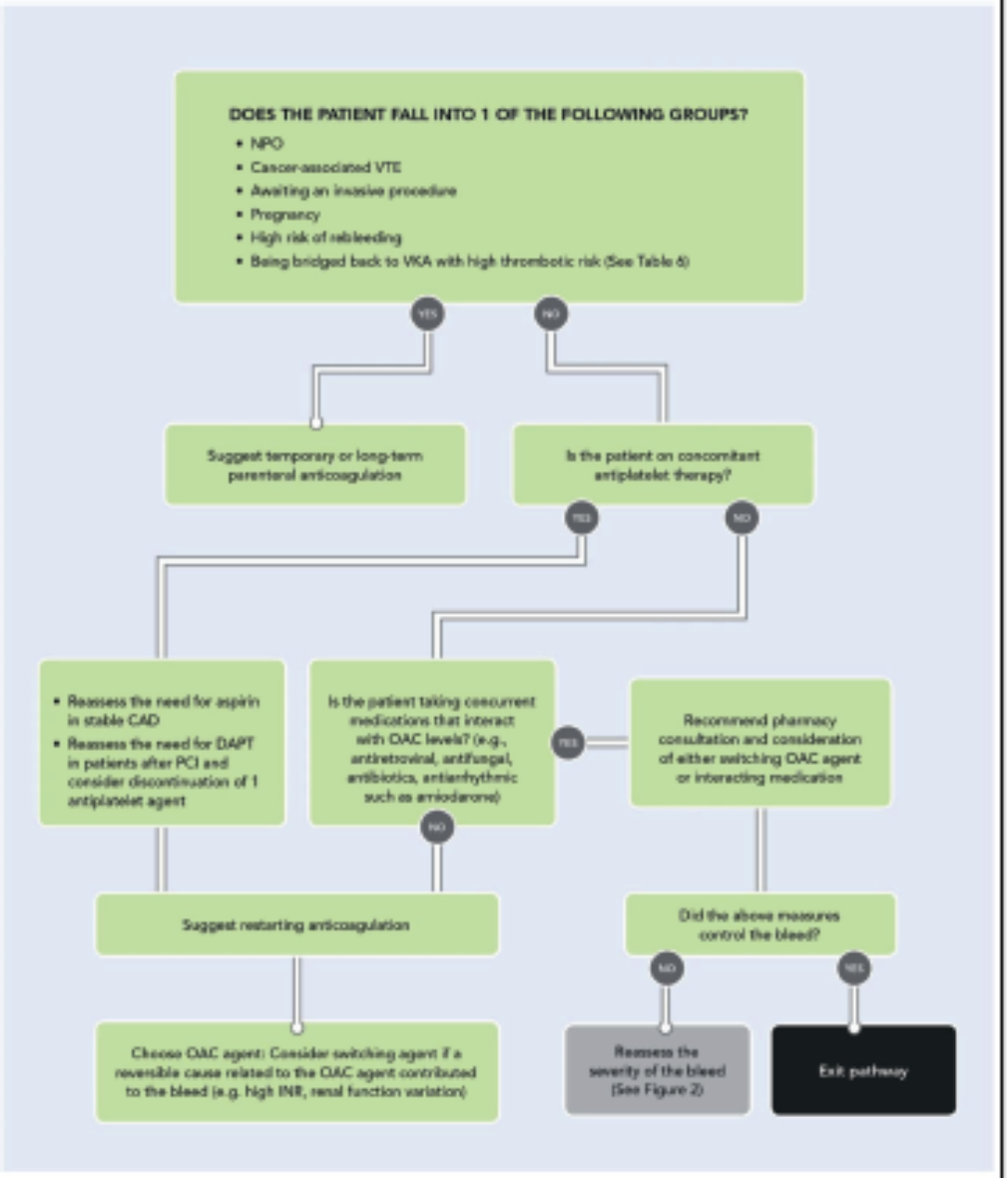
FIGURE 4 Considerations for Restarting Anticoagulation
DOES ≥1 OF THE FOLLOWING CLINICAL INDICATIONS APPLY?
• PAF with CHA2DS2-VASc score ≥1
• Temporary indication of OAC: postsurgical prophylaxis, OAC after an anterior MI without LV thrombus, recovered acute stress cardiomyopathy (e.g., Takotsubo cardiomyopathy, first-time provoked DVT >3 months ago, bioprosthetic valve placement >3 months ago)
YES
NO
Suggest discontinuing anticoagulation
DOES ≥1 OF THE FOLLOWING FACTORS APPLY?
• Bleed occurred in a critical site (see Table 1)
• Patient is at high risk of rebleeding or of death/disability with rebleeding
• Surgical/invasive procedure planned
• After informed discussion, patient declines or does not wish to restart OAC at this time (see Table 2)
YES
NO
Suggest delaying restarting anticoagulation (see Figure 6)
Suggest restarting anticoagulation (see Figure 5)

再投与の仕方

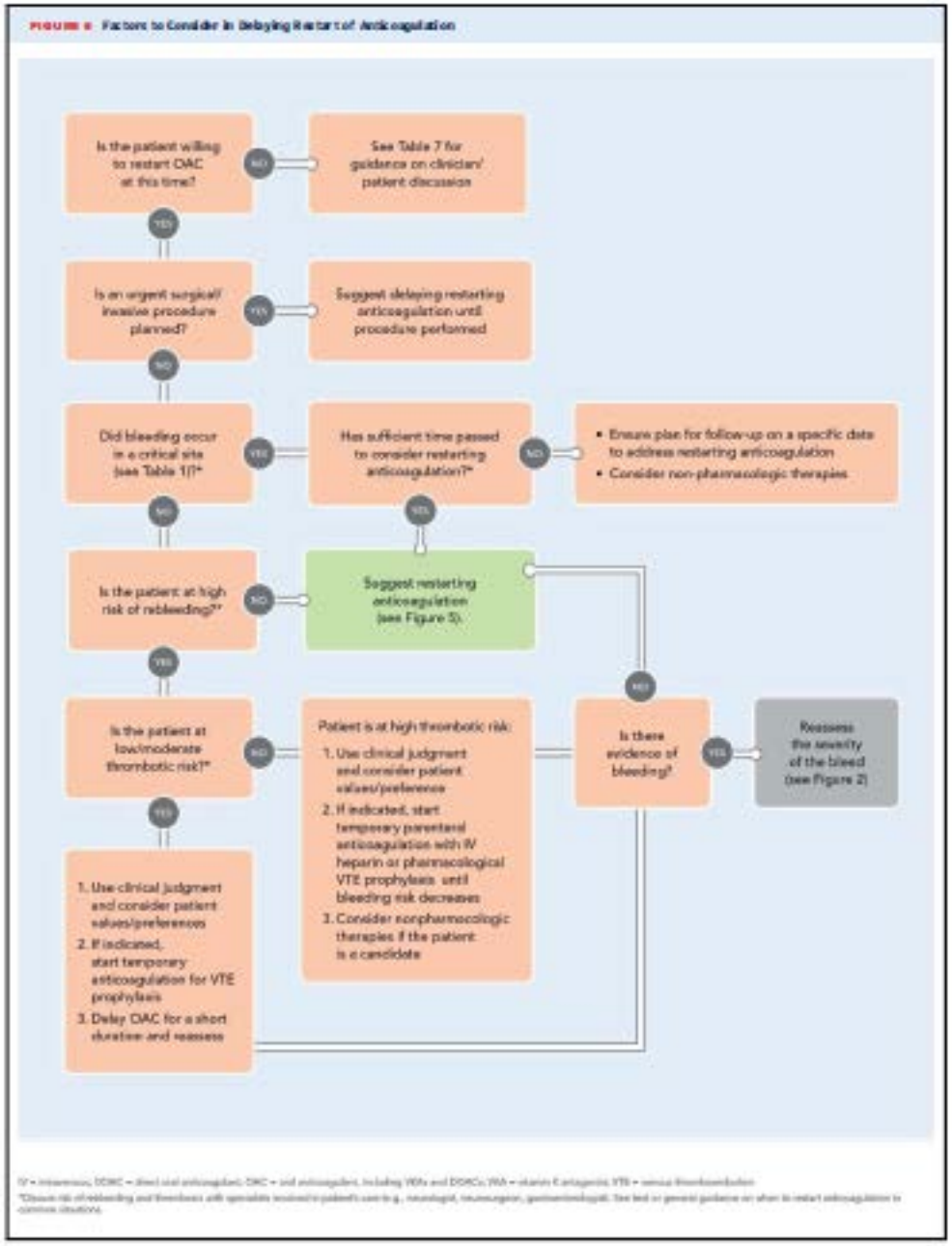
TABLE 6 Indications for Anticoagulation With High Thrombotic Risk

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

FIGURE 3 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.


Is the patient willing to restart OAC at this time?
NO
See Table 7 for guidance on clinician/patient discussion
YES
Is an urgent surgical/invasive procedure planned?
YES
Suggest delaying restarting anticoagulation until procedure performed
NO
Did bleeding occur in a critical site (see Table 1)?*
YES
Has sufficient time passed to consider restarting anticoagulation?*
NO
• Ensure plan for follow-up on a specific date to address restarting anticoagulation
• Consider non-pharmacologic therapies
YES
NO
Is the patient at high risk of rebleeding?*
NO
Suggest restarting anticoagulation (see Figure 3).
YES
Is the patient at low/moderate thrombotic risk?*
NO
Patient is at high thrombotic risk:
1. Use clinical judgment and consider patient values/preference
2. If indicated, start temporary parenteral anticoagulation with IV heparin or pharmacological VTE prophylaxis until bleeding risk decreases
3. Consider nonpharmacologic therapies if the patient is a candidate
YES
1. Use clinical judgment and consider patient values/preferences
2. If indicated, start temporary anticoagulation for VTE prophylaxis
3. Delay OAC for a short duration and reassess
NO
Is there evidence of bleeding?
YES
Reassess the severity of the bleed (see Figure 2)

再開の延期

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.

上記の事について十分に患者さんとコンセンサス得る事が大事です。