VENTURA COUNTY HEALTH CARE AGENCY

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CPG.56 Management of Bleeding Associated with Anticoagulants and Antiplatelet Therapies

The contents of this clinical practice guideline are to be used as a guide. Healthcare professionals should use sound clinical judgment and individualize patient care. This CPG is not meant to be a replacement for training, experience, CME or studying the latest literature and drug information.

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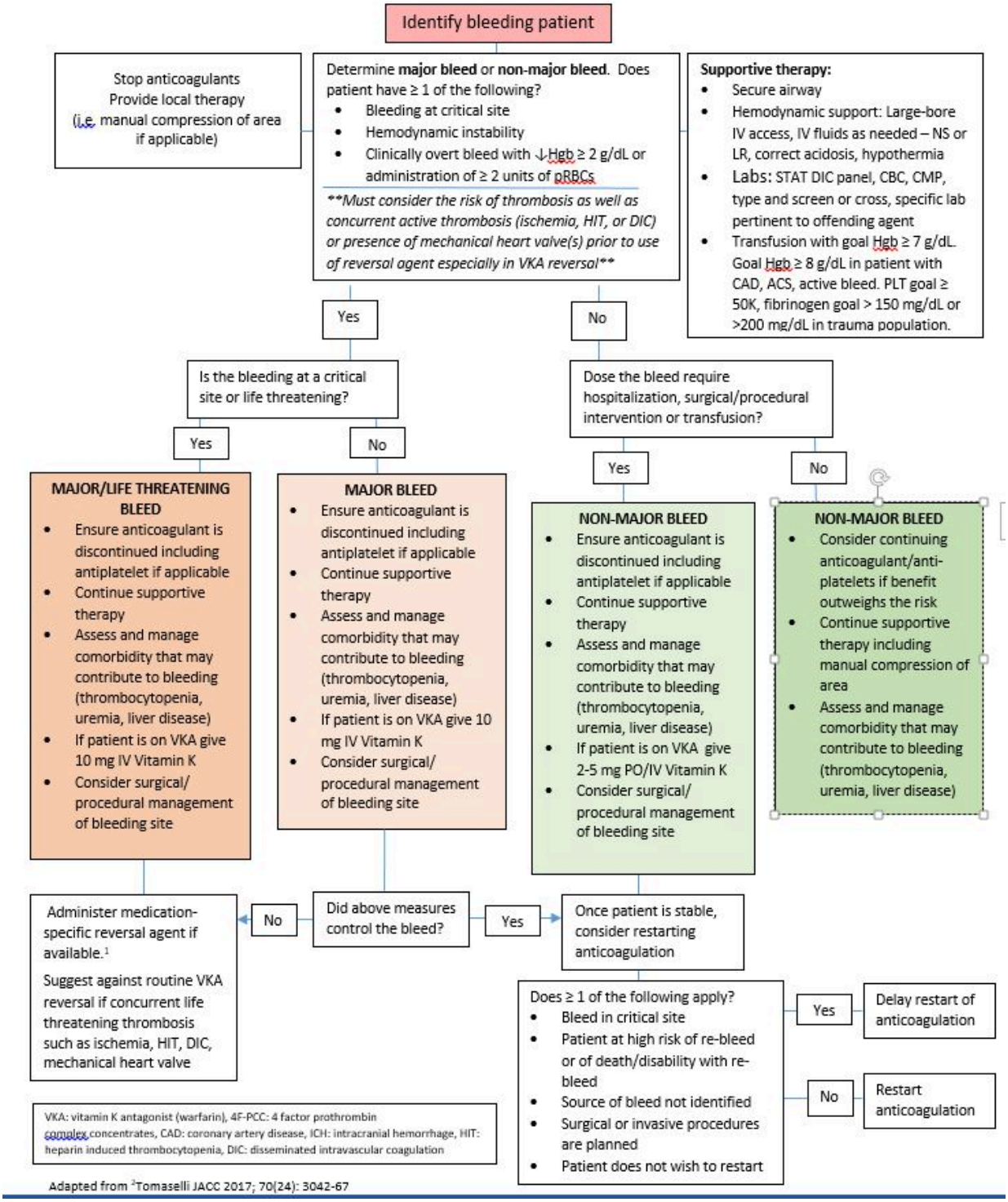
Summary Diagram



CLINICAL PEARLS OF MANAGING MAJOR AND NON-MAJOR BLEEDS[2]

Major Bleed

- Consider the risk and benefits of reversal of anticoagulation in the setting of concurrent life- threatening clot.
- Reversal of anticoagulant is recommended if available. See below for individual medication.
- Obtaining local hemostatic measures and resuscitation should be implored while waiting for reversal agent.
- Recommend using NS or LR while being mindful of potential development of hyperchloremic acidosis with aggressive use of NS. No benefit of colloids over crystalloids have been identified.
- Consider Massive Transfusion Protocol (MTP) when patient is requiring ≥ 3 units of pRBC within 1 hour.
- Consider adjunctive therapy with tranexamic acid and/or desmopressin.
- Use of blood product and adjunctive therapy may also be guided by use of rotational thromboelastometry (ROTEM) technology.

Non-Major Bleed

- Reversal of anticoagulant is not routinely recommended.
- For the decision to hold offending medication temporarily until patient is clinically stable and when to restart the therapy, consider the following:
  - Intensity of anticoagulation desired/needed
  - Nature of bleed
  - Need for invasive procedure or hospital admission
    - Refer to VCMC/SPH perioperative management of antithrombotic therapy document.

ASSESSING BLEED SEVERITY[2]

Bleeding Classification and Signs/Symptoms

- Major Bleed
  - A. Bleeding associated with hemodynamic compromise
    - i. Tachycardia (usually first sign)
    - ii. Systolic blood pressure < 90 mmHg or decrease of more than 40 mmHg from baseline
    - iii. Orthostatic blood pressure change (SBP ↓ ≥ 20 mmHg or DBP ↓ ≥ 10 mmHg)
    - iv. Mean arterial pressure (MAP) < 65 mmHg
    - v. Clinical surrogate marker for organ perfusion (i.e. urine output < 0.5 mL/kg/h)
  - B. Occurs in an anatomically critical site

CRITICAL SITE	TYPES OF BLEED	SIGNS AND SYMPTOMS
INTRACRANIAL	Intraparenchymal, subdural, epidural, subarachnoid	Intense headache, emesis, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures
OTHER CENTRAL NERVOUS	Intraocular	Eye pain, vision changes, blindness
	Intra- or extra-axial spinal	Back pain, weakness or numbness, bowel or bladder dysfunction, respiratory failure
CARDIAC	Pericardial tamponade	SOB, tachycardia, hypotension, JVD, tachypnea, muffled heart sounds, rub
AIRWAY	Posterior epistaxis	Hemoptysis, SOB, hypoxia
GASTROINTESTINAL	Hemothorax	Tachypnea, tachycardia, hypotension
	Intra-abdominal	Abdominal pain, distension, hypotension, tachycardia
	Retroperitoneal	Back/flank/hip pain, tachycardia, hypotension
EXTREMITY	Intra-articular	Joint pain, swelling, decreased range of motion
	Intramuscular	Pain, swelling, pallor, paresthesia, weakness, diminished pulse

  - C. Hemoglobin drop of ≥ 2 g/dL or requires transfusion (≥ 2 units of packed RBCs)
    - i. This is useful for bleeding event during hospitalization.
    - ii. Patients who present to the hospital with an acute bleed, initial hemoglobin may be artificially high/ normal due to hemoconcentration.
- Non-Major Bleed
  - A. All other bleeding that is not considered a major bleed.

LABORATORY MEASUREMENTS[2]

- DIC panel: aPTT, PT/INR, fibrinogen, D-dimer
- CBC
- CMP
- Type and screen for minor bleed
- Type and cross and hold for major bleed with high probability of transfusion
  - American Association of Blood Bank (AABB) benchmark is > 50% of type and crossed blood should result in actual transfusion
- Any of the following lab pertinent to individual medication

Medications	Pertinent laboratory values
Heparin	aPTT, anti-Xa unfractionated heparin
Enoxaparin	Anti-Xa LMWH Note: PT and aPTT are not adequate for monitoring anticoagulant effects
Fondaparinux	Anti-Xa – not available at VCMC/SPH Note: PT or aPTT is not useful monitoring tool because the medication does not inactivate thrombin.
Argatroban	aPTT
Alteplase	Fibrinogen
Warfarin	PT/INR
Dabigatran	Ecarin clotting time (ECT) and Thrombin time (TT) are most useful; however, not available at VCMC/SPH *aPTT
Apixaban	Anti-Xa specific for each drug is most useful; however, the specific therapeutic range has not been determined. Also, this is not available at VCMC/SPH. *PT/INR and aPTT are insensitive to apixaban.
Rivaroxaban Edoxaban	Anti-Xa specific for each drug is most useful; however, specific therapeutic range have not been determined. Also, this is not available at VCMC/SPH. *May also prolong PT/INR.
***Prolonged PT/INR or aPTT suggest therapy or above-therapy levels are present. Normal PT/INR or aPTT does not exclude therapy or above-therapy levels.**	

BLOOD PRODUCTS[2]

For patients who require ≥ 3 units of pRBCs within one (1) hour, activate massive transfusion protocol (MTP). May consider the use of rotational thromboelastometry (ROTEM) to target blood product use.

Laboratory values	Goal	Blood product to use
Hemoglobin	≥ 7 g/dL	Packed Red Blood Cell (pRBC)
Hemoglobin in patient with coronary artery disease/ACS, active bleeding	≥ 8 g/dL	pRBC
Platelets	≥ 50 x 10^9/L	Platelets
Fibrinogen	> 150 mg/dL	Cryoprecipitate
INR	< 1.5	*Fresh Frozen Plasma (FFP)
*For warfarin related elevation in INR, see page 11 ****		

ADJUNCTIVE MEDICATIONS[2]

Medication	Desmopressin acetate[3]
Mechanism of action	Desmopressin is a synthetic analogue of an antidiuretic hormone. It is more potent than arginine vasopressin (naturally occurring) in increasing plasma levels of factor VIII activity. It also increases platelet membrane glycoprotein expression. Onset: ~1 hour, Duration: ~4-8 hours
Dose	0.3 mcg/kg IVPB
Administration	Intravenously over 30 minutes.
Clinical pearls	• Potentially useful in patients with platelet dysfunction from uremia. • See dosing and recommendation for bleeding in the setting of antiplatelet use below under "Antiplatelet" section. • Be aware there are many formulations of desmopressin available. • Tachyphylaxis may develop with repeated doses. • Decrease in urine output and hyponatremia may occur.

Medication	Tranexamic acid[4]
Mechanism of action	Tranexamic acid has antifibrinolytic effects by stabilizing fibrin matrix through competitive inhibiting plasminogen activation. It is about 10 times more potent than aminocaproic acid.
Dose	• 1 gram IVPB over 10 minutes, usually followed by 1 gram IVPB over 8 hours. • Post-Partum Hemorrhage within 3 hours of birth:[5] 1 gram IVPB over 10 minutes. Repeat dose of 1 gram IVPB over 10 minutes if bleeding continues after 30 minutes of initial dose.
Administration	IV bolus over 10 minutes as well as infusion over 8 hours.
Clinical pearls	• Use embedded into VCMC/SPH massive transfusion protocol. • Patients benefit the most if tranexamic acid is given within 3 hours of major bleed related to traumatic event (CRASH 2 trial). • Also utilized in peri- and postoperatively, Jehovah Witness patients who do not want blood transfusions, spontaneous intracranial bleeds (CRASH 3 trial - pending results).

ANTICOAGULANT SPECIFIC REVERSAL STRATEGIES[2]

PARENTERAL

Unfractionated heparin (UFH)[6,7]

Heparin is a glycosaminoglycan which combines with antithrombin III (AT III) and blocks thrombosis by inactivating activated factor X and ultimately inhibiting prothrombin's (factor II) conversion to thrombin (activated factor II).

Medication specific reversal agent	Protamine sulfate
Mechanism of action	Alkaline protamine sulfate ionically combines with heparin to form a stable complex and thereby neutralizing the anticoagulant effects of heparin.
Dose	• 1 mg of protamine intravenously for every 100 units of UFH administered over the last 3 hours. • Maximum of 50 mg per dose.
Administration	Intravenously over 10 minutes.
Clinical pearls	• ◦ Use of protamine may cause bradyarrhythmia, hypotension, anaphylactoid reaction, pulmonary edema. ◦ Decision to use protamine should be based on the severity of bleed (see page 4) and be reserved for those with major life threatening bleed - bleeding at a critical location who may need emergent surgery. ◦ For hemodynamically stable patient with potential bleed from a non-life threatening area, holding heparin infusion or doses with close continued monitoring may be sufficient. ◦ Heparin has a short half-life of 90 minutes. ◦ Prophylactic doses of heparin are not routinely reversed unless aPTT is significantly elevated.

Low molecular weight heparin – enoxaparin (Lovenox)[7,8]

Enoxaparin inhibits factor Xa and IIa (thrombin) activity. This will result in decreased conversion of fibrinogen to fibrin and subsequently inhibiting fibrin-mediated clot formation. Enoxaparin has a higher ratio of anti-factor Xa to anti-factor IIa activity compared to heparin.

Medication specific reversal agent	**Protamine sulfate**
Mechanism of action	Alkaline protamine sulfate ionically combines with heparin to form a stable complex and thereby neutralizing the anticoagulant effects of heparin. Due to the different ratio of anti-factor Xa and IIa activity compared to heparin, protamine is only able to partially neutralize the effects of enoxaparin (~60%).
Dose	• ◦ If enoxaparin administered ≤ 8 hours: 1 mg of protamine intravenously for every 1 mg of enoxaparin. ◦ If enoxaparin administered > 8 hours or second dose is required: 0.5 mg of protamine intravenously for every 1 mg of enoxaparin. ◦ Maximum of 50 mg per dose.
Administration	Intravenously over 10 minutes.
Clinical pearls	• ◦ May cause bradyarrhythmia, hypotension, anaphylactoid reaction, pulmonary edema. ◦ Protamine may not be necessary if enoxaparin was administered ≥ 12 hours ago. ◦ Decision to use protamine should be based on the severity of bleed (see page 4) and be reserved for those with major life threatening bleed - bleeding at a critical location who may need emergent surgery. ◦ Prophylactic doses of enoxaparin are not routinely reversed unless anti-Xa LMWH is significantly elevated.

Factor Xa inhibitor - fondaparinux (Arixtra)[2,9,10]

Fondaparinux selectively binds to antithrombin III (ATIII) and inhibits factor Xa to prevent thrombus development.

Medication specific reversal agent	**None available**
Adjunctive therapy	Recombinant factor VIIa (NovoSeven) may be used (low quality of evidence) Hemodialysis
Mechanism of action	Recombinant factor VIIa is structurally similar to human factor VIIa. It promotes hemostasis through activation of the intrinsic coagulation pathway.
Dose	Recombinant factor VIIa 90 mcg/kg IV bolus
Administration	Give IV over 2-5 minutes.
Clinical pearls	• Discontinuation of medication and supportive therapy is main treatment. • Half-life may be extended in those with renal impairment. • About 20% of fondaparinux may be cleared by hemodialysis. • Fondaparinux use is restricted within VCMC/SPH for use only in those who have documented heparin induced thrombocytopenia (HIT).

Argatroban[11,12]

Argatroban is a selective direct thrombin inhibitor. It reversibly inhibits the catalytic site of thrombin. This will result in inhibition of conversion of fibrinogen to fibrin, thrombin-antithrombin III complex formation, platelet aggregation, activation of coagulation factors V, VIII, and XIII, protein C.

Medication specific reversal agent	**None available**
Adjunctive therapy	4 Factor Prothrombin Complex Concentrate (4F-PCC)
Mechanism of action	4F-PCC contains vitamin K dependent coagulation factors II, VII, IX, X and protein C and S derived from pulled human blood. By providing the factors it initiates the coagulation cascade. See Vitamin K antagonist section for further details.
Dose	4F-PCC 50 units/kg IVPB x1 (Max dose: 5,000 units)
Administration	4F-PCC: Infusion not to exceed 8.4 mL/min (typically administered within 10 minutes)
Clinical pearls	• Argatroban half-life is 30 to 51 minutes. • This short half-life may be extended to 181 minutes in those with hepatic impairment. • Do not use rFVIIa (NovoSeven) or FFP[1]

Thrombolytics - Alteplase[1,13,14]

Alteplase is a tissue plasminogen activator. It enhances the conversion of plasminogen to plasmin which initiates fibrinolysis.

Medication specific reversal agent	**Tranexamic acid**
Adjunctive therapy	Cryoprecipitate
Mechanism of action	Tranexamic acid has antifibrinolytic effects by stabilizing fibrin matrix through competitive inhibiting plasminogen activation. It is about 10 times more potent than aminocaproic acid.
Dose	Tranexamic acid 1000 mg IVPB x1 Cryoprecipitate 10 units
Administration	Tranexamic acid: Infuse over 10 minutes Cryoprecipitate: Infuse over 10-30 minutes
Clinical pearls	• Additional doses of cryoprecipitate may be administered based on fibrinogen levels with goal of > 150 mg/dL. • Platelet transfusion are not recommended by the 2018 AHA/ASA guideline on ischemic stroke management.[13] • No recommendation was provided by the Neurocritical care society (2016)[1] nor AHA/ASA Ischemic Stroke guideline (2018)[13] regarding platelet transfusion in the setting of ICH from alteplase use.

ENTERAL

Vitamin K antagonist (VKA) - warfarin[12,15,16]

Warfarin inhibits the regeneration of vitamin K epoxide. This will inhibit the synthesis of vitamin-K dependent clotting factors: factor II, VII, IX, X, protein C, and protein S.

Medication specific reversal agent	• **Phytonadione (Vitamin K) +** • **4-factor prothrombin complex concentrate (4F-PCC) - Kcentra**
Adjunctive therapy	• Fresh frozen plasma (FFP) – only if 4F-PCC is not available.
Mechanism of action	• *Phytonadione* provide vitamin that is necessary for the synthesis of factor II, VII, IX, and X. Its ability to restore intrinsic hepatic carboxylation of vitamin K dependent clotting factor is dose dependent. • *4 Factor Prothrombin complex concentrate* contains vitamin K dependent coagulation factors II, VII, IX, X and protein C and S derived from pulled human blood. By providing the factors that have been suppressed by the use of VKA, it initiates coagulation cascade.

Ingredient	Factor half-life (hrs)	Content per 500 unit vial	Content per 1,000 unit vial
Factor II	60 – 72	380 – 800 units	760 – 1,600 units
Factor VII	4 – 6	200 – 500 units	400 – 1,000 units
Factor IX	20 – 30	400 – 620 units	800 – 1,240 units
Factor X	24 – 40	500 – 1,020 units	1,000 – 2,040 units
Protein C	8 – 10	420 – 820 units	840 – 1640 units
Protein S	40 – 60	240 – 680 units	480 – 1360 units
Heparin		8-40 units	16-80 units
Antithrombin III		4-30 units	8-60 units
Sodium citrate		40-80 mg	80-160 mg

- Onset of action

Medication	Route	Onset of action
Phytonadione	Intravenous	4-6 hours
	Oral	18-24 hours
	Subcutaneous	Not recommended
4F-PCC	Intravenous	20 - 30 minutes

<table>
<tr><td></td><td></td></tr>
<tr><td>Dose</td><td></td></tr>
<tr><td>Major/Life threatening bleed</td><td>Phytonadione 10 mg IVPB over 60 minutes <u>AND</u> 4F-PCC based on table below
<table>
<tr><th>4F-PCC Kcentra</th><th>INR</th><th>Dose (Units/kg)*</th><th>Maximum (Units)</th></tr>
<tr><td></td><td>2 – 3.9</td><td>25</td><td>2,500</td></tr>
<tr><td></td><td>4 – 6</td><td>35</td><td>3,500</td></tr>
<tr><td></td><td>> 6</td><td>50</td><td>5,000</td></tr>
</table>
*Dosing based on Factor IX content of 4F-PCC</td></tr>
<tr><td>Non-major bleed</td><td>• Routine use of reversal agent is not recommended.
• It is imperative to assess the thrombosis risk before considering administration of phytonadione due to delayed onset of action as well as longer duration of action.
• May consider the use of phytonadione 2 – 5 mg IV/PO* if patient needs transfusions, hospitalization, urgent procedure.

*Onset of action is different based on route of administration.</td></tr>
<tr><td>Elevated INR without bleed[17]</td><td>
<table>
<tr><th>INR</th><th>Action</th></tr>
<tr><td>< 4.5</td><td>Hold warfarin, restart once INR is therapeutic at a lower dose.</td></tr>
<tr><td>4.5-10</td><td>Hold warfarin, restart once INR is therapeutic at a lower dose.
Do not recommend use of phytonadione. Phytonadione compared to placebo resulted:
• Major bleeding event was similar
• Thromboembolism rates were similar</td></tr>
<tr><td>> 10</td><td>Hold warfarin.
Use ORAL phytonadione 2.5 mg
Resume warfarin once INR is therapeutic at a lower dose.</td></tr>
</table>
</td></tr>
<tr><td>No bleeding + Need to reversal for procedure[18]</td><td>• Interrupt therapy only if procedure has uncertain, intermediate, or high bleed risk
• Refer to CPG periprocedural management of anticoagulation for complete recommendation.
<table>
<tr><th>INR</th><th>Action</th></tr>
<tr><td>1.5-1.9</td><td>Hold warfarin for 3 – 4 days if normal INR is desired</td></tr>
<tr><td>2-3</td><td>Hold warfarin for 5 days
Recheck INR within 24 hours of the procedure</td></tr>
<tr><td>> 3</td><td>Hold warfarin for at least 5 days.
Recheck INR within 24 hours of the procedure</td></tr>
</table>
</td></tr>
<tr><td>Administration</td><td>Phytonadione: Infuse over 60 minutes
4F-PCC: Infusion not to exceed 8.4 mL/min (typically administered within 10 minutes)</td></tr>
<tr><td>Clinical pearls</td><td>• Potential anaphylaxis with phytonadione use – do not push IV phytonadione.
• Phytonadione will have a delayed onset of action; therefore, 4F-PCC is administered at the same time in major life threatening bleed.
• High doses of phytonadione use can lead to warfarin resistance in those who will need to re-start anticoagulation with warfarin after stabilization.</td></tr>
</table>

	• Phytonadione may be re-dosed based on repeat INR in 24-48 hours from initial dose. • 4F-PCC is **contraindicated** in patients with **DIC, HIT**, known **anaphylaxis**. • Benefit of 4F-PCC use compared to fresh frozen plasma (FFP) transfusion are the following: ◦ No need to check for ABO compatibility ◦ Contains about 25 x the concentration of factors per volume ◦ Allows for faster infusion – about 8x faster • After 4F-PCC, INR should be measured within 1 hour to confirm decrease in INR then serially checked and re-dose with 4F-PCC if needed to meet goal INR. Repeated doses may *increase thrombotic complications*. • FFP should only be given *if* 4F-PCC is not available. Dose of FFP is 10-15 mL/kg.

Direct thrombin inhibitor - Dabigatran (Pradaxa)[19,20]

Dabigatran is an oral direct thrombin inhibitors and it inhibits both free and clot-bound thrombin as well as thrombin-induced platelet aggregation. This ultimately prevents thrombus development.

Medication specific reversal agent	**Idarucizumab (Praxbind)**
Adjunctive therapy	• Activated charcoal • Hemodialysis
Mechanism of action	Idarucizumab is a monoclonal antibody fragment that neutralizes the anticoagulant effect of dabigatran by binding to dabigatran and its metabolites.
Dose	Activated charcoal 50 grams if ingestion within 2 hours Idarucizumab 5 g (2.5 grams vial x 2 vials) IV bolus
Administration	Flush line with NS prior to infusion of idarucizumab Give as 2 consecutive IV bolus.

Clinical pearls	• Pharmacological reversal should be guided by clinical assessment of bleeding rather than laboratory testing.
	• Consider the use of activated charcoal for patient with recent ingestion within 2 hours, without gastrointestinal bleed, low aspiration risk, and without altered mental status.
	• When deciding to use idarucizumab, consider the following:
	  • Last dose anticoagulant administered
	  • Estimated time of initiation of bleed
	  • Half-life ($t_{1/2}$) of the anticoagulant: 12-17 hours, extend to 15-34 hours in renal impairment
	  • Possible drug – drug interaction
	• Idarucizumab should be administered when bleeding occurs within 3-5 x half-lives of drug exposure.
	• Dabigatran have high volume of distribution (50 – 70 L). After the initial dose of idarucizumab, redistribution of dabigatran from the adipose tissues back into the blood stream may cause continued bleeding.
	• There is limited data to support the use of second dose of Idarucizumab; however, may consider re-dose in 24 hours of initial dose for continued clinically significant bleed.
	• Dabigatran is dialyzable. Up to 77% can be dialyzed over 5-hour dialysis session.

Factor Xa inhibitor – apixaban, rivaroxaban, edoxaban[1,2,21-24]

Factor Xa inhibitors selectively inhibits factor Xa and does not require cofactor (antithrombin III) for activity.

Medication specific reversal agent	**Apixaban, rivaroxaban: Recombinant coagulation Factor Xa (Andexxa) – Not available at VCMC/SPH** **Edoxaban: None**
Adjunctive therapy	• Activated charcoal • 4 Factor Prothrombin Complex Concentrate (4F-PCC)
Mechanism of action	Recombinant coagulation factor Xa sequesters the factor Xa inhibitor (apixaban and rivaroxaban ONLY). It also inhibits the activity of tissue factor pathway inhibitor (TFPI) that increases tissue factor-initiated thrombin generation.
Dose	• Recombinant coagulation factor Xa is not available • Activated charcoal 50 grams if ingestion within 2 hours • 4F-PCC 50 units/kg IVPB x 1 (Max dose: 5,000 units)
Administration	4F-PCC: Infusion not to exceed 8.4 mL/min (typically administered within 10 minutes)
Clinical pearls	• Pharmacological reversal should be guided by clinical assessment of bleeding rather than laboratory testing. • Consider the use of activated charcoal for patient with recent ingestion within 2 hours, without gastrointestinal bleed, low aspiration risk, and without altered mental status. • Use of activated charcoal for recent ingestion of rivaroxaban is limited due to rapid absorption of the medication. • When deciding to use 4F-PCC, must deliberate the following: • Last dose anticoagulant administered • Estimated time of initiation of bleed • Half-life of the anticoagulant • Possible drug – drug interaction • 4F-PCC should be administered when bleeding occurs within 3-5 x half-lives of drug exposure. • Half-life of the factor Xa inhibitors are prolonged in the setting of renal or hepatic dysfunction.

Medication	Elimination	Half-life ($t_{1/2}$)	Extended $t_{1/2}$ in renal or hepatic dysfunction?
Apixaban	27% renal; majority fecal	12 hr	Yes
Rivaroxaban	66% renal; 28% fecal	5 hr	Yes
Edoxaban	50% renal	10-14 hr	Yes
Factor Xa inhibitors are not dialyzable.			

ANTIPLATELET THERAPY[1.3]

**It is controversial whether antiplatelet agents use influence incidence, morbidity, or mortality of intracranial hemorrhage. Utility of reversal is also unknown.

Medication specific reversal agent	**None**
Adjunctive therapy	• Desmopressin • Platelet transfusion *only if* undergoing neurosurgical procedure
Mechanism of action	Desmopressin is a synthetic analogue of an antidiuretic hormone. It is more potent than arginine vasopressin (naturally occurring) in increasing plasma levels of factor VIII activity. It also increases platelet membrane glycoprotein expression. Onset: ~1 hour, Duration: ~4-8 hours
Dose	• Desmopressin 0.3 mcg/kg IVPB x 1 dose • Platelet transfusion 1 single-donor apheresis unit
Administration	Desmopressin: Intravenously over 30 minutes.
Clinical pearls	• Platelet function is restored once 3-5 half-lives of antiplatelet agent have passed in those medications with reversible mechanism of action. • For those with irreversible platelet inhibition, even after stopping of the medication, normal platelet function is not restored until new platelets are synthesized. • Average life span of platelets: 8-20 days

Mechanism of action		**Medication**
Irreversible	COX 1 and 2 inhibitor	Aspirin
	P2Y12 ADP receptor inhibitor	Clopidogrel, prasugrel, ticlopidine
	GP2b/3a antagonist	Abciximab
Reversible	COX 1 and 2 inhibitor	Ibuprofen, naproxen
	Adenosine reuptake inhibitor	Dipyridamole
	P2Y12 ADP receptor inhibitor	Ticagrelor
	PDE III inhibitor	Cilostazol
	GP2b/3a antagonist	Eptifibatide, tirofiban

• Do not reverse bleed due to NSAIDS (ibuprofen, naproxen) or GP2b/3a antagonist even if neurosurgical intervention is needed.

CONSIDERATION FOR RESTARTING ANTICOAGULATION[2]

Evaluation of indication of anticoagulation

Scenario 1: Anticoagulation may potentially be *stopped.*

- Paroxysmal atrial fibrillation with CHA2DS2-VASc score ≤ 1.
- Initial use of anticoagulation was for a temporary indication such as postsurgical prophylaxis, anticoagulation after an anterior myocardial infarction without left ventricular thrombus, recovered acute stress cardiomyopathy (Takotsubo), first time provoked VTE > 3 months ago, or bioprosthetic valve placement > 3 months ago.

Scenario 2: Earlier restart of anticoagulation may be warranted once hemodynamically stable.

INDICATIONS WITH HIGH THROMBOTIC RISK	
Mechanical valve prosthesis	• Mechanical valve + AF or CHF or prior stroke/TIA • Caged-ball or tilting disc aortic valve prosthesis • Stroke/TIA within 6 months
Atrial Fibrillation (AF)	• AF with CHA2DS2-VASc score ≥ 6 • Stroke/TIA within 3 months • Stroke risk ≥ 10% per year • Rheumatic valve disease or mitral stenosis
Venous thromboembolism (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)	

Discussion with Patient on Risks and Benefits

Full discussion with patient (patient family) deliberating potential sequelae from both stopping or restarting anticoagulation is needed.

Timing

Patient should be clinically stable. Continue to have open communication with specialist (neurosurgery, cardiology, neurology, gastroenterology, etc) to discuss appropriate timing of restart.

Strategies

- Use "Decision tree for direct oral anticoagulants vs vitamin K antagonist vs parenteral anticoagulants" as a guide on proper selection of anticoagulants.
- Select medication with medication specific reversal agent.
- Select medication with shorter half-life.
- May start with parenteral prophylactic doses and escalate dose to full anticoagulation as tolerated.
- Full review of medication is needed to identify potential drug-drug interaction that may have contributed to bleeding event. This should include inpatient, outpatient, over the counter, and herbal medications.
- Consider renal and or liver dysfunction when selecting an agent.

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All revision dates: 8/19/2019, 8/13/2019

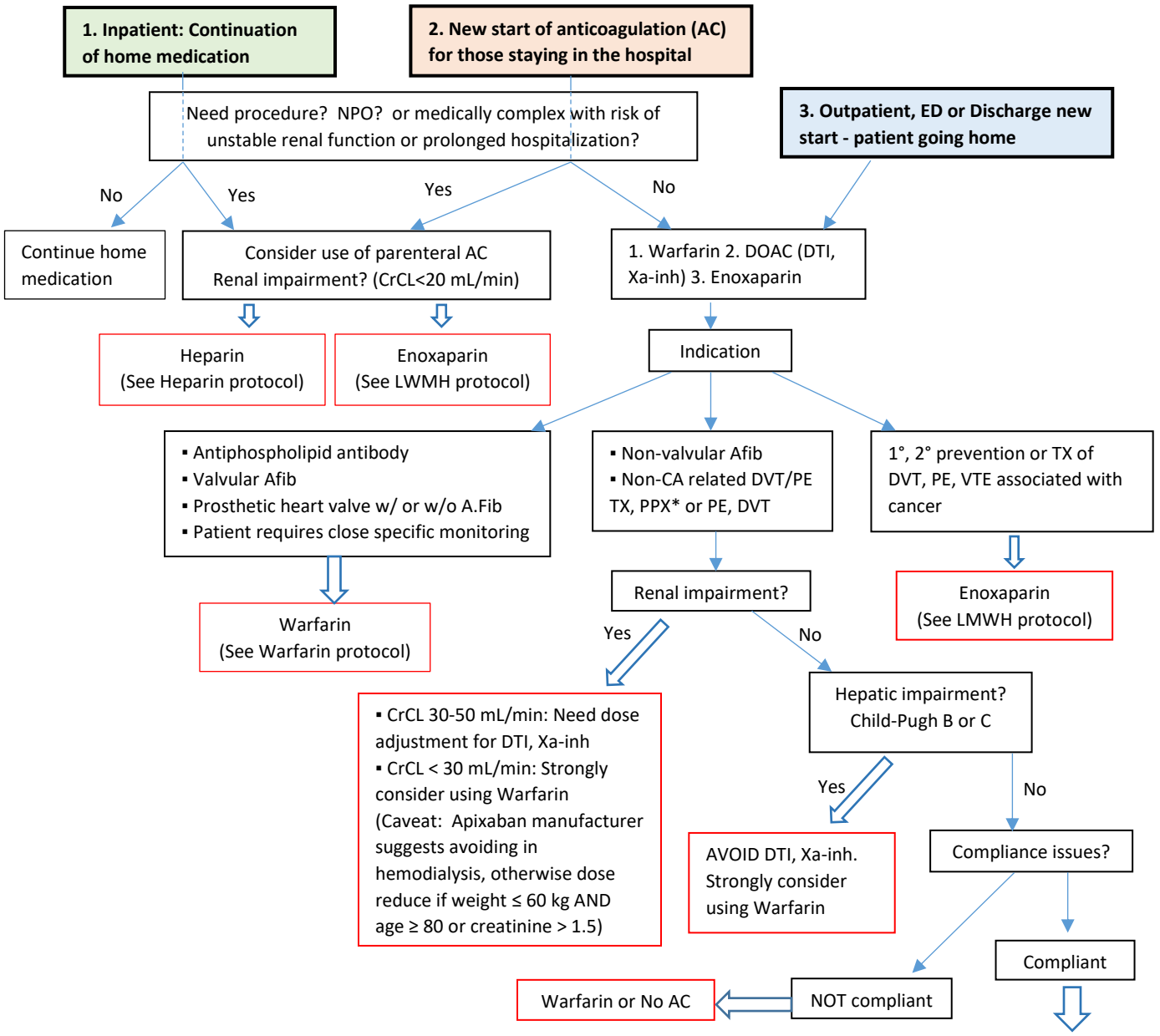
Attachments

No Attachments

Approval Signatures

Step Description	Approver	Date
Surgery, Trauma, Medicine, Medical Executive and Oversight Committees	Tracy Chapman: VCMC - Med Staff	8/19/2019
P&T Committee	Jason Arimura: VCMC - Pharmacy	8/19/2019

Decision Tree for Direct Oral Anticoagulants (DOACs) vs. Vitamin K Antagonists vs. Parenteral Anticoagulants



Medication-specific Issues and Attributes that may influence prescribing for DTI, Xa-Inh	
Frequency of Administration	Daily: edoxaban, rivaroxaban; BID: dabigatran, apixaban. (Note: for DVT/PE treatment, rivaroxaban is BID x 21 days, then daily)
For DVT/ PE treatment, require parenteral anticoagulant before transition to DOAC	Dabigatran and edoxaban (parenteral initial 5-10 days before starting each medication) (Note: rivaroxaban and apixaban require initial higher +/- more frequent dose)
Existence of antidote	Dabigatran antidote - Idarucizumab; Rivaroxaban and apixaban antidote – andexanet alfa; NO antidote for edoxaban at time of this writing
High creatinine clearance	CrCL > 95 mL/min: AVOID edoxaban
Coronary artery disease	Consider avoiding dabigatran
High bleed risk	Consider apixaban, trend towards less *gastrointestinal* bleeding
Insurance coverage	Gold Coast: all DTI & Xa-Inh covered, Medical: rivaroxaban only; other insurances: vary
Special populations (pregnant, very high or low weight: See "Guideline for the Prescribing of Direct Oral Anticoagulants (DOACs)"	

Abbreviations: Pt - patient, DTI - direct thrombin inhibitor (dabigatran), Xa-Inh - Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban), TX - treatment, DVT - deep vein thrombosis, VTE – venous thromboembolism, PPX - prophylaxis, MI - myocardial infarction, CrCL - creatinine clearance, Afib - Atrial fibrillation, LMWH - low molecular weight heparin, PA - prior authorization

Anticoagulation Committee: 11/2017, P & T Committee: 6/2018,
Medicine/Med Exec 7/2018, Oversight 7/2018