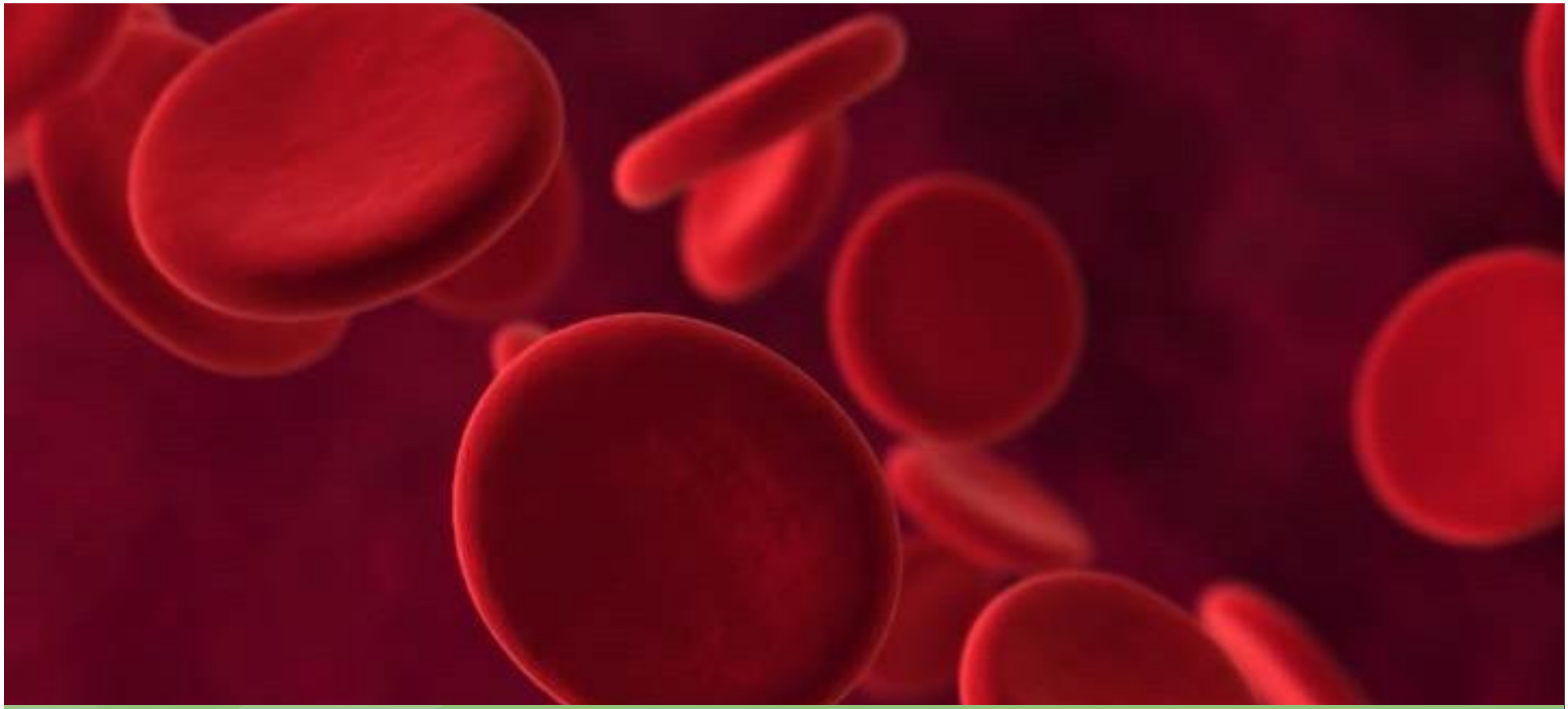

Recommendations for Anticoagulation Therapies

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Direct Oral Anticoagulants (DOACs) Guide

Anticoagulation and Thrombophilia Clinic, Minneapolis Heart Institute®, Abbott Northwestern Hospital.
Tel: 612-863-6800

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	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
FDA Approved Indications and Dosage	**NVAF** • 5 mg PO BID • 2.5 mg PO BID: If ≥ 2 of the following: age ≥80 years, weight ≤60 kg or Cr ≥ 1.5 mg/dL • Usage if Cr > 2.5 mg/dL or CrCl < 25 mL/min is based on pharmacokinetics and not on clinical studies. Caution is advised. **VTE treatment** • 10 mg PO BID for 7 days, then 5 mg PO BID • No dose adjustment based on renal function • Usage if CrCl < 25 mL/min is based on pharmacokinetics and not on clinical studies. Caution is advised. **VTE secondary prevention** • 2.5 mg PO BID • CrCl < 25 mL/min: no clinical studies **VTE prophylaxis in THR/TKR** • Start 12-24 hours postop • THR: 2.5 mg BID PO for 35 days • TKR: 2.5 mg BID PO for 12 days • CrCl < 30 mL/min: no clinical studies	**NVAF** • CrCl > 95 mL/min: NOT recommended (drug may be cleared too rapidly and adequate drug levels not attained) • CrCl 51-95 mL/min: 60 mg PO once daily • CrCl 15-50 mL/min: 30 mg PO once daily • CrCl < 15 mL/min: not recommended • **VTE treatment** • Begin after 5-10 days of initial therapy with a parenteral anticoagulant • CrCl > 50 mL/min: 60 mg PO once daily • CrCl 15-50 mL/min or weight ≤60 kg or on P-gp inhibitor[§]: 30 mg PO once daily **VTE secondary prevention** • Not approved **VTE prophylaxis in THR/TKR** • Not approved	**NVAF** • CrCl > 50 mL/min: 20 mg PO daily with evening meal • CrCl ≤ 50 mL/min: 15 mg PO daily with evening meal **VTE treatment** • CrCl ≥30 mL/min: 15 mg PO BID for 21 days, then 20 mg PO daily • CrCl < 30 mL/min: not recommended **VTE secondary prevention** • CrCl ≥ 30 mL/min: 10 mg PO daily, with or without food, after at least 6 months of standard treatment. • CrCl < 30 mL/min: not recommended **VTE prophylaxis in THR/TKR** • Start 6-10 hours post-op THR: 10 mg PO daily for 35 days • TKR: 10 mg PO daily for 12 days • Avoid if CrCl < 30 mL/min **Reduction of Risk of Major Cardiovascular Events** • Chronic CAD and/or PAD: 2.5 mg PO BID in combination with aspirin 81 mg PO daily	**Prophylaxis of VTE in adults hospitalized for acute medical illness with moderate or severe restricted mobility** • 160 mg PO initial single dose, followed by 80 mg same time daily with food for 35 to 42 days • CrCl 15-29 mL/min: 80 mg PO initial single dose, followed by 40 mg same time daily with food for 35 to 42 days • CrCl < 15 mL/min: not recommended • With concomitant use of P-gp inhibitor[§]: 80 mg PO initial single dose, followed by 40 mg same time daily with food for 35 to 42 days	**NVAF** • CrCl >30 mL/min: 150 mg PO BID • CrCl 15-30 mL/min: 75 mg PO BID • CrCl < 15 mL/min: not recommended **VTE treatment and secondary prevention** • For VTE treatment, an initial 5-10 days of parenteral anticoagulation is required before initiating dabigatran • CrCl >30 mL/min: 150 mg PO BID • CrCl ≤30 mL/min: not recommended **VTE prophylaxis in THR** • CrCl >30 mL/min: 110 mg for the first day, then 220 mg PO daily • CrCl ≤30 mL/min or on dialysis: dosing recommendations not available • CrCl <50 mL/min with concomitant use of P-gp inhibitor[§]: avoid co-administration **VTE prophylaxis in TKR** • Not approved

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Dosage Forms	Tablets: 2.5 mg, 5 mg	Tablets: 15 mg, 30 mg, 60 mg	Tablets: 2.5 mg, 10 mg, 15 mg, 20 mg	Capsules: 40 mg, 80 mg	Capsules: 75 mg, 110 mg, 150 mg • Keep in original container; remove only at time of use. • Close bottle immediately after use. Keep tightly closed. • Do not put in pillbox or medication organizer. • Use within 4 months after opening bottle.
Able to Crush Medication	• Yes • Both 2.5 mg and 5 mg tablets may be crushed and suspended in 60 mL D5W and immediately delivered through an NGT • No information available regarding oral administration of crushed and suspended	• No data are available regarding bioavailability upon crushing and/or mixing edoxaban tablets into food, liquids, or administration through feeding tubes.	• Yes • The 15 mg and 20 mg tablets may be crushed and mixed with applesauce for oral use or with 50 mL of water for NG or gastric tube feeding (avoid if distal to the stomach). After administration, oral or enteral feeding should immediately follow the dose.	• May dissolve in water or apple juice, or mix with applesauce. For administration by NG or feeding tube, dissolve in water. • After administration, oral or enteral feeding should immediately follow the dose.	• No • Do not chew, break, or open capsules (bioavailability increases by 75% if capsule is opened)
Administration with food	With or without food	With or without food	• 20 mg: with food • 15 mg: with food • 2.5 mg,10 mg: with or without food	With food	With or without food
Half-life	8-15 hours	10-14 hours	5-13 hours	19-27 hours	12-17 hours
T-max	3-4 hours	1-2 hours	2-4 hours	3-4 hours	1-3 hours
Metabolism	• Renal 27% • Hepatic 73%	• Renal 50% • Metabolism, biliary/intestinal 50%	• Renal 50% • Hepatic • 1/3 eliminated non-metabolized	• Feces: 85% unchanged drug • Renal: 11-18%	• Renal 80%

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Side Effects	• Bleeding • Thrombocytopenia • Hypersensitivity reaction	• Bleeding • Abnormal LFTs • Rash • Anemia	• Bleeding • Thrombocytopenia • Hypersensitivity reaction • Stevens-Johnson Syndrome Agranulocytosis • Hepatitis	• Bleeding • Hypokalemia • Hypertension • Headache • Hypersensitivity reaction	• Bleeding • GI: dyspepsia, abdominal and epigastric pain • GI bleed • Thrombocytopenia • Hypersensitivity reaction
Pregnancy Category **Lactation**	• Not studied and should be avoided • Lactation: not studied in humans and should be avoided	• Not studied and should be avoided • Lactation: not studied in humans and should be avoided	• Not studied and should be avoided • Lactation: Not studied in humans and should be avoided	• No data in pregnancy but treatment likely to increase risk of hemorrhage during pregnancy and delivery. • Lactation: not studied in humans and should be avoided	• Not studied and should be avoided • Lactation: not studied in humans and should be avoided
Contraindications	• Active bleeding Hypersensitivity • Severe hepatic impairment Mechanical heart valves (not studied)	• Active bleeding Hypersensitivity • Moderate or severe hepatic impairment • Mechanical heart valves (not studied)	• Active bleeding • Hypersensitivity • Severe liver impairment • Mechanical heart valves (not studied)	• Active bleeding • Hypersensitivity	• Active bleeding • Hypersensitivity • Mechanical heart valves ○ REALIGN trial terminated early due to significantly more thromboembolic and bleeding events
	DOACs are not recommended for patients with a history of thrombosis diagnosed with antiphospholipid syndrome (APS) and triple positive antibodies (lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein antibodies) as they may increase the risk of thrombosis.				

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Anticoagulation Laboratory Monitoring Usually not required. Consider in case of bleeding, surgery, compliance concern (see table at end of document)	• Anti-factor Xa level • PT (in seconds)	• Anti-factor Xa level • No good correlation with PT or aPTT	• Anti-factor Xa level • PT (in seconds)	**Not applicable.**	• Dabigatran trough level: 45-95 ng/mL (drawn ≤ 30 minutes before the next scheduled dose) • TT (thrombin time) • ECT (ecarin clotting time) • aPTT • Hemoclot
Drug interactions*	**Combined P-gp and strong CYP3A4 inhibitors*** • doses >2.5 mg BID: reduce dose by 50% • 2.5 mg BID: avoid use can lead to increased exposure to apixaban and increase the risk of bleeding **Combined P-gp and strong CYP3A4 inducers*** • avoid use • can lead to decreased exposure to apixaban and may decrease efficacy **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** • may increase bleeding risk	**P-gp inhibitors§** • NVAF: no dose reduction recommended with concomitant use • VTE treatment: 30 mg PO once daily **Anticoagulant, Antiplatelet, NSAID*** • may increase bleeding risk **P-gp inducers*** • avoid use	**Combined P-gp and strong CYP3A4 inhibitors*** • avoid use • can lead to increased exposure of rivaroxaban (from 30-160%) and increase bleeding risk **Combined P-gp and strong CYP3A4 inducers*** • avoid use • can lead to decreased exposure (up to 50%) and may decrease efficacy **Combined P-gp and moderate CYP3A4 inhibitor*** • CrCl 15-80 mL/min: avoid use unless benefit > risk. **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** • may increase bleeding risk	**P-gp inhibitors§** • reduce betrixaban dose by 50% • can lead to increased exposure to betrixaban and increase risk of bleeding	**P-gp inhibitors*** • NVAF+CrCl 30-50 mL/min: consider dabigatran 75 mg BID • NVAF+CrCl 15-30 mL/min: avoid • VTE+ CrCl<50 mL/min: avoid • can lead to increased exposure to dabigatran and risk of bleeding **P-gp inducers*** • avoid use • can lead to reduced exposure to dabigatran and may decrease efficacy **Anticoagulant, Antiplatelet, NSAID, SSRI, SNRI*** • may increase bleeding risk

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Evidence for Use of DOAC in NVAF vs. Warfarin	**ARISTOTLE** mean $CHADS_2$ score: 2.1 • Superior: hemorrhagic stroke • Superior: major bleeding ICH and fatal bleed: lower • Superior: vascular mortality	**ENGAGE AF-TIMI 48** $CHADS_2$ score ≤ 3: 77% of subjects • Not an approved FDA indication. • CrCl 15-95: non-inferior for stroke or systemic embolism • Superior: hemorrhagic stroke Superior: major bleeding Superior: cardiovascular mortality • Edoxaban 60 mg showed consistent efficacy and safety results vs. warfarin in 2824 patients with valvular AF (aortic stenosis, aortic insufficiency, mitral insufficiency, valve bioprosthesis, repair or plasty) despite the fact that patients with valvular heart disease had higher CV mortality, MACE and major bleeding risk than those with NVAF.	**ROCKET-AF** mean $CHADS_2$ score: 3.5 • Non-inferior: all stroke • Major bleed: similar • ICH and fatal bleeding: lower • Higher GIB and need for transfusion	**Not applicable.**	**RE-LY** mean $CHADS_2$ score: 2.1 • Superior: ischemic and hemorrhagic stroke • Major bleeding: similar (higher in age ≥75 years) • CH and fatal bleeding: lower • GIB: higher • Superior: vascular mortality

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Evidence for VTE Prophylaxis for THR vs. Enoxaparin	**ADVANCE 3** • Superior with no difference in bleeding	Not an approved FDA indication. **STARS J-V (hip replacement)** • Superior with no difference in bleeding **STARS J-IV (hip fracture)** • Similar with no difference in bleeding	**RECORD 1** **RECORD 2** • Superior with no difference in bleeding	**Not applicable.**	**RE-NOVATE I** **RE-NOVATE II** • Non-inferior
VTE Prophylaxis for TKR vs. Enoxaparin	**ADVANCE 2** • Superior with no difference in bleeding	Not an approved FDA indication. **STARS E-3** • Superior with no difference in bleeding	**RECORD 3** **RECORD 4** • Superior with no difference in bleeding	**Not applicable.**	Not an approved FDA indication. **RE-MODEL** **RE-MOBILIZE** • Non-inferior **RE-NOVATE I** **RE-NOVATE II** • Non-inferior
Evidence for VTE Management vs. LMWH/VKA	**AMPLIFY** • Non-inferior: recurrent VTE/ mortality • Major bleeding: lower	**HOKUSAI VTE STUDY** • Non-inferior: recurrent VTE • Superior: fatal and intracranial bleeding, clinically relevant bleeding	**EINSTEIN** • Non-inferior: recurrent VTE/ mortality • Major bleeding: lower (pooled analysis)		**RE-COVER** • Non-inferior: recurrent VTE/ mortality • Major bleed: similar • Clinically relevant non-major and any bleed: lower

	Direct Factor Xa Inhibitors				Direct Thrombin (Factor IIa) Inhibitor
	apixaban (Eliquis®)	**edoxaban (Savaysa®)**	**rivaroxaban (Xarelto®)**	**betrixaban (Byvexxa®)**	**dabigatran (Pradaxa®)**
Evidence for VTE Risk Reduction after Initial Treatment	**AMPLIFY-EXT** • Superior vs. placebo with similar major bleeding	Not an approved FDA indication (not studied).	**EINSTEIN-EXT** • Superior vs. placebo with higher major bleeding **EINSTEIN CHOICE** • Rivaroxaban 10 and 20 mg were superior to aspirin for recurrent VTE risk with similar risk of bleeding		**RE-MEDY** • Non-inferior vs. warfarin, similar major bleeding **RE-SONATE** • Superior vs. placebo, higher major bleeding
Evidence for Reduction of Major Cardiovascular Events	**Not applicable.**	**Not applicable.**	**COMPASS** • Rivaroxaban 2.5 mg BID daily plus aspirin 100 mg once daily was superior to aspirin alone for the reduction of CV composite outcomes including nonfatal MI, stroke and CV mortality.	**Not applicable.**	**Not applicable.**

Peri-procedural Anticoagulation	Refer to **Management of Periprocedural Anticoagulation**
Switching between Anticoagulants	Refer to **Switching To and From Various Anticoagulants**

Anticoagulation Laboratory Considerations

Direct Factor Xa Inhibitors
(apixaban/Eliquis®, betrixaban/Byvexxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)

Apixaban and Rivaroxaban

- Heparin level (aka anti-Xa level)
  - This assay shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
  - A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity
- PT/INR
  - The PT (reported in seconds) shows some correlation with direct factor Xa inhibitor level; correlation with the calculated INR is weaker.
  - A normal PT likely rules out clinically significant levels of direct factor Xa inhibitor.
  - Due to variability of PT/INR reagents, this test is not recommended to rule out the presence of the direct factor Xa inhibitor. Heparin levels (aka anti-Xa) should be ordered instead.

Edoxaban and Betrixaban

- Heparin level (aka anti-Xa)
  - This assay shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
  - A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity
- PT/INR and aPTT
  - No good correlation with PT or aPTT

Note: Specific assays for apixaban, betrixaban, edoxaban, or rivaroxaban are not currently available.

Direct Thrombin (Factor IIa) Inhibitor
(dabigatran/Pradaxa®)

Dabigatran

- Dabigatran level
  - The preferred test if available (performed at Allina Health Central Lab at Allina Commons)
  - Target dabigatran trough level (drawn 30 minutes or less before the next scheduled dose): 45-95 ng/mL
- Thrombin time (TT)
  - Useful to rule out presence of dabigatran
  - A normal thrombin time essentially rules out clinically significant levels of dabigatran
- aPTT
  - Can be used if dabigatran level and TT tests are not available.
  - aPTT is less sensitive than TT and may be normal at trough drug level
  - An elevated aPTT cannot quantify the amount of dabigatran present
- PT/INR
  - Less sensitive than TT and aPTT

Direct Oral Anticoagulant (DOAC) Comparison		
Key	***Drug Interactions**	**‡ Supplemental Documents**
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs (e.g., ibuprofen, naproxen) NVAF: Non-Valvular Atrial Fibrillation P-gp: P-glycoprotein SNRI: Serotonin-Norepinephrine Reuptake Inhibitors (e.g., venlafaxine/Effexor®) SSRI: Selective Serotonin Reuptake Inhibitors (e.g., sertraline/Zoloft®, fluoxetine/Prozac®) T-max: time when maximum plasma concentration reached THR, TKR: Total Hip, Total Knee Replacement DOAC: Direct Oral Anticoagulant VTE: Venous Thromboembolism (PE and/or DVT)	§P-gp inhibitors: azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, verapamil Combined P-gp and strong CYP3A4 inhibitors: e.g., fluconazole, ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin Combined P-gp and strong CYP3A4 inducers: e.g., rifampin, carbamazepine, phenytoin, St. John's wort Combined P-gp and moderate CYP3A4 inhibitor: e.g., diltiazem, verapamil, dronedarone, erythromycin P-gp inhibitors: dronedarone, ketoconazole P-gp inducers: e.g., rifampin	Management of Bleeding Associated with Direct Oral Anticoagulants Management of Periprocedural Anticoagulation Switching To and From Various Anticoagulants

Disclaimer

"Guidelines are not meant to replace clinical judgment or professional standards of care. Clinical judgment must take into consideration all the facts in each individual and particular case, including individual patient circumstances and patient preferences. They serve to inform clinical judgment, not act as a substitute for it. These guidelines were developed by a Review Organization under Minn. Statutes §145.64 et. seq., and are subject to the limitations described as Minn. Statues §145.65."

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Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

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Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Bleeding Category				
	Mild Bleeding (all criteria below)	**Moderate Bleeding** (all criteria below)	**Major Bleeding** (one or more of the below)	**Life-Threatening Bleeding** (one or more of the below)
Hemoglobin decrease and/or transfusion needs	• No significant decrease in hemoglobin • No blood transfusion necessary	• Bleeding associated with ○ decrease in hemoglobin of less than 2 g/dL or ○ transfusion of < 2 units of blood	• Bleeding associated with ○ decrease in hemoglobin of at least 2 g/dL or ○ transfusion of at least 2 units of blood	• Bleeding associated with ○ decrease in hemoglobin of at least 5 g/dL or ○ transfusion of at least 4 units of blood
Symptoms	• Asymptomatic contained, local bleeding	• Symptomatic bleeding excluding critical organs (e.g., intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular, or pericardial)	• Symptomatic bleeding in a critical area or organ (e.g. intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular, or pericardial)	• Potentially fatal hemorrhage • Symptomatic intracranial bleed • Hypotension requiring use of intravenous inotropic agents • Surgical intervention necessary

General Measures				
	Mild Bleeding	**Moderate**	**Major**	**Life-Threatening**
Anticoagulant management	▪ Hold one or more anticoagulant doses based on bleeding severity and renal function ▪ Consider other anticoagulant if ≥ 2 doses of drug need to be interrupted and/or it can no longer be used. Consider bridging agent if CHADS2 score > 4. ▪ Check and monitor for ○ possible medication interactions ○ renal function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ hepatic function to verify correct dosing of rivaroxaban and apixaban (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ restart anticoagulation when bleeding is controlled and no contraindications.	▪ Hold anticoagulant ▪ Consider activated charcoal (1-2 gm/kg) ○ If < 2 hours since last dose of dabigatran or rivaroxaban ○ If < 6 hours since last dose of apixaban ○ For edoxaban, there are currently no data or ongoing studies to evaluate if activated charcoal can be used in cases of overdose/toxicity. ▪ • Check and monitor for ○ possible medication interactions ○ renal function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide') ○ hepatic function to verify correct dosing (see 'Direct Oral Anticoagulants (DOACs) Guide')		
Lab	None recommended	Monitor CBC		
Interventions	Local bleeding control	Local bleeding control		

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Factor Xa Inhibitors (apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
General approach	See general measures above	• See general measures above	• See general measures above • Maintain adequate diuresis	• See general measures above • Maintain adequate diuresis
Bleeding source recommendations		• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult. • Local hemorrhage including hematoma: compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult. • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult. • Local hemorrhage including hematoma: Compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. • Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult. • Pericardial: cardiac surgery and cardiology consults. • Retroperitoneal: general surgery consult
Transfusion		• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Recommend blood transfusion

Labs		• Not recommended	• Check heparin levels (aka anti-Xa)
			  ○ if not available, check PT (in seconds) to estimate medication clearance (see Lab Considerations)
				• Check heparin levels (aka anti-Xa)
				  ○ if not available, check PT (in seconds) to estimate medication clearance (see Lab Considerations)

Hemodialysis		• Not beneficial	• Not beneficial	• Not beneficial
Recombinant Coagulation Factor Xa, inactivated-zhzo (AndexXa®)		• Not recommended	• If continuous active bleeding and abnormal heparin level (aka anti-Xa) or PT and patient taking: ○ apixaban or rivaroxaban: Consider recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) • Betrixaban, edoxaban: not indicated	• Patient taking apixaban or rivaroxaban: recommend recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) • Betrixaban, edoxaban: not indicated

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Factor Xa Inhibitors (apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
PCC or aPCC, rFVIIa		• Not recommended	• If continuous active bleeding and abnormal heparin level (aka anti-Xa) or PT and patient taking: ○ apixaban or rivaroxaban: consider recombinant coagulation factor Xa, inactivated-zhzo (AndexXa®) ○ betrixaban or edoxaban: consider PCC (Kcentra®). ▪ See PCC dosing table ▪ If PCC not available, aPCC or rFVIIa	• Patient taking apixaban or rivaroxaban if AndexXa not available: recommend PCC (Kcentra®). • Patient taking betrixaban or edoxaban: recommend PCC (Kcentra®). ○ If Kcentra not available, consider aPCC or rFVIIaas soon as possible (see Alternatives dosing table).
Coverage with another anticoagulant		• Consider another anticoagulant if ≥ 2 doses of the drug need to be interrupted and/or can no longer be used. Consider bridging agent if $CHADS_2$ score > 4.	• Cover with another anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.	• Cover with another anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.
Resume anticoagulation		• Restart anticoagulation when bleeding is controlled and no further risk of bleeding.	• Decision about restarting anticoagulation should be based on risks and benefits.	• Decision about restarting anticoagulation should be based on risks and benefits.

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Thrombin (factor IIa) Inhibitor (dabigatran/Pradaxa®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
General approach	See general measures above	• See general measures above	• See general measures above • Maintain adequate diuresis	• See general measures above • Maintain adequate diuresis
Bleeding source recommendations		• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: compression and surveillance imaging • Intracranial or intraspinal bleed: neurology and neurosurgery consults. Intraocular: ophthalmology consult • Intramuscular or intra-articular: orthopedic consult • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult	• GI tract: GI consult • Vascular: vascular surgery and/or interventional radiology consult • Local hemorrhage including hematoma: Compression and surveillance imaging Intracranial or intraspinal bleed: • neurology and neurosurgery consults. • Intraocular: ophthalmology consult Intramuscular or intra-articular: orthopedic consult • Pericardial: cardiac surgery and cardiology consults • Retroperitoneal: general surgery consult
Transfusion		• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Consider transfusion if symptomatic anemia or hemoglobin < 7 g/dL	• Recommend blood transfusion
Labs		• Not recommended	• Check dabigatran level • If dabigatran level not available, check thrombin time (TT) • if TT not available, check aPTT (see Lab Considerations)	• Check dabigatran level • If dabigatran level not available, check thrombin time (TT) • if TT not available, check aPTT (see Lab Considerations)
Hemodialysis		• Not recommended	• Consider hemodialysis ○ especially if abnormal renal function, continuous active bleeding and abnormal dabigatran level, TT or aPTT	• Recommend hemodialysis as soon as possible
idarucizumab (Praxbind®)		• Not recommended	• If continuous active bleeding and abnormal dabigatran level, TT or aPTT (see Lab Considerations), consider idarucizumab (Praxbind®)	• Recommend idarucizumab (Praxbind®) as soon as possible. If not available, recommend PCC (Kcentra®)

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Direct Thrombin (factor IIa) Inhibitor (dabigatran/Pradaxa®)				
	Mild	**Moderate**	**Major**	**Life-Threatening**
PCC or aPCC, rFVIIa		• Not recommended	• Consider PCC (Kcentra®) ONLY if idarucizumab is not available and active bleeding with an abnormal dabigatran level, TT or aPTT (see Lab Considerations) • If PCC not available, recommend aPCC or rFVIIa (see PCC dosing table).	• Recommend PCC (Kcentra®) as soon as possible ONLY if idarucizumab (Praxbind®) is not available. • If PCC not available, recommend aPCC or rFVIIa (see PCC dosing table).
Coverage with another anticoagulant	**See general measures above**	• Consider other anticoagulant if ≥ 2 doses of dabigatran need to be interrupted and/ or it can no longer be used. Consider bridging agent if $CHADS_2$ score > 4.	• Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.	• Cover with other anticoagulant (preferably low intensity unfractionated heparin) when deemed safe, especially if $CHADS_2$ score > 4.
Resume anticoagulation		• Restart anticoagulation when bleeding is controlled and no further risk of bleeding.	• Decision about restarting anticoagulation should be based on risks and benefits.	• Decision about restarting anticoagulation should be based on risks and benefits.

First-line Reversal Agents for Direct Factor Xa Inhibitors			
	Dose	**Side Effects**	**Considerations**
Recombinant Coagulation Factor Xa, inactivated-zhzo (AndexXa®) **To reverse apixaban or rivaroxaban only.**	• If last dose of apixaban or rivaroxaban taken ≥ 8 hours prior, OR last apixaban dose ≤ 5 mg OR last rivaroxaban dose ≤ 10 mg taken < 8 hours prior (or unknown): ○ 400 mg AndexXa IV infused at 30 mg/min followed within 2 minutes by 4 mg/min IV for up to 120 minutes • If last apixaban dose > 5 mg (or unknown) OR last rivaroxaban dose > 10 mg (or unknown) taken < 8 hours prior (or unknown when): ○ 800 mg AndexXa IV infused at 30 mg/min followed within 2 minutes by 8 mg/min IV for up to 120 minutes	• Systemic thromboembolism • UTI • Pneumonia • Infusion-related reaction	• Indicated for reversal of anticoagulation in patients treated with apixaban or rivaroxaban only. • AndexXa was FDA-approved based on change in anti-Xa activity in healthy volunteers. • Improvement in hemostasis has not been established. • Safety and efficacy of more than one dose have not been established. • Re-elevation or incomplete reversal of anticoagulant activity can occur. • Arterial and venous thromboembolic events have occurred within 30 days post-reversal with AndexXa. • Resume anticoagulant therapy as soon as appropriate. • Not studied in patients going for urgent or emergent surgeries or procedures.
Kcentra© (PCC, Four-Factor Prothrombin Complex Concentrate)	• **Kcentra 50 units/kg IV** ○ May repeat dose in 12 hours if bleeding continues ○ Maximum dose 5000 units/day ○ Dosing may change based on bleeding severity and thrombotic risk of patient	• DIC • Systemic thromboembolism	• Contains heparin. • Contraindicated in patients with known heparin-induced thrombocytopenia (HIT).

Alternatives if Kcentra is Unavailable		
	Dose	**Side Effects**

Active Prothrombin Complex Concentrate (aPCC, Feiba©)	• **aPCC 50-80 units/kg IV**
	  ○ May repeat dose in 12 hours if bleeding continues
	  ○ Maximum dose: 200 units/kg/day
	  ○ Dosing may change based on bleeding severity and thrombotic risk of patient
	  ○ Does not contain heparin
		• DIC
		• systemic thromboembolism

Recombinant active factor VII (rVIIa, NovoSeven©)	• **rVIIa 20 mcg/kg IV**
	  ○ May repeat dose every 2 hours until hemostasis achieved or until treatment judged ineffective.
	  ○ Maximum dose: 90 mcg/kg
	  ○ Dosing may change based on bleeding severity and thrombotic risk of patient
	  ○ Does not contain heparin
		• DIC
		• systemic thromboembolism

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

First-line Reversal Agent for Dabigatran (Pradaxa)			
	Dose/Administration	**Side Effects**	**Considerations**
idarucizumab (Praxbind©)	• **idarucizumab 5 gm IV divided in two 2.5 gm doses** • Administer as two consecutive infusions by hanging vials or as consecutive bolus injections of both vials one after another via syringe • A pre-existing IV line may be used but must be flushed with saline prior to infusion. No other infusion should be administered via the same IV access. • There is limited data to support administration of an additional 5 gm dose in 24 hours • Dosing may change based on bleeding severity and thrombotic risk of patient	• Headache • Hypokalemia • Delirium • Constipation • Pyrexia • Pneumonia	• Idarucizumab is a specific reversal agent for dabigatran with no impact on the effect of other anticoagulants or antithrombotic therapies. • Dabigatran can be re-initiated 24 hours after administration of idarucizumab when clinically appropriate. • Serious adverse reactions have been reported in patients with hereditary fructose intolerance due to sorbitol excipient • Idarucizumab is also indicated for reversal of dabigatran-related anticoagulation prior to emergency surgery/urgent procedures

Management of Bleeding Associated with Direct Oral Anticoagulants (DOACs)

Lab Considerations

Direct Factor Xa Inhibitors
(apixaban/Eliquis®, betrixaban/Bevyxxa®, edoxaban/Savaysa®, rivaroxaban/Xarelto®)

Rivaroxaban and apixaban

Heparin level (aka anti-Xa)

- The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
- A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity

PT/INR

- The PT (reported in seconds) shows some correlation with direct factor Xa inhibitor level; correlation with the calculated INR is weaker.
- A normal PT likely rules out clinically significant levels of direct factor Xa inhibitor.
- Due to variability of PT/INR reagents, this test is not recommended to try to rule out the presence of the direct factor Xa inhibitor. Heparin levels (aka anti-Xa) should be ordered instead.

Edoxaban and Betrixaban

Heparin level (aka anti-Xa)

- The assay used to calculate heparin levels shows reasonable linear correlation with increasing levels of direct factor Xa inhibitors
- A heparin (anti-Xa) level of <0.1 units/mL suggests lack of significant factor Xa inhibitor activity

PT/INR

- No good correlation with PT or aPTT

Direct Thrombin (factor IIa) Inhibitor
(dabigatran/Pradaxa®)

Dabigatran level

- The preferred test if available (performed at Allina Health Central Lab at Allina Commons)

Thrombin time (TT)

- Useful to rule out presence of dabigatran
- A normal thrombin time essentially rules out clinically significant levels of dabigatran

aPTT

- Can be used if dabigatran level and TT tests are not available.
- aPTT is less sensitive than TT and may be normal at trough drug level
- An elevated aPTT cannot quantify the amount of dabigatran present

PT/INR

- Less sensitive than TT and aPTT

NOTE: *Specific assays for apixaban, betrixaban, edoxaban, or rivaroxaban are not currently available.*

Disclaimer

"Guidelines are not meant to replace clinical judgment or professional standards of care. Clinical judgment must take into consideration all the facts in each individual and particular case, including individual patient circumstances and patient preferences. They serve to inform clinical judgment, not act as a substitute for it. These guidelines were developed by a Review Organization under Minn. Statutes §145.64 et. seq., and are subject to the limitations described as Minn. Statues §145.65."

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Switching To and From Anticoagulants

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From	To	Conversion Recommendation
DOACs*		
Apixaban[1]**	heparin, bivalirudin, or argatroban infusion	Stop apixaban Begin infusion at time when next dose of apixaban is due
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	Stop apixaban Begin new agent at time when next dose of apixaban is due
	warfarin	Stop apixaban Start warfarin and consider bridging agent at next apixaban due time Start INR monitoring 2 days after stopping apixaban (INR values drawn sooner may be falsely elevated by apixaban) Stop bridging agent when INR is at goal
	Other DOAC (betrixaban, dabigatran, edoxaban, rivaroxaban)	Stop apixaban Begin other DOAC when next dose of apixaban is due
Betrixaban[2]**	heparin, bivalirudin, or argatroban infusion	Stop betrixaban Begin infusion at time when next dose of betrixaban is due
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	Stop betrixaban Begin new agent at time when next dose of betrixaban is due
	warfarin	Stop betrixaban Start warfarin and consider bridging agent at next betrixaban due time Start INR monitoring 2 days after stopping betrixaban (INR values drawn sooner may be falsely elevated by betrixaban) Stop bridging agent when INR is at goal
	Other DOAC (apixaban, dabigatran, edoxaban, rivaroxaban)	Stop betrixaban Begin other DOAC when next dose of betrixaban is due
Dabigatran[3]*	heparin, bivalirudin, or argatroban infusion	Stop dabigatran CrCl ≥ 30 mL/min – start infusion 12 hours after last dose of dabigatran CrCl < 30 mL/min – start infusion 24 hours after last dose of dabigatran
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	Stop dabigatran CrCl ≥ 30 mL/min – start agent 12 hours after last dose of dabigatran CrCl < 30 mL/min – start agent 24 hours after last dose of dabigatran

From	To	Conversion Recommendation
DOACs*		
	warfarin	CrCl ≥ 50 mL/min, start warfarin 3 days before stopping dabigatran CrCl 30-49 mL/min, start warfarin 2 days before stopping dabigatran CrCl 15-29 mL/min, start warfarin 1 day before stopping dabigatran CrCl < 15 mL/min, not recommended Start INR monitoring 2 days after stopping dabigatran (INR values drawn sooner may be falsely elevated by dabigatran)
	apixaban, betrixaban, edoxaban	Stop dabigatran Initiate new DOAC at the time of the next regularly scheduled dose of dabigatran
	rivaroxaban	Stop dabigatran Initiate rivaroxaban ≤2 hours prior to the next regularly scheduled dose of dabigatran
Edoxaban[4]**	heparin, argatroban, or bivalirudin infusion	Stop edoxaban Begin infusion at time when next dose of edoxaban is due
	LMWH/subcutaneous agents (dalteparin, enoxaparin, fondaparinux)	Stop edoxaban Begin agent at time when next dose of edoxaban is due
	warfarin	If taking 60 mg daily edoxaban – reduce dose to 30 mg daily and begin warfarin concomitantly. Discontinue when INR is at goal If taking 30 mg daily edoxaban – reduce dose to 15 mg daily and begin warfarin concomitantly. Discontinue when INR is at goal **OR** Begin parenteral anticoagulant (bridge therapy) and warfarin at the time the next dose of edoxaban is due. When INR is at goal, discontinue parenteral anticoagulant.
	Other DOAC (apixaban, betrixaban, dabigatran, rivaroxaban)	Stop edoxaban Begin new DOAC at time when next dose of edoxaban is due
Rivaroxaban[5]**	heparin, bivalirudin, or argatroban infusion	Stop rivaroxaban Begin infusion at time when next dose of rivaroxaban is due
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	Stop rivaroxaban Begin agent at time when next dose of rivaroxaban is due

From	To	Conversion Recommendation
DOACs*		
	warfarin	Stop rivaroxaban Start warfarin and consider starting bridging agent at next rivaroxaban due time Start INR monitoring 2 days after stopping rivaroxaban (INR values drawn sooner may be falsely elevated by rivaroxaban) Stop bridging agent once goal INR is achieved
	Other DOAC (apixaban, betrixaban, dabigatran, edoxaban)	Stop rivaroxaban Begin DOAC at time when next dose of rivaroxaban is due

From	To	Conversion Recommendation
Heparinoids/SC Agents		
Heparin Infusion	LMWH, subcutaneous	Stop heparin infusion Start agent at time heparin infusion is stopped If more conservative strategy is preferred, start LMWH/SC agent 2 hours after heparin infusion is stopped
	apixaban, betrixaban, dabigatran, rivaroxaban	Stop heparin infusion Start DOAC at the time of stopping heparin infusion
	edoxaban	Stop heparin infusion Start edoxaban 4 hours after stopping heparin infusion
	warfarin	Begin when clinically indicated May overlap therapy to achieve therapeutic INR Heparin dosage should decrease as INR increases
	argatroban/bivalirudin infusion	Stop heparin infusion Start argatroban/bivalirudin infusion immediately after heparin infusion is stopped
LMWH/ subcutaneous (enoxaparin, dalteparin, fondaparinux)	heparin infusion	Stop LMWH/SC agent Start heparin infusion at time when next dose of LMWH/SC agent is due
	dabigatran, rivaroxaban	Stop LMWH/SC agent Start DOAC ≤2 hours prior to the time of the next scheduled dose of LMWH/SC agent

From	To	Conversion Recommendation
Heparinoids/SC Agents		
	apixaban, betrixaban, edoxaban	Stop LMWH/SC agent Start DOAC at time when next dose of LMWH/SC agent is due
	warfarin	Begin when clinically indicated May overlap therapy to achieve goal INR
	argatroban/bivalirudin infusion	Stop LMWH/SC agent Start argatroban/bivalirudin infusion at time when next dose of LMWH/SC agent is due

From	To	Conversion Recommendation
Vitamin K Antagonists		
Warfarin	heparin, argatroban, or bivalirudin infusion	Stop warfarin Initiate infusion when INR ≤ 2
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	Stop warfarin Initiate agent when INR < 2
	apixaban, betrixaban, dabigatran	Stop warfarin Start DOAC when INR < 2
	edoxaban	Stop warfarin Start edoxaban when INR ≤ 2.5
	rivaroxaban	Stop warfarin Start rivaroxaban when INR < 3

From	To	Conversion Recommendation
IV Direct Thrombin Inhibitors		
Argatroban	heparin infusion	If HIT has been ruled out, stop argatroban infusion Start heparin infusion immediately after argatroban is stopped. Consider hepatic function in making decision.

From	To	Conversion Recommendation
IV Direct Thrombin Inhibitors		
	LMWH, subcutaneous	If HIT has been ruled out, stop argatroban infusion Administer LMWH immediately after argatroban infusion is stopped. Consider hepatic function in making decision.
	warfarin	Begin when clinically indicated May overlap therapy to achieve therapeutic CFX Argatroban needs should decrease as CFX decreases
	apixaban, betrixaban, dabigatran, edoxaban	Stop argatroban infusion Start DOAC at the time of stopping argatroban
	rivaroxaban	Stop argatroban infusion Start rivaroxaban 4 hours after stopping argatroban
Bivalirudin	heparin infusion	If HIT has been ruled out, stop bivalirudin infusion Start heparin infusion immediately after bivalirudin infusion is stopped. Consider renal function in making decision.
	LMWH/subcutaneous agents (enoxaparin, fondaparinux, dalteparin)	If HIT has been ruled out, stop bivalirudin infusion Administer agent immediately after bivalirudin infusion is stopped. Consider renal function when making decision.
	warfarin	Begin when clinically indicated May overlap therapy to achieve therapeutic CFX Bivalirudin dosage should decrease as CFX decreases
	apixaban, betrixaban, dabigatran, edoxaban	Stop bivalirudin infusion Start DOAC at the time of stopping bivalirudin
	rivaroxaban	Stop bivalirudin infusion Start rivaroxaban 4 hours after stopping bivalirudin

* Direct Oral Anticoagulant
** For patients with end-stage renal disease or on intermittent or chronic hemodialysis, it is recommended to use warfarin instead of a direct oral anticoagulant (e.g., dabigatran, apixaban, betrixaban, edoxaban, rivaroxaban

Dosing Information for DOACs
Refer to the Allina Health **Direct Oral Anticoagulants (DOACs) Guide** *For detailed prescription information, refer to the manufacturer's package insert for each medication.*

Disclaimer

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Management of Periprocedural Anticoagulation

- Warfarin
- DOACs
- Bleeding Risks
- Thrombotic Risks
- Cardiac Electrophysiology
- Cardiac Catheterization Lab
- Neuraxial Access or Peripheral Nerve Procedures

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Management of Periprocedural Anticoagulation (Warfarin)

<table>
<tr><th colspan="8">Warfarin (Coumadin, Jantoven)</th></tr>
<tr><td>Bleeding Risk</td><td colspan="4">High/Intermediate/Low</td><td colspan="3">Minor</td></tr>
<tr><td>Thrombotic Risk</td><td>Ultra High Risk</td><td>High</td><td colspan="2">Intermediate</td><td>Low</td><td>High</td><td>Intermediate</td><td>Low</td></tr>
<tr><td>Days to stop warfarin prior to procedure</td><td colspan="4">Stop warfarin 5 days prior to procedure</td><td colspan="2">Continue warfarin with goal INR ~2.0</td><td>Consider holding warfarin 2 days prior to procedure</td></tr>
<tr><td rowspan="3">Bridging</td><td>Begin therapeutic dose LMWH 3 days prior to procedure</td><td>Consider therapeutic dose LMWH 3 days prior to procedure Base decision on input from patient, proceduralist, and PCP.</td><td colspan="2">Evidence for or against bridging is unclear and recommendations should be based on patient and procedure characteristics. If bridging, then begin therapeutic dose LMWH 3 days prior to procedure.</td><td rowspan="3">Bridging not indicated</td><td colspan="3" rowspan="3">Bridging not indicated</td></tr>
<tr><td>Give last dose of LMWH 24 hours prior to procedure</td><td rowspan="2">Give last dose of LMWH 24 hours prior to procedure</td><td colspan="2" rowspan="2">Give last LMWH dose 24 hours prior to procedure</td></tr>
<tr><td>Admit to hospital for therapeutic IV heparin overnight, stopping 6 hours prior to procedure</td></tr>
<tr><td>Other therapeutic considerations</td><td colspan="4">None</td><td colspan="3">Consider addition of tranexamic acid or aminocaproic acid mouthwash for dental procedures.
Tranexamic acid dosing for dental procedures: Oral rinse, 4.8% solution. Hold 10 mL in mouth and rinse for 2 minutes, then spit out. First dose 10 minutes prior to procedure. Repeat 4 times daily (~every 6 hours) for 2 days after procedure. Patient should not eat or drink for 1 hour after using oral rinse (Carter, 2003).</td></tr>
<tr><td>INR Check</td><td colspan="8">Check INR day of procedure.</td></tr>
<tr><td>Resuming post-op</td><td colspan="8">Resume anticoagulation as soon as possible postoperatively.</td></tr>
<tr><td>Other considerations</td><td colspan="8">Warfarin hold times and INR recommendations are based on the assumption that the patient has relatively good compliance with warfarin and INR values are generally within the range of 2-3. If patient has INR values outside that range or poor medication compliance, the recommendations should be adjusted per physician recommendation.</td></tr>
</table>

Management of Periprocedural Anticoagulation (DOACs)

<table>
<tr><th></th><th>Bleeding Risk</th><th></th><th colspan="3">High</th><th colspan="3">Intermediate</th><th colspan="3">Low</th><th colspan="3">Minor</th><th rowspan="2">Other considerations</th></tr>
<tr><th></th><th>Thrombotic Risk</th><th></th><th>Ultra-High, High</th><th>Inter-mediate</th><th>Low</th><th>Ultra-High, High</th><th>Inter-mediate</th><th>Low</th><th>Ultra-High, High</th><th>Inter-mediate</th><th>Low</th><th>Ultra-High, High</th><th>Inter-mediate</th><th>Low</th></tr>
<tr><td colspan="15">Direct Factor Xa Inhibitors</td></tr>
<tr><td>apixaban (Eliquis)</td><td>Days to stop apixaban prior to procedure

<u>Risk factors</u>
Age ≥ 80 yr
Weight ≤ 60 kg
Cr ≥ 1.5 mg/dL</td><td>≤ 1 risk factor</td><td>2 days</td><td rowspan="3">4 days</td><td rowspan="3">2 days</td><td rowspan="3">4 days</td><td rowspan="3">1 day</td><td rowspan="3">2 days</td><td rowspan="3">continue apixaban</td><td rowspan="3">consider holding 1 day prior if high bleeding concern</td><td rowspan="4">Bridging: not indicated

Resuming Anticoagulation; Following the procedure, anticoagulation should be resumed as soon as safe based on hemostasis and bleeding risk, at least 24-48 hours postoperatively.

Labs: If high bleedinging risk, consider checking an anti-Xa level (apixaban, betrixaban, edoxaban, rivaroxaban) or PT (apixaban, rivaroxaban) the morning of procedure to assess anticoagulant effect.</td></tr>
<tr><td>2 risk factor</td><td>3 days</td></tr>
<tr><td>3 risk factors</td><td>4 days</td></tr>
<tr><td>betrixaban (Bevyxxa)</td><td>Days to stop betrixaban prior to procedure</td><td colspan="9">At least 4 days</td><td>continue betrixaban</td><td>consider holding 3 days prior if high bleeding concern</td></tr>
<tr><td rowspan="3">edoxaban (Savaysa)</td><td rowspan="3">Days to stop edoxaban prior to procedure</td><td>CrCl 50-95</td><td>2 days</td><td>3 days</td><td>2 days</td><td>3 days</td><td>1 day</td><td>2 days</td><td rowspan="3">continue edoxaban</td><td>consider holding 1 day prior if high bleeding concern</td></tr>
<tr><td>CrCl 30-</td><td>3 days</td><td rowspan="2">4 days</td><td rowspan="2">3 days</td><td rowspan="2">4 days</td><td rowspan="2">2 days</td><td rowspan="2">3 days</td><td rowspan="2">consider holding 2 days prior if high bleeding concern</td></tr>
<tr><td>CrCl 15-29</td><td>4 days</td></tr>
<tr><td rowspan="3">rivaroxaban (Xarelto)</td><td rowspan="3">Days to stop rivaroxaban prior to procedure</td><td>CrCl ≥ 50</td><td>2 days</td><td>3 days</td><td>2 days</td><td>3 days</td><td>1 day</td><td>2 days</td><td rowspan="3">continue rivaroxaban</td><td>consider holding 1 day prior if high bleeding concern</td></tr>
<tr><td>CrCl 30-49</td><td>3 days</td><td rowspan="2">4 days</td><td rowspan="2">3 days</td><td rowspan="2">4 days</td><td rowspan="2">2 days</td><td rowspan="2">3 days</td><td rowspan="2">consider holding 2 days prior if high bleeding concern</td></tr>
<tr><td>CrCl 15-29</td><td>4 days</td></tr>
</table>

Other therapeutic considerations		Consider addition of tranexamic acid or aminocaproic acid mouthwash for dental procedures. Tranexamic acid dosing for dental procedures: Oral rinse, 4.8% solution. Hold 10 mL in mouth and rinse for 2 minutes, then spit out. First dose 10 minutes prior to procedure. Repeat 4 times daily (~every 6 hours) for 2 days after procedure. Patient should not eat or drink for 1 hour after using oral rinse (Carter, 2003).

Table continues on next page with Direct Thrombin (Factor IIa) Inhibitors

Management of Periprocedural Anticoagulation (DOACs)

	Bleeding Risk		High			Intermediate			Low			Minor			Other considerations
	Thrombotic Risk		Ultra-High, High	Inter-mediate	Low	Ultra-High, High	Inter-mediate	Low	Ultra-High, High	Inter-mediate	Low	Ultra-High, High	Inter-mediate	Low	
Direct Thrombin (Factor IIa) Inhibitors															
dabigatran (Pradaxa)	Days to stop dabigatran prior to procedure	CrCl ≥ 80	4 days			2 days	4 days		1.5 days	2 days		continue dabigatran		consider holding 1 day prior if high bleeding concern	**Bridging:** not indicated **Resuming Anticoagulation:** Following the procedure, anticoagulation should be resumed as soon as safe based on hemostasis and bleeding risk, at least 24-48 hours postoperatively. **Labs:** If high bleeding risk, consider checking dabigatran level, thrombin time or aPTT the morning of procedure to assess anticoagulation effect.
		CrC l 50-79				3 days			2 days						
		CrC l 30-49	5 days	6 days		4 days	5 days		3 days	4 days				consider holding 2 days prior if high bleeding concern	
		CrC l 15-29		7 days		5 days	7 days		4 days	5 days					
Other therapeutic considerations												Consider addition of tranexamic acid or aminocaproic acid mouthwash for dental procedures. Tranexamic acid dosing for dental procedures: Oral rinse, 4.8% solution. Hold 10 mL in mouth and rinse for 2 minutes, then spit out. First dose 10 minutes prior to procedure. Repeat 4 times daily (~every 6 hours) for 2 days after procedure. Patient should not eat or drink for 1 hour after using oral rinse (Carter, 2003).			

Management of Periprocedural Anticoagulation (Bleeding Risks)

Procedural BLEEDING Risk			
High	**Intermediate**	**Low**	**Minor**
Complex cardiac surgery (CABG, valvular surgery, trans-septal procedures) Complex ophthalmologic surgery Hepatectomy or liver biopsy Nephrectomy or kidney biopsy Neurosurgical and spine surgery Plastic Surgery Spinal anesthesia Splenectomy Vascular surgery	Abdominal surgery (non-vascular) Simple cardiac procedures, cardiac catheterization Extensive oral surgery or ENT procedures Genitourinary procedures Endoscopic procedures (if intervention is possible, i.e., polypectomy, sphincterotomy) Joint replacement surgery Thoracotomy	Cholecystectomy Abdominal hernia repair Abdominal hysterectomy	Dental procedures (single or multiple tooth extraction, endodontic procedure/root canal) Dermatologic procedures (excision of basal cell or squamous cell carcinoma, actinic keratosis, malignant or premalignant nevi, Mohs procedure) Endoscopic procedures (if no planned intervention) Ophthalmologic procedures (cataracts or glaucoma procedures)

Management of Periprocedural Anticoagulation (Thrombotic Risks)

Patient THROMBOTIC Risk			
Ultra High	**High**	**Intermediate**	**Low**
History of thromboembolism when anticoagulation held	1) Mechanical valves a) Any mitral or tricuspid valve prosthesis b) Older caged ball (Starr-Edwards) or tilting disc (Bjork-Shiley, Medtronic-Hall) aortic prosthesis c) Bileaflet (St Jude, Carbomedics) aortic valves with additional risk factors* d) Stroke or TIA in past 6 months 2) Atrial fibrillation a) $CHADS_2$ score 5-6 b) Rheumatic valvular heart disease c) Stroke or TIA in past 3 months 3) VTE a) VTE in past 3 months b) Severe thrombophilia (e.g. antiphospholipid syndrome) c) Multiple thrombophilic conditions	1) Mechanical valves a) Bileaflet (St Jude, Carbomedics) aortic valves with additional risk factors* 2) Atrial fibrillation a) $CHADS_2$ score 3-4 3) VTE a) VTE within the past 3-12 months b) Recurrent VTE c) Mild thrombophilia (e.g. factor V Leiden mutation) d) Active cancer (treated within 6 months or palliative)	1) Mechanical valves (non-mitral) a) Bileaflet without atrial fibrillation or other stroke risk factors* 2) Atrial fibrillation a) $CHADS_2$ score 0-2 3) VTE b) Single VTE > 6 months ago without other stroke risk factors*
***Additional risk factors for thromboembolism with mechanical valves:** atrial fibrillation, prior thromboembolism, hypercoagulable condition, EF < 30%, or multiple valves			

	$CHADS_2$, Scoring	
C	**1**	CHF
H	**1**	HTN
A	**1**	Age > 75
D	**1**	Diabetes Mellitus
S_2	**2**	Stroke or TIA

Cardiac EP Service Recommendations for Anticoagulation prior to Cardioversion

Electrophysiology Procedure Anticoagulation and Antiplatelet Recommendations							
		New Implants (PPM, ICD, CRT)	**Generator Changes**	**Extractions**	**Epicardial, Left-sided VT and PVC Ablation**	**Atrial Fibrillation/ Flutter Ablation**	**Watchman Device**
DFTs		Therapeutic anticoagulation for 3 consecutive weeks (or TEE) in presence of atrial arrhythmia	Not indicated unless specified by EP MD	N/A	N/A	N/A	N/A
$CHADS_2$ score 5-6, HCM, prior stroke off a/c, mechanical mitral or tricuspid valve, stroke < 6 months prior to procedure		Talk with EP MD regarding anticoagulation recommendation					
warfarin	Pre-procedure (CHADS2 score ≤ 4)	Hold 2 days prior to procedure, unless DFTs indicated and/or patient with atrial arrhythmia.	Hold 2 days prior to procedure, unless DFTs indicated and/or patient with atrial arrhythmia. Procedure goal INR 2-2.5	Goal INR ≤ 1.6 for procedure	Goal INR ≤ 1.6 for procedure	Goal INR 2-2.5 for 3 weeks prior to procedure	Goal INR 1.7-2.5 for procedure Lots of time: Transition to warfarin any time prior to procedure There is limited time: Start Coumadin 5 days prior to procedure & discontinue DOAC 2 days prior to procedure
	Post-procedure	Restart the evening of the procedure	Restart the evening of the procedure	Restart the evening of the procedure	Restart the evening post procedure, minimum of 8 weeks	Restart the evening post procedure, minimum of 8 weeks	Restart the evening post procedure, minimum of 45 days
	TEE pre-procedure	N/A	N/A	N/A	If INR subtherapeutic any time in 3 weeks prior to procedure and patient in atrial fibrillation on the day of the procedure.	If INR subtherapeutic any time in 3 weeks prior to procedure and patient in atrial fibrillation on the day of the procedure. Timing: day prior or morning of or intra-procedure.	TEE performed with all Watchman device placements

Cardiac EP Service Recommendations for Anticoagulation prior to Cardioversion

Electrophysiology Procedure Anticoagulation and Antiplatelet Recommendations							
		New Implants (PPM, ICD, CRT)	**Generator Changes**	**Extractions**	**Epicardial, Left-sided VT and PVC Ablation**	**Atrial Fibrillation/ Flutter Ablation**	**Watchman Device**
enoxaparin (Lovenox, SQ) heparin (IV)	Pre-procedure	No heparin products (IV or SQ) for 6 hours prior to procedure	No heparin products (IV or SQ) for 6 hours prior to procedure	No heparin products (IV or SQ) for 6 hours prior to procedure	No heparin products (IV or SQ) for 4 hours prior to procedure	No heparin products (IV or SQ) for 4 hours prior to procedure	No heparin products (IV or SQ) for 4 hours prior to procedure
	Post-procedure ($CHADS_2$ score ≤ 4	No heparin products (IV or SQ) indicated for patients with $CHADS_2$ score ≤ 4	No heparin products (IV or SQ) indicated for patients with $CHADS_2$ score ≤ 4	No heparin products (IV or SQ) indicated for patients with $CHADS_2$ score ≤ 4	Restart (without bolus if IV): timing per EP MD recommendation	Restart (without bolus if IV): timing per EP MD recommendation	Restart (without bolus if IV): timing per EP MD recommendation
	Post-procedure ($CHADS_2$ score >4)	Restart (without bolus if IV): timing per EP MD recommendation	Restart (without bolus if IV):timing per EP MD recommendation	Restart (without bolus if IV): timing per EP MD recommendation	Restart: timing per EP MD recommendation	Restart: timing per EP MD recommendation	Restart: timing per EP MD recommendation
	TEE pre-procedure	N/A	N/A	N/A	N/A	If INR subtherapeutic any time in 3 weeks prior to procedure and patient in atrial fibrillation on the day of the procedure. **Timing:** day prior or morning of or intra-procedure.	TEE performed with all Watchman device placements

Cardiac EP Service Recommendations for Anticoagulation prior to Cardioversion

Electrophysiology Procedure Anticoagulation and Antiplatelet Recommendations							
		New Implants (PPM, ICD, CRT)	**Generator Changes**	**Extractions**	**Epicardial, Left-sided VT and PVC Ablation**	**Atrial Fibrillation/ Flutter Ablation**	**Watchman Device**
edoxaban (Savaysa) **rivaroxaban (Xarelto)**	Pre-procedure (CHADS2 score ≤ 4)	Hold for 1 dose prior to the procedure (evening prior to procedure vs morning of procedure depending on patient's regimen)	Hold for 1 dose prior to the procedure (evening prior to procedure vs morning of procedure depending on patient's regimen)	CrCl > 50: hold 2 days CrCl 15-49: hold 3 days	CrCl > 50: hold 2 days CrCl 15-49: hold 3 days	If taken with morning meal: hold the morning of procedure If taken with evening meal: continue uninterrupted	Discontinue with start of warfarin for procedure
	Post-procedure	Restart with evening dose	Restart with evening dose	Restart with evening dose 48 hours post procedure	Restart the evening post procedure, minimum of 8 weeks	Restart the evening post procedure, minimum of 8 weeks	Not indicated
	TEE pre- or intra-procedure	N/A	N/A	N/A	Day prior to, or morning of, or intra-procedure if patient in atrial fibrillation/flutter on the day of the scheduled ablation	If uninterrupted anticoagulation for 21 consecutive days: no TEE indicated If subtherapeutic anticoagulation: day prior to, or morning of, or intra-procedure on the day of the scheduled ablation	TEE performed with all Watchman device placements
apixaban (Eliquis) **dabigatran (Pradaxa)**	Pre-procedure (CHADS2 score ≤ 4)	Hold dose the evening prior and morning of procedure	Hold dose the evening prior and morning of procedure	Eliquis: hold 2 days Pradaxa: CrCl > 80: hold 2 days CrCl 50-79: hold 3 days CrCl 30-49: hold 4 days CrCl 15-29: hold 5 days	Eliquis: hold 2 days Pradaxa: CrCl > 80: hold 2 days CrCl 50-79: hold 3 days CrCl 30-49: hold 4 days CrCl 15-29: hold 5 days	Hold dose the morning of procedure	Discontinue with start of warfarin for procedure
	Post-procedure	Restart with evening dose	Restart with evening dose	Restart with evening dose 48 hours post procedure	Restart the evening post procedure, minimum of 8 weeks	Restart the evening post procedure, minimum of 8 weeks	Not indicated
	TEE pre or intra-procedure	N/A	N/A	N/A	Day prior to, or morning of, or intra-procedure if patient in atrial fibrillation/flutter on the day of the scheduled ablation	If uninterrupted anticoagulation for 21 consecutive days: no TEE indicated If subtherapeutic anticoagulation: day prior to, or morning of, or intra-procedure on the day of the scheduled ablation	TEE performed with all Watchman device placements

Cardiac EP Service Recommendations for Anticoagulation prior to Cardioversion

Electrophysiology Procedure Anticoagulation and Antiplatelet Recommendations							
		New Implants (PPM, ICD, CRT)	**Generator Changes**	**Extractions**	**Epicardial, Left-sided VT and PVC Ablation**	**Atrial Fibrillation/ Flutter Ablation**	**Watchman Device**
aspirin **clopidogrel (Plavix)** **prasugrel (Effient)** **ticagrelor (Brilinta)**	Pre-procedure (CHADS2 score ≤ 4), PCI/CABG > 12 months	Uninterrupted if only agent, otherwise hold 7 days	Uninterrupted if only agent, otherwise hold 7 days	Uninterrupted if only agent, otherwise hold 7 days	uninterrupted	uninterrupted	Continue aspirin uninterrupted; clopidogrel as below
	Post-procedure	Restart on 5th day post procedure	Restart on 5th day post procedure	Restart on 5th day post procedure	Restart evening after procedure	Restart evening after procedure	Refer to Dr. Goessl
	Stent < 6 months	uninterrupted	uninterrupted	uninterrupted	uninterrupted	uninterrupted	Refer to Dr. Goessl
	Stent 6-12 months	single agent	single agent	single agent	single agent	single agent	Refer to Dr. Goessl

Cardiac EP Service Recommendations for Anticoagulation prior to Cardioversion

1. Warfarin with INR ≥ 2.0 or Pradaxa 150 mg BID or Xarelto 20 mg daily or Eliquis 5 mg BID for at least 21 consecutive days prior to procedure.
    a. If question/concern of patient medical compliance or any known missed doses with DOAC, recommend low threshold for performing TEE guided DCCV.
    b. Renal dose of:
        i. Pradaxa 75 mg BID for Cr Cl 15-30 mL/min
        ii. Xarelto 15 mg QD for Cr Cl 15-50 mL/min
        iii. Eliquis 2.5 mg if 2 of the 3: age > 80 years, creatinine ≥ 1.5 mg/dL, weight < 60 kg
2. If sub-therapeutic anticoagulation (INR < 2.0 or not on DOAC 21 consecutive days), then patient will need TEE prior to cardioversion.
    a. TEE outcome and plan of care based on TEE MD findings:
        i. Need for 3 weeks of anticoagulation with or without repeat TEE at time of future cardioversion will be determined by patient care team
3. If patient presents with clearly defined onset of arrhythmia < 48 hours, then DCCV can be performed without TEE.
4. Treat with anticoagulation for a minimum of 1 month post cardioversion and long-term per risk stratification using $CHA2DS_2VASc$ score.
5. Patients who undergo TEE guided DCCV should be anti-coagulated at the time of TEE guided DCCV. It is recommended to start anticoagulation <u>at the time the decision was made</u> to proceed with TEE guided Cardioversion.
    a. Started on warfarin and IV heparin with therapeutic level prior to TEE/cardioversion and continued until INR ≥ 2.0
        i. Therapeutic heparin level 0.3-0.5 units/mL or
        ii. Therapeutic aPTT ≥ 55 seconds
            1. based on ACUTE trial: aPTT 1.5-2.5 times the control, ANW control value 27-35 seconds
    b. Started on warfarin with Lovenox 1 mg/kg SQ q 12 h. Lovenox bridge until INR ≥ 2.0
        i. Minimum of first dose of Lovenox 2 hours prior to procedure
        ii. If possible, 2-3 doses of Lovenox prior to the TEE/DCCV (allows for steady state)
    c. Pradaxa 75-150 mg BID (no heparin bridge necessary)
        i. Minimum of first dose of Pradaxa 2 hours prior to TEE/DCCV (caution use with NPO status due to GI upset)
        ii. When possible 2-3 days of Pradaxa prior to TEE/DCCV (allows for steady state)
    d. Xarelto 15-20 mg QD (no heparin bridge necessary)
        i. Minimum of first dose of Xarelto 2 hours prior to TEE/DCCV (contraindicated to start/give dose with NPO status due to bio-availability concerns)
        ii. When possible 2-3 days of Xarelto prior to TEE/DCCV (allows for steady state)
    e. Eliquis 2.5-5 mg BID (no heparin bridge necessary)
        i. Minimum of first dose of Eliquis 2 hours prior to TEE/DCCV
        ii. When possible 2-3 days of Eliquis prior to TEE/DCCV (allows for steady state)

Management of Periprocedural Anticoagulation (Cardiac Catheterization Lab)

PROCEDURE	ANTICOAGULANT	ELECTIVE	EMERGENT
Right heart catheterization	warfarin	Can be done without stopping warfarin if INR <3.0	Can be done without stopping warfarin
	DOAC*	Can be done without stopping DOAC	Can be done without stopping DOAC
Left heart catheterization (such as coronary angiography and PCI)	warfarin	Can be done without stopping warfarin if INR <3.0	Can be done without stopping warfarin
	DOAC*	**Stop DOAC before procedure** (see below Table)	Can be done without stopping DOAC
CTO PCI, PCI with hemodynamic support, Complex PCI	warfarin	**Stop warfarin – INR should be <1.6****	Can be done without stopping warfarin
	DOAC*	**Stop DOAC before procedure** (see below Table)	Can be done without stopping DOAC
Endomyocardial biopsy	Warf warfarin arin	**Stop warfarin – INR should be <1.6****	Can be done without stopping warfarin
	DOAC*	**Stop DOAC before procedure** (see below Table)	Can be done without stopping DOAC

*DOAC: direct oral anticoagulants: dabigatran, apixaban, edoxaban, rivaroxaban

**Biopsy with higher INR will be considered on a case by case basis for transplant patients after ≥ 3 months from transplantation

Management of Periprocedural Anticoagulation (Cardiac Catheterization Lab)

DIRECT FACTOR XA INHIBITORS	DAYS TO HOLD
apixaban (Eliquis)	2 days
edoxaban (Savaysa)	
Creatinine clearance: 50-95	2 days
Creatinine clearance: 15-49	3 days
rivaroxaban (Xarelto)	
Creatinine clearance: > 50	2 days
Creatinine clearance: 15-49	3 days
DIRECT THROMBIN FACTOR IIA INHIBITOR	**DAYS TO HOLD**
dabigatran (Pradaxa)	
Creatinine clearance: >80	2 days
Creatinine clearance: 50-79	3 days
Creatinine clearance: 30-49	4 days
Creatinine clearance: 15-29	5 days

Creatinine clearance calculator: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

References

http://akn.allina.com/content1/groups/patient-care/@akn-pharmacy/documents/patient_care_documents/243996.pdf
http://akn.allina.com/content1/groups/patient-care/@akn-pharmacy/documents/patient_care_documents/243992.pdf

Management of Periprocedural Anticoagulation (Neuraxial Access or Peripheral Nerve Procedures)

Anticoagulation Guidelines for Neuraxial Access or Peripheral Nerve Procedures

Below are guidelines to prevent spinal hematoma following Epidural/Intrathecal/Spinal procedures and perineural hematoma following peripheral nerve procedures. Procedures include epidural injections/infusions, intrathecal injections/infusions/pumps, spinal injections, peripheral nerve catheters, and plexus infusions. Decisions to deviate from guideline recommendations given the specific clinical situation are the decision of the provider. See 'Additional Comments' section for more details.

	PRIOR to Neuraxial/Nerve Procedure	**WHILE Neuraxial/Nerve Catheter in Place**	**AFTER Neuraxial/Nerve Procedure**	**Comments**
Anticoagulant	How long should I hold prior to neuraxial procedure? (i.e., minimum time between the last dose of anticoagulant and spinal injection OR neuraxial/nerve placement)	Can I give anticoagulants concurrently with neuraxial, peripheral nerve catheter, or plexus placement?	When can I restart anticoagulants after neuraxial procedures? (i.e., minimum time between catheter removal or spinal/nerve injection and next anticoagulation dose)	What additional information do I need to consider?
Low-Molecular Weight Heparins, Unfractionated Heparin, and Fondaparinux				
Unfractionated Heparin SQ **Prophylaxis** Dosing	5000 units Q 12 hrs – no time restrictions	Yes	2 hrs	Maximum total heparin dose of 10,000 units per day (5000 SQ Q12 hrs) Heparin 5000 units SQ 8 hrs is **NOT** recommended with concurrent neuraxial catheter in place For IV prophylactic dosing, use 'treatment' IV dosing recommendations.
Unfractionated Heparin SQ/IV **Treatment** Dosing	SQ: 8-10 hrs IV: 4 hrs	No	2 hrs	See 'Additional Comments'
Enoxaparin (Lovenox), Dalteparin (Fragmin) **Prophylaxis** Dosing	12 hrs	No Note: May be used for **Enhanced Treatment Protocol**	4 hrs	**Caution in combination with other hemostasis-altering medications** See 'Additional Comments' for **Enhanced Treatment protocol** specifics
Enoxaparin (Lovenox), Dalteparin (Fragmin) **Treatment** Dosing	24 hrs	No	4 hrs	Recommendations for treatment remain same regardless of dosing (1mg/kg twice daily vs. 1.5mg/kg daily for enoxaparin)
Fondaparinux (Arixtra)	4 days	No	24 hrs	See 'Additional Comments'
Vitamin K Antagonist				
Warfarin (Coumadin)	INR <1.4 See comments*	No Yes for peripheral nerve catheters	2 hrs	*Typically takes holding warfarin 4-5 days prior to insertion *See reference specific to warfarin
Factor Xa Inhibitor				
Rivaroxaban (Xarelto)	3 days	No Yes for peripheral nerve catheters	6 hrs	
Apixaban (Eliquis)	3 days	No Yes for peripheral nerve catheters	6 hrs	

Management of Periprocedural Anticoagulation (Neuraxial Access or Peripheral Nerve Procedures)

	PRIOR to Neuraxial/Nerve Procedure	**WHILE Neuraxial/Nerve Catheter in Place**	**AFTER Neuraxial/Nerve Procedure**	**Comments**
Anticoagulant	How long should I hold prior to neuraxial procedure? (i.e., minimum time between the last dose of anticoagulant and spinal injection OR neuraxial/nerve placement)	Can I give anticoagulants concurrently with neuraxial, peripheral nerve catheter, or plexus placement?	When can I restart anticoagulants after neuraxial procedures? (i.e., minimum time between catheter removal or spinal/nerve injection and next anticoagulation dose)	What additional information do I need to consider?
Edoxaban (Savaysa)	3 days	No Yes for peripheral nerve catheters	6 hrs	
Betrixaban (Bevyxxa)	5 days	No Yes for peripheral nerve catheters	6 hrs	
Direct Thrombin Inhibitors				
Dabigatran (Pradaxa)	4 days 6 days (renal disease)	No – See additional comments Yes for peripheral nerve catheters	6 hrs	
Argatroban (Argatra)	4-6 hrs or aPTT <40 sec	No	2 hrs	t1/2 = 39-51 minutes – see 'Additional comments
Bivalirudin (Angiomax)	4-6 hrs or aPTT <40 sec 18 hrs if HD dependent	No	2 hrs	T1/2 22-40 minutes Up to 3.5 hours in HD
NSAIDS & Antiplatelet				
NSAIDs	No time restrictions	Yes	May resume immediately after catheter removal/procedure	For planned procedure may consider holding NSAID based on half-life. See 'Additional Comments'
COX-2 Inhibitors	No time restrictions	Yes	May resume immediately after catheter removal/procedure	See 'Additional Comments'
Aspirin	No time restrictions – see comments	Yes – if no concurrent drugs affecting coagulation	May resume immediately after catheter removal/procedure	For planned procedure, consider holding ASA for 3 days in primary prophylaxis and 12 hrs in secondary prophylaxis. Recommendations are the same regardless of dose (81 mg versus 325 mg)
Clopidogrel (Plavix)	7 days	No	12 h 75 mg dose 24 h ≥300 mg dose	
Prasugrel (Effient)	7 days	No	24 hrs	Per ASRA recommendations
Ticagrelor (Brillinta)	5 days	No	24 hrs	Per ASRA recommendations
Cangrelor (Kengreal)	1 hour	No	24 hrs	No data, recommendations based on pharmacokinetics and recs from the same drug class
Dipyridamole/Aspirin (Aggrenox)	7 days	No	24 hrs	Per ASRA recommendations
Cilostazol (Pletal)	2 days	No	2 hrs	Per ASRA recommendations, limited information available.
Pentoxifylline (Trental)	7 days	No	2 hrs	Limited information available to guide use
Vorapaxar (Zontivity)	28 days	No	24 hrs	No data, recommendations based on pharmacokinetics and recs from P2Y12 antagonist drug class

Management of Periprocedural Anticoagulation (Neuraxial Access or Peripheral Nerve Procedures)

	PRIOR to Neuraxial/Nerve Procedure	**WHILE Neuraxial/Nerve Catheter in Place**	**AFTER Neuraxial/Nerve Procedure**	**Comments**
Anticoagulant	How long should I hold prior to neuraxial procedure? (i.e., minimum time between the last dose of anticoagulant and spinal injection OR neuraxial/nerve placement)	Can I give anticoagulants concurrently with neuraxial, peripheral nerve catheter, or plexus placement?	When can I restart anticoagulants after neuraxial procedures? (i.e., minimum time between catheter removal or spinal/nerve injection and next anticoagulation dose)	What additional information do I need to consider?
Glycoprotein IIb/IIIa Inhibitors				
Abciximab (Reopro)	5 days	No	8 hrs	
Eptifibatide (Integrelin)	24 hrs	No	8 hrs	
Tirofiban (Aggrastat)	24 hrs	No	8 hrs	

Additional Comments

Low-Molecular Weight Heparin

- Concurrent antiplatelet medications are contraindicated. Case reports since 2003 have demonstrated an increase in spinal hematoma incidence when LMWH is administered with other antiplatelet agents. [1, 5, 6]
- The guidelines have recommended against twice-daily dosing, but have accepted that once-daily dosing is safe.[1]
- ***Enhanced Treatment Protocol NOTE approved for enoxaparin 40mg SQ daily, NOT 30mg SQ every 12 hours:***
  - Must wait 8 hrs after catheter PLACEMENT before giving dose
  - Must wait 12 hrs after last dose before REMOVING catheter

Fondaparinux (Arixtra)

- Studies have looked at the use of fondaparinux with indwelling catheters. The practice is currently not recommended in the United States, however, the interval as described in the EXPERT study showed no increased incidence of spinal epidural hematoma.[7]

Warfarin (Coumadin)

- The guidelines have consistently recommended an INR of <1.5 before removal of epidural catheter, although it has been questioned. A series of 11,235 patients received epidural analgesia for total knee replacement in which they were given 5-10 mg of warfarin the night before surgery. Epidural catheters were removed within 48 hours, and the mean INR of 1,030 patients at the time of removal was 1.5 (nearly 40% of this subset). No spinal hematomas were reported in this series.[8]
- Peripheral nerve catheters: in a review of 3588 patients receiving a variety of prophylactic dosed anticoagulants (LMWH, fondaparinux, warfarin, and ASA), no recorded perineural hematomas were documented after receiving single or continuous peripheral nerve blocks.[10]

Unfractionated Heparin

- Assessment of sensory and motor function should be monitored for at least 12 hours after catheter removal.
- is this needed? Noted above

Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)

- Lack of information available and looking at the population these agents are often used for (HIT patients who need therapeutic anticoagulation), no recommendations can be made.[1,2]
- Recommendations are based on half-life elimination of the medication and waiting approximately five half-lives for the medication to clear.

NSAIDs and Antiplatelet Agents

- Nonsteroidal anti-inflammatory drugs alone do not increase the risk of bleeding, however in combination with UFH, LMWH, oral anticoagulants, and thrombolytics, there is an increased frequency of bleeding and spinal hematoma.[1]
- Nabumetone is part of the Enhanced Recovery order set
- For selective COX-2 inhibitors, there is no evidence of any effects on platelet aggregation or increased bleeding tendency.[4]
- Recommended discontinuation times of NSAIDs for planned procedures vary by the half-life of the drug. Discontinuation for 5 half-lives is sufficient to allow the drug's effects on platelets to be inactive (see table below).

Agent	Recommended Discontinuation Time, days
diclofenac	1
etodolac	2
ibuprofen	1
indomethacin	2
ketorolac	1

Agent	Recommended Discontinuation Time, days
meloxicam	4
nabumetone	6
naproxen	4
oxaprozin	10
piroxicam	10

Aspirin

- 81 mg versus 325 mg: Recommendations remain the same regardless of dose
- It is known that low-dose aspirin (60-325 mg) creates the largest effect on platelet function, however a study in high-risk obstetric patients who were given aspirin 60 mg daily with epidural anesthesia produced no neurologic deficits.[9]

Glycoprotein IIb/IIIa Inhibitors

- Used only in acute coronary syndromes in combination with anticoagulants and aspirin, and generally cardiac procedures are usually conducted as emergencies, so neuraxial blockade is contraindicated
- Platelet counts should always be obtained due to thrombocytopenia effects if neuraxial blockade is required.[2]

Conclusion

An assortment of guidelines can be found on neuraxial access in the anticoagulated patients with slight variations between each. The United States (American Society of Regional Anesthesia and Pain Medicine) guidelines tend to be more conservative versus those in Europe (European Society of Anaesthisology). Much of what is known is based on case reports and limited trial reviews. New anticoagulants (rivaroxaban and dabigatran) and antiplatelet agents (ticagrelor and prasurgrel) have information regarding use perioperatively and postoperatively listed in the product insert, however this information does not specifically address neuraxial access. Close patient monitoring for sensory and motor dysfunction should be reviewed frequently postoperatively. Performing neuraxial procedures before, during, and after anticoagulation is a controversial topic, and providers should be aware of the risks of such procedures in the anticoagulated patient.

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DVT and PE Anticoagulation Prophylaxis in Medically Ill Patients

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July 1, 2019	DVT AND PE ANTICOAGULATION PROPHYLAXIS IN MEDICALLY ILL PATIENTS

Introduction:

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) remains a major health problem with very high mortality rate and economic toll to the U.S. health system. It is highly prevalent and is considered among the major causes for death in the U.S. Nearly one third will have a recurrent event. It is estimated that 100.000 people die each year of VTE. Almost half of VTE occurs during or after hospitalization, and PE accounts for 10% of inpatient mortality. Hospitalized medically ill patients are under significant increased risk for VTE during and after their hospital stay. Although VTE prophylaxis for medically ill inpatients is crucially important, clear guideline and standard recommendations are lacking.

This document provides up-to-date and evidence-based recommendations for the VTE prophylaxis in medically ill hospitalized patients.

Evidence:

Around 15 million patients are admitted yearly in the U.S. with a medical, non-surgical illness.[1] Close to 8 million medically ill hospitalized patients are at risk for VTE with estimated 200.000 cases reported yearly despite prophylaxis.[2,3] Factors that increase risk for VTE in medically ill hospitalized patients include age, different comorbidities, immobility, hypercoagulability and renal insufficiency. [4] Among hospitalized medically ill patients, 75% have multiple risk factors increasing VTE risk up to 8 folds than the general population.[4,5] Around 21% of these VTE cases are fatal translating into 40.000 deaths yearly.[2] 75% of fatal VTE occur in a medically ill hospitalized patients.[4] Patients admitted with VTE have longer hospital stay and higher cost (up to $50.000 in difference) than other admissions.[6] Furthermore, medically ill patients have increased VTE-related readmission rate that reaches up to 28%.[6] Based on a large retrospective analysis, more than 50% of 6 month VTE cumulative risk occurs in the first month following hospitalization, and 57% of VTE occurs post-discharge despite inpatient prophylaxis.[7]

The 2012 ACCP guidelines recommended using low molecular weight heparin (LMWH), low dose (bid or tid) unfractionated heparin (LDUH), or fondaparinux in acutely ill hospitalized patients at increased risk for thrombosis (Grade 1B).[8] Most of the trials included acutely ill hospitalized patients (mean age was >65 years), admitted for congestive heart failure (CHF), severe respiratory disease, or acute infectious, rheumatic, or inflammatory conditions who were immobilized and had at least one more risk factor (e.g. age >40, active cancer, previous VTE, or serious infection). Duration of prophylaxis use ranged from 6-21 days or discharge from hospital, whichever came first.[4] Meta-analysis of multiple trials demonstrated that anticoagulant thrombophylaxis was associated with significant reduction in fatal PE and symptomatic DVT but without significant difference for non-fatal PE, major bleeding, and all-cause mortality.[4] Based on pooled analysis data, there was no significant difference seen between LDUH and LMWH for DVT, PE, overall mortality and HIT. However, there was less bleeding events seen with LMWH.[4] There is no compelling data to suggest that LDUH tid dosing, compared with bid dosing, reduces VTE or causes more bleeding.[4] In summary, there is no clear evidence in the current literature to support choosing one form of pharmacoprophylaxis over another in the medical population based on outcomes or from a cost-effectiveness standpoint. It would be reasonable to make choices based on patient preference, compliance, and ease of administration (eg, oral vs injection, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs.[4]

VTE prophylaxis with enoxaparin (6-14 days) in medically ill patients can significantly attenuate and reduce risk of VTE from 10-20 to 2-6%. [9-

[11] VTE or VTE related mortality rate is 2 times more on day 35 compared to day 10 post-hospitalization despite receiving prophylaxis with enoxaparin. [9] Extended duration of prophylaxis with enoxaparin versus with placebo to 28 days after standard enoxaparin dosage (EXCLAIM trial) showed significant reduction of VTE but with an expense of increased major bleeding. [12] The MAGELLAN trial found that in hospitalized patients for medical illness, rivaroxaban 10 mg for 31-39 days was non-inferior at 10 days and superior at 35 days for VTE rate compared to enoxaparin 6-14 days but with more major bleeding at both 10 and 35 days.[9] The ADOPT trial showed that in medically ill patients with an additional VTE risk, apixaban 2.5 mg twice daily was not superior to enoxaparin 6-14 days for VTE or related mortality with more major bleeding.[11] In patients admitted for acute medical illness with expected moderate/severe immobility in addition to age and other risks for VTE, the APEX trial demonstrated that extended betrixaban dose for 35-42 days was superior to 6-14 days of enoxaparin for VTE or related mortality with no significant difference in major but with slightly more clinically non-major bleeding.[13] The MARINER trial showed that rivaroxaban 10 mg daily, given to medical patients for 45 days after hospital discharge, was not associated with a significantly lower risk of symptomatic VTE and related death than placebo.[14]

Mechanical methods of thrombophylaxis including graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCs), and venous foot pumps (VFPs) were mostly studied in surgical patients. Based on pooled analyses, GCS did not show significant reduction in symptomatic VTE with some increased risk for skin breakdown.[4] No good quality studies of IPV or VFP devices in hospitalized medical patients.[4] Despite the uncertain benefit, mechanical thrombophylaxis with GCC or IPCs may be preferable to no prophylaxis in patients at risk for VTE who are at high risk for bleeding.[4]

In making recommendations regarding DVT prophylaxis in hospitalized medical patients, the ACCP recommended individualized approach based on balancing the benefits of reducing VTE with the risk of bleeding using risk assessment models (RAM). ACCP 2012 guidelines used Padua Prediction Scoring system (Table 1), which includes 11 common VTE risks and categorized medical hospitalized patients as low (< 4 points) and high (≥ 4 points) risk.[15] The evidence-derived IMPROVE VTE RAM utilized seven clinical risk factors that were independently associated with VTE risk in medically ill patients. The model used 1–3 points to designate three tiers of VTE risk: low VTE risk (symptomatic VTE < 1.0 %) designated with a score of 0–1, at-risk (or moderate VTE risk) with a VTE event rate of ~1.0–1.5 % designated with a score of 2 to 3, and high VTE risk with a VTE event rate of 4% or more, designated with a score of 4 or more (Table 2)[3].

The strongest risk factors to estimate bleeding risk in medical hospitalized patients are active gastrointestinal ulcer, bleeding in 3 months before admission, and PLT count of less than $50X10^9$/L, followed by age >85 years, hepatic failure, severe renal failure, and critical care unit admission.[4] The evidence-derived IMPROVE Bleed RAM used 13 clinical and laboratory factors and designated a score of 7 or more to identify a patient cohort (~10% of the population) at high risk of bleeding (major bleed risk 4.1% vs 0.4%) (Table 3)[3]. Both validated VTE as well as bleed risk scores (Padua and IMPROVE VTE and IMPROVE Bleed RAMs) can be used during admission to determine an individual medical patient's risk of VTE and major bleeding, allowing for a tailored (patient-centric) approach to thromboprophylaxis at the bedside.[3]

Medical patients with a Padua VTE score of 4 or more or an IMPROVE VTE score of more than 2, provided that they have an IMPROVE Bleed Risk score of < 7, would be at VTE risk and would warrant pharmacologic prophylaxis during their hospital stay. Those with an IMPROVE

Bleed Risk score of 7 or more should likely receive mechanical means of prophylaxis.[3]

Based on the trial results of extended prophylaxis with either enoxaparin or DOACs, it is prudent at this time to recommend either 6-14 days of prophylaxis with LMWH, LDUH, or fondaparinux, or oral betrixaban for 35-42 days.

Recommendations:

1- For acutely ill hospitalized medical patients at increased risk of thrombosis (Padua score of ≥ 4 or IMPROVE VTE risk score of ≥3), and low risk of bleeding (IMPROVE bleeding risk score of <7), we recommend anticoagulant thromboprophylaxis with LMWH, LDUH (bid or tid), fondaparinux or betrixaban.
   a) We suggest using LMWH over LDUH.
   b) In patients with history of HIT, we suggest using fondaparinux.
   c) In patients with CrCl < 30 ml/min, we suggest using LDUH.
   d) We suggest using betrixaban as an alternative to LMWH based on medication coverage and convenience (oral vs injectable).
   e) We suggest not to use other direct oral anticoagulants.

2- For acutely ill hospitalized medical patients at low risk of thrombosis (Padua score of < 4 or IMPROVE VTE risk score of < 3), we recommend against pharmacologic or mechanical thromboprophylaxis.

3- For acutely ill hospitalized medical patients at increased risk of thrombosis (Padua score of ≥ 4 or IMPROVE VTE risk score of ≥3), who are bleeding or at risk for bleeding (IMPROVE bleeding risk score of ≥7):
   a) We recommend against anticoagulant prophylaxis.
   b) We suggest optimal use of mechanical thrombophylaxis with GCS, or IPC.
   c) When bleeding risk decreases, and VTE risk persists, we suggest that pharmacologic thrombophylaxis substituted for mechanical prophylaxis.

4- In acutely ill hospitalized patients who receive an initial course of thrombophylaxis:
   a) We suggest against extending the duration of thrombophylaxis beyond the period of patient immobilization or acute hospitalization when heparin is used
   b) We recommend extended thrombophylaxis to 35-42 days when betrixaban is used.

5- We suggest against using thrombophylaxis in chronically immobilized patients including nursing home residents.

6- For dosing, refer to table 4.

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APPENDIX

Variable	Score
Active cancer	3
Previous VTE	3
Decreased mobility	3
Thrombophilia	3
Previous trauma or surgery within that last month	2
Age≥ 70	1
Heart and/or respiratory failure	1
Ischemic stroke or acute myocardial infarction	1
Acute rheumatologic disorder and/or acute infection	1
Obesity	1
Hormonal therapy	1

Table 1: Padua predictive score for VTE among hospitalized medical patients.
Score ≥ 4: high risk for VTE
Score < 4: low risk for VTE

VTE Risk Factor	Points
Previous VT	3
Known thrombophilia**	2
Cancer***	2
Current lower limb paralysis	2
Immobilization****	1
ICU/CCU stay	1
Age >60 years	1

Table 2: IMPROVE VTE Risk Model

ICU, intensive care unit; CCU, coronary care unit. A score of 0–1 constitutes low VTE risk. A score of 2–3 constitutes moderate VTE risk. A score of 4 or more constitutes high VTE risk. ** A congenital or acquired condition leading to an excess risk of thrombosis. *** May include active cancer (excluding non-melanoma skin cancer) or a history of cancer within 5 years. **** Strict definition is complete immobilization confined to bed or chair ≥ 7 days; modified definition is complete immobilization ≥ 1 day.

Variable	Score
Active gastric or duodenal ulcer	4.5
Prior bleeding within the last 3 months	4
Thrombocytopenia (<50x10^9/L)	4
Age ≥ 85 years	3.5
Liver failure (INR>1.5)	2.5
Severe kidney failure (GFR< 30 mL/min/m^2)	2.5
Admission to ICU or CCU	2.5
Central venous catheter	2
Rheumatic disease	2
Active malignancy	2
Age: 40-84 years	1.5
Male	1
Moderate kidney failure (GFR: 30-59 mL/min/m^2)	1

Table 3: IMPROVE Bleeding Risk Score

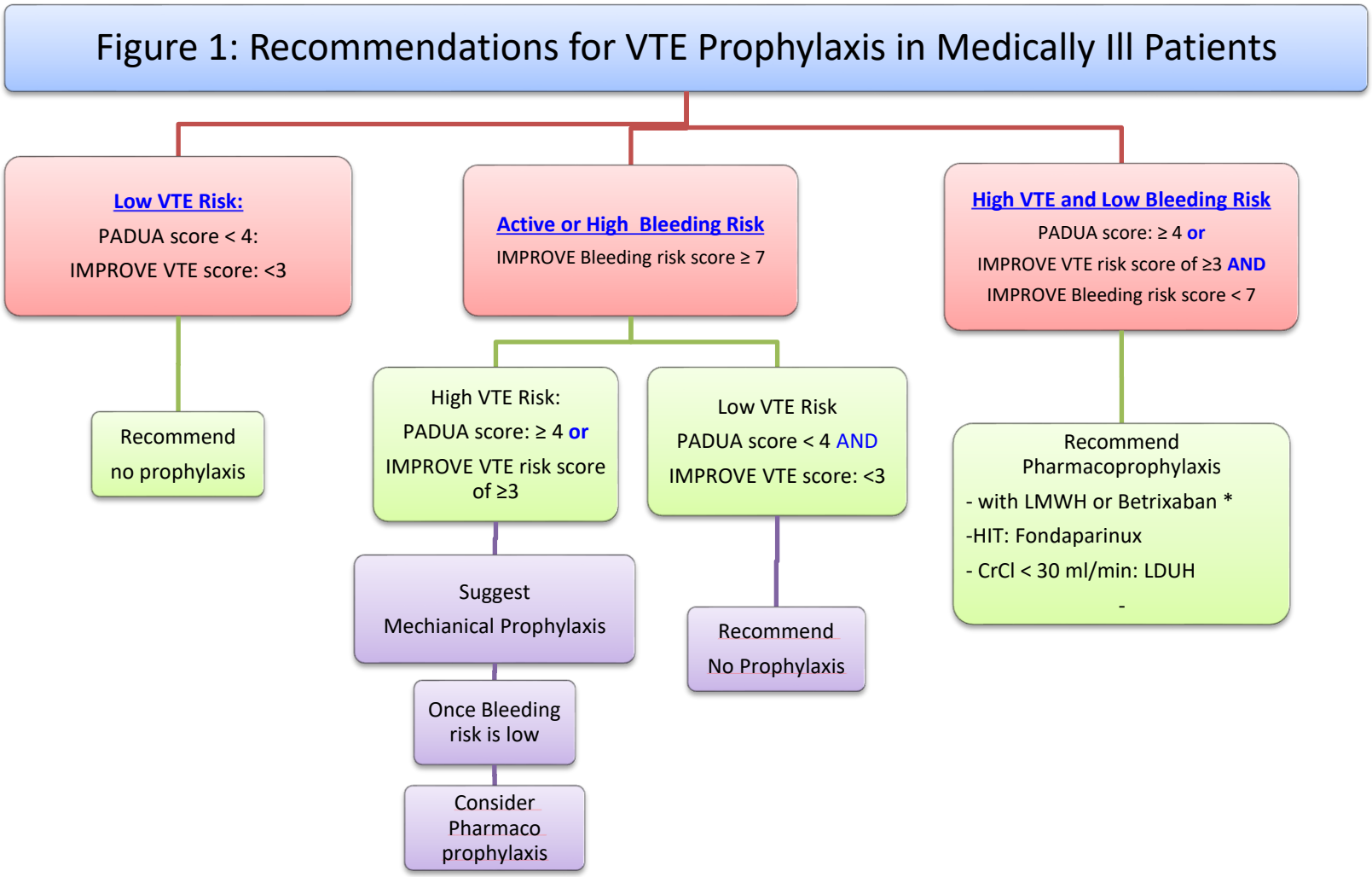
ICU, intensive care unit; CCU, critical care unit; CV, central venous; GFR, glomerular filtration rate; INR, international normalized ratio.

Interpretation: A score of 7 or more constitutes high bleed risk.

Anticoagulant	**Dose**
LDUH	<55kg or >65 years old: heparin 5000 units subcutaneous every 12 hours ≥55kg or ≥65 years old: heparin 5000 units subcutaneous every 8 hours
Enoxaparin	BMI <40 kg/m2: 40 mg SC qd BMI >40 kg/m2: 40 mg SC q12h OR 0.5mg/kg SC q12-24h
Fondaparinux	2.5 mg SC qd Should be avoided if a CrCl<30 or weight <50 kg
Betrixaban	-160 mg po first day followed by 80 mg po for 35-42 days - 80 mg po first day followed by 40 mg po for 35-42 days if concurrent use of P-gp inhibitors or CrCl of 15-30 mL/min

Table 4: Anticoagulant prophylaxis dosing information
BMI: Body mass index; CrCl: creatinine clearance; LDUH: low dose unfractionated heparin, po: oral; SC: subcutaneous.

Figure 1: Recommendations for VTE Prophylaxis in Medically Ill Patients



ESRD: End Stage Renal Disease; HIT: Heparin Induced Thrombocytopenia; LDUH: Low Dose Unfractionated Heparin, LMWH: Low Molecular Weight Heparin; VTE: Venous Thromboembolism .

***** We suggest using betrixaban as an alternative to LMWH based on medication coverage and convenience (oral vs injectable).

Thromboprophylaxis for Congenital Heart Patients

1. Simple, moderate, or complex congenital heart disease (CHD): follows our current guideline pre-cardioversion
2. Complex CHD with sustained or recurrent intra-atrial reentrant tachycardia (IART) or atrial fibrillation should be on long-term anticoagulation
3. Moderate CHD with sustained or recurrent IART or atrial fibrillation: long-term anticoagulation is reasonable
4. Moderate or complex CHD: vitamin K-dependent anticoagulant of choice (pending safety and efficacy data on newer agents)
5. Simple CHD with nonvalvular IART or atrial fibrillation: vitamin K-dependent anticoagulant, aspirin, or DOAC is reasonable option based on $CHA2DS_2VASc$ score and bleeding risk

Complexity	Type of congenital heart disease in adult patients	
Simple	*Native disease* - Isolated congenital aortic valve disease - Isolated congenital mitral valve disease (except parachute valve, cleft leaflet) - Small atrial septal defect - Isolated small ventricular septal defect (no associated lesions) - Mild pulmonary stenosis - Small patent ductus arteriosus	*Repaired conditions* - Previously ligated or occluded ductus arteriosus - Repaired secundum or sinus venosus atrial septal defect without residua - Repaired ventricular septal defect without residua
Moderate	- Aorto-left ventricular fistulas - Anomalous pulmonary venous drainage, partial or total - Atrioventricular septal defects, partial or complete - Coartation of the aorta - Ebstein anomaly - Infundibular right ventricular outflow obstruction of significance - Ostium primum atrial septal defect - Patent ductus arteriosus, not closed - Pulmonary valve regurgitation, moderate to severe - Pulmonary valve stenosis, moderate to severe - Sinus of Valsalva fistula/aneurysm	- Sinus venosus atrial septal defect - Subvalvular or supravalvular aortic stenosis - Tetralogy of Fallot - Ventricular septal defect with; o Absent valve or valves o Aortic regurgitation o Coarctation of the aorta o Mitral disease o Right ventricular outflow tract obstruction o Straddling tricuspid or mitral valve o Subaortic stenosis
Severe/complex	- Conduits, valved or nonvalved - Cyanotic congenital heart disease, all forms - Double-outlet ventricle - Eisenmenger syndrome - Fontan procedure - Mitral atresia - Single ventricle (also called double inlet or outlet, common, or primitive)	- Pulmonary atresia, all forms - Pulmonary vascular obstructive disease - Transposition of the great arteries - Tricuspid atresia - Truncus arteriosus/hemitruncus - Other abnormalities of atrioventricular or ventriculoarterial connection not included above (e.g., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)
Adapted from Warnes CA., et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol. 2008;52:1890-1947.		

Updated 3/14/2018

DVT and PE Anticoagulation Management Recommendations

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July 1, 2019	DVT AND PE ANTICOAGULATION MANAGEMENT RECOMMENDATIONS

Introduction:
Over the past six decades, warfarin has proven effective in reducing the risk of recurrent venous thromboembolism (VTE) in patients with acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE). However, there have been multiple challenges with using warfarin including delayed onset of action, need for bridging and monitoring as well as many drug-drug and drug-food interactions. Hence, long years of research have led to the development of direct oral anticoagulants (DOACs). Of the four currently FDA-approved DOACs, one is a direct thrombin inhibitor (dabigatran) and the other three are direct factor Xa inhibitors (apixaban, edoxaban and rivaroxaban). DOACs have been found to be at least as effective as warfarin with fewer bleeding complications. This document provides evidence based recommendations for the anticoagulation management of VTE.

Evidence:
DOACs provide more convenient treatment of VTE in the outpatient setting compared to heparin + warfarin due to less monitoring, and drug-drug and drug-food interactions. The 2016 CHEST guidelines suggest treatment of DVT of the leg and PE, in the absence of cancer, with a DOAC over warfarin therapy (Grade 2B) based on the potential for less bleeding and greater convenience with similar efficacy.[1] There is growing evidence to support the use of apixaban and rivaroxaban in cancer related VTE management. Dabigatran and edoxaban require 5-10 days of parenteral anticoagulation prior to their use whereas rivaroxaban and apixaban can be started immediately for the management of acute VTE. The clinical trials with rivaroxaban and apixaban demonstrated similar efficacy outcomes compared to heparin + warfarin with less major bleeding.[2,3,4] Insurance coverage of the DOACs is variable but improving. There are manufacturer provided copay discounts available for patients with private insurance but not for those with state funded insurance. Most patients, regardless of insurance status, are able to get 1 month of medication free of charge through manufacturer provided discount cards. Patient selection is important to maximize efficacy, safety, and compliance with therapy. Exclusion criteria based on criteria used in the clinical trials and other theoretical contraindications are necessary to assess candidacy for DOAC treatment (Table 1, see appendix). Warfarin might be considered in case of severe allergies to the DOACs or in patients with end stage renal disease (ESRD).

The 2016 CHEST Guidelines for Antithrombotic Therapy for VTE Disease support home treatment of low-risk PE (Grade 2B) and DVT (Grade 1B) in clinically stable patients with good cardiopulmonary reserve, good social support with ready access to medical care, and who are expected to be compliant with follow-up.[1] For PE, the CHEST guidelines support the use of the PE severity index (PESI) to identify patients with a low mortality risk (~1% at 30 days) who may be suitable for home management acknowledging that the risk score is only one of many considerations when determining the need for hospital admission after PE (Table 2, see appendix).[1,5,6] The PESI has been simplified (Table 2, see appendix) for usability with retention of its prognostic accuracy.[7] A score of 0 (i.e. the patient has no variables of the score) is deemed low risk. Please refer to "Massive and Submassive Pulmonary Embolism Algorithm" document for further recommendations regarding thrombolytic therapy in patients with PE.

Recommendations:

1- We suggest using a DOAC over heparin/warfarin for the management of lower or upper extremity DVT and or PE not associated with cancer.
2- We particularly suggest using apixaban or rivaroxaban without parenteral anticoagulation, to help simplify transitions of care. Consider out of pocket cost.
3- We suggest using apixaban, rivaroxaban or low molecular weight heparin (LMWH) over warfarin in cancer associated lower extremity DVT and or PE. The choice should be based on convenience and cost.
4- Warfarin might be considered in case of severe allergy to DOACs or in case of ESRD.
5- In patients with lower or upper extremity DVT and or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months.
6- Suggest treatment at home or early discharge over standard discharge in low-risk patients with adequate home circumstances:
   A. Clinically stable with good cardiopulmonary reserve
   B. No recent bleeding, severe renal or liver disease, or severe thrombocytopenia (i.e., <70,000/mm3)
   C. Expected to be compliant with treatment and
   D. Patient feels well enough to be treated at home
7- Consider using the simplified PESI (Table 2) to help identify low risk patients with PE who may be eligible for outpatient treatment. This should not replace clinical judgement.
8- In patients with acute proximal DVT of the leg, we suggest anticoagulation therapy alone over catheter directed thrombolysis (CDT).
9- Consider CDT in patients with severe lower extremity DVT (e.g., phlegmasia), high risk of post-thrombotic syndrome, and low risk of bleeding.
10- In patients with acute upper extremity DVT involving the axillary or more proximal veins, we suggest anticoagulation therapy alone over thrombolysis.
11- Consider using CDT for severe upper extremity DVT with high risk for post-thrombotic syndrome and low risk for bleeding, especially in cases with underlying thoracic outlet syndrome (TOS). First rib resection can follow CDT in patients with TOS.
12- In catheter-induced upper extremity DVT involving the axillary or more proximal veins, we suggest anticoagulation therapy. We favor anticoagulation for up to three months if the thrombosis is symptomatic, associated with cancer, or the catheter remains in place. A longer duration of anticoagulation may be warranted if the catheter remains in place, particularly for patients with cancer. It is reasonable to continue using the catheter as long as it is functional. If the catheter is not functioning, the catheter can be removed as long as the patient is on therapeutic anticoagulation.
13- We recommend against the use IVC filter in patients with acute DVT or PE who are treated with anticoagulants.
14- We recommend three months of anticoagulation for provoked proximal DVT and or PE.
15- In patients with unprovoked VTE, we suggest (for first event) or recommend (for recurrent event) extended anticoagulation therapy over three months period in patients with low or moderate bleeding risk. We recommend (for first event) or suggest (recurrent event) three months of anticoagulation in patients with high risk of bleeding.
16- In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g., annually).

17- We suggest aspirin over no aspirin in patients with unprovoked proximal DVT or PE who are stopping anticoagulation therapy and have no contraindication to aspirin.
18- In Patients with isolated sub-segmental PE without proximal DVT, we suggest clinical surveillance over anticoagulation in patients with low, and suggest anticoagulation over surveillance in patients with high, risk for VTE recurrence.
19- In high risk symptomatic patients with provoked or unprovoked distal (below the popliteal vein) DVT, we recommend three months of anticoagulation over shorter or longer periods. Asymptomatic lower risk patients with high risk of bleeding can be followed by ultrasound periodically (e.g., every 2 weeks).
20- In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS. However, we recommend using them in patients with symptomatic edema.
21- Please refer to "Massive and Submassive Pulmonary Embolism Algorithm" document for further recommendations regarding thrombolytic therapy in patients with PE.
22- Please refer to the DOAC related protocols for dosing, management of bleeding and peri-procedural anticoagulation recommendations.
23- Please refer to the warfarin and heparin protocols for dosing and monitoring.

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APPENDIX

Table 1: Proposed Exclusion Criteria for the use of a DOAC[#]

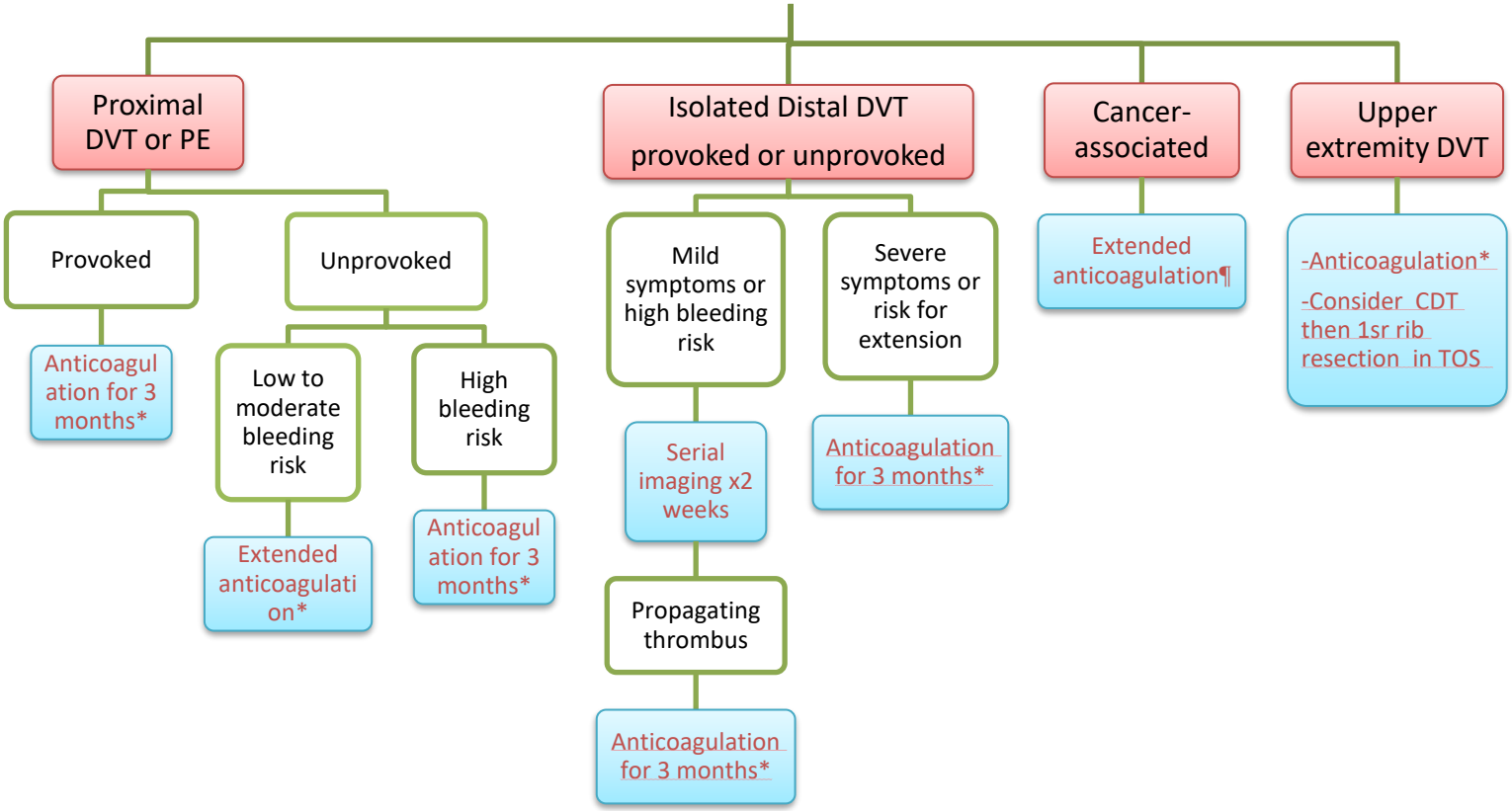
Patient History	Lab Values/Vitals	Medications	Social History
Active cancer treatment	**Hgb < 10 g/dL with evidence of bleeding**	**Dual Antiplatelet Therapy**	**No prescription insurance coverage**
Mechanical Heart Valve	**Platelets < 70 K**	**Major Drug Interactions with Rivaroxaban/ Apixaban** (Strong dual inducers of P-gp and CYP3A4 eg, rifampin, phenytoin, carbamazepine, St. John's wort)	**Homeless**
Concern for active bleeding	**CrCl < 30ml/min for rivaroxaban* CrCl < 25ml/min for apixaban***		**Known history of poor compliance with medications and/or follow up**
Bleeding risk outweighs risk of thromboembolic event	**ALT >3 times ULN or T Bili >1.5 time ULN**		**EtOH or IV drug abuse**
Bacterial endocarditis	**Blood Pressure >180/110 mmHg**	**Major Drug Interactions with Rivaroxaban** (strong dual inhibitors of P-gp and CYP3A4 eg, ketoconazole, itraconazole, ritonavir, clarithromycin)	
HIT ≤ 3 months		Severe allergy to the DOAC*	
Pulmonary arterial hypertension			
Child-Pugh Class B/C Cirrhosis or elevated INR related to liver disease			
Pregnancy			

*Warfarin might be considered in case of severe allergies to the DOACs or in case of end stage renal disease (ESRD).
CrCl: creatinine clearance; DOAC: direct oral anticoagulant, EtOH: ethanol, Hgb: hemoglobin, HIT: heparin induced thrombocytopenia ULN: upper limit of normal, P-gp: permeability glycoprotein.

Table 2: Original and Simplified PESI Score [5,6,7]

Parameter	Original version[214]	Simplified version[218]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

Figure 1: Anticoagulation Therapy Algorithm for VTE



CDT: catheter directed thrombolysis, DOAC: direct oral anticoagulant, DVT: deep vein thrombosis, LMWH: low molecular weight heparin, PE: pulmonary embolism, TOS: thoracic outlet syndrome.

***** We favor using a DOAC over enoxaparin + warfarin.
¶ We favor apixaban, rivaroxaban, or low molecular weight heparin over warfarin.

Thrombophilia Work-up Recommendations

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July 22, 2019	THROMBOPHILIA WORK-UP RECOMMENDATIONS

Introduction:

The most common presentations of venous thromboembolism (VTE) are lower extremity deep vein thrombosis (DVT) and/or pulmonary embolism (PE). Arterial thromboembolic events (ATE) are less common but can lead to more serious outcome. The etiologies for thromboembolism can be divided into two main groups: hereditary and acquired, and some events can be triggered by both. Detailed medical, social and family history are critically important to help identify the underlying etiology. Inherited thrombophilic conditions including gene mutations and or protein deficiencies are less frequent. Making decisions regarding indication, timing and or appropriate laboratory testing for thrombophilia can be challenging, especially in the acute event.

This document reviews hereditary and acquired etiologies for thromboembolism, and provides appropriate work up recommendations based on the current evidence.

Evidence:

A very careful patient and family history may help identify different etiologies for thromboembolism and can help make decisions regarding appropriate work up plan. Differentiating between provoked and unprovoked event is crucially important since the work up and management plans are different [1-2]. Risks factors that should be questioned include history of immobility, pregnancy, trauma, surgery, or recent hospitalization. Other risks that should be investigated include past history of thromboembolism, presence of prothrombotic disorders, medications and drug use, obstetric history, constitutional symptoms, and family history of thromboembolism (table 1)[3-5].

Physical exam may reveal signs of malignancy, hepatic vein thrombosis, polycythemia vera, and nephrotic syndrome.

Initial work up including a CBC, hepatic and renal function tests, basic coagulation tests, venous duplex ultrasound and or chest CT, may help identify the underlying etiology [6-7]. Testing patients with VTE for hypercoagulable disorders (especially inherited thrombophilias) and malignancy is controversial [7-9]. Several trials report no difference in recurrence rates in patients with or without inherited thrombophilia, on or off anticoagulation [7-13]. Further testing should only be considered if testing results would affect management plan for patients and/or their family members, especially if hormonal therapy is considered [7-13]. This should be weighed against the harms of testing including a lack of improved survival, inappropriate anticoagulation and undue anxiety in the patient (and/or asymptomatic relatives). In general, other than age-appropriate cancer screening, routine evaluation for occult malignancy in patients with thromboembolism is not warranted [14-15]. For all patients in whom testing is being considered, it is critical to consider patients' values and preferences [10].

Here we discuss our work-up recommendations for patients with thromboembolism.

Recommendations:

1- All patients with diagnosed VTE should have thorough history and physical exam to determine if the VTE is provoked versus unprovoked.
2- Risks that should be investigated include:
   A- Immobility, pregnancy, trauma, surgery, or recent hospitalization.
   B- Past personal or family history of thromboembolism.
   C- Presence of prothrombotic disorders (eg, autoimmune disorders, malignancy, myeloproliferative disorders, nephrotic syndrome, inflammatory bowel disease).
   D- Hormonal medications (eg, hormonal contraceptives, hormonal replacement), or drugs that can induce the development of lupus anticoagulants or antiphospholipid antibodies (eg, hydralazine, procainamide, phenothiazines).
   E- Illicit drug use (eg, amphetamines, cocaine).
   F- Obstetric history: recurrent fetal loss may suggest underlying thrombophilia such as antiphospholipid syndrome.
   G- Constitutional symptoms: weight loss, loss of appetite and night sweats may indicate underlying malignancy.
3- Appropriate systemic physical exam may reveal the underlying etiology:
   A- Breast cancer: lymphadenopathy or breast masses
   B- Hepatic vein thrombosis: ascites and hepatomegaly
   C- Polycythemia Vera: unexplained splenomegaly
   D- Nephrotic syndrome: edema
4- For all patients with VTE, we recommend the following work up:
   A- CBC with blood smear:
      - Thrombocytosis and or high red blood cell count may indicate myeloproliferative disorder
      - Pancytopenia may indicate paroxysmal nocturnal hemoglobinuria (PNH)
      - Thrombocytopenia with history of heparin use may indicate heparin induced thrombocytopenia (HIT)
      - Schystocytes with cell fragmentation may indicate DIC
   B- Renal and hepatic function tests
   C- Basic coagulation labs including aPTT and PT/INR
   D- ESR and CRP in selected patients with possible underlying malignancy and or autoimmune disorder
5- For most patients, extensive imaging other than that required for the diagnosis of VTE (eg, lower extremity ultrasound, CT pulmonary angiogram) is not necessary.
6- Additional testing for thrombophilia (Figure 1):
   A- Patients with provoked VTE or first unprovoked VTE should not be tested since management and outcome are not necessarily altered by results.
   B- Patients with recurrent unprovoked event and documented family history of unprovoked VTE in a first degree relative younger than 45 years:
      i) Consider testing for inherited thrombophilia (levels of protein S, protein C, and antithrombin, factor V Leiden and prothrombin gene mutations) in a patient who is not interested in long-term anticoagulation and is considering hormonal therapy.
      ii) Consider testing for inherited thrombophilia in a patient who is not interested in long-term anticoagulation as long as patient

is willing to accept aggressive risk lowering recommendations (eg, smoke cessation, life style modifications, more aggressive thromboprophylaxis when at risk) in case testing is positive.

iii) Consider testing for inherited thrombophilia in a first degree relative who is considered for hormonal therapy.

iv) Consider testing for inherited thrombophilia in a first degree relative as long as he or she is willing to accept aggressive risk lowering recommendations in case testing is positive.

C- Patients with unprovoked event and no family history of VTE

i) Consider testing young patients (< 45 years) for inherited thrombophilia and antiphospholipid syndrome (lupus anticoagulants, anticardiolipin and B2 glycoprotein antibodies) if results would alter management plan (avoiding hormonal exposure, aggressive risk lowering recommendations).

ii) Consider testing patients with recurrent VTE for inherited thrombophilia and antiphospholipid syndrome if results would alter management plan (avoiding hormonal exposure, aggressive risk lowering recommendations).

iii) Consider testing patients with unusual locations of VTE (portal hepatic, mesenteric, or cerebral veins) for inherited thrombophilia and antiphospholipid syndrome. Consider evaluation for JAK2 mutations and paroxysmal nocturnal hemoglobinuria (PNH) in patients with portal or hepatic vein thrombosis.

iv) Consider testing patients with warfarin induced skin necrosis for protein C and protein S levels and factor V Leiden mutation.

D- Patients with arterial thrombosis

i) Consider testing for antiphospholipid syndrome

ii) Consider testing for PNH in patients with anemia

iii) Consider testing JAK2 mutations in patients with possible underlying myeloproliferative disorders

iv) Consider testing for heparin induced thrombosis (HIT) by ordering heparin antibodies in patients with heparin exposure and ≥ 50% reduction of platelet count.

v) Consider testing for lipoprotein a level in patients with family history of premature cardiovascular disease.

E- Patients that should not be tested for thrombophilia

i) Provoked VTE

ii) First unprovoked VTE

iii) Upper extremity DVT

iv) Active malignancy

v) Inflammatory bowel disease

vi) Confirmed myeloproliferative disorders

vii) HIT

viii) Retinal vein thrombosis

7- Timing of tests:

A- Acute thrombosis and anticoagulants (heparin, warfarin, DOACs) affect levels and/or functional activity of many thrombophilia testing (Table 2).

B- If testing is considered, recommend testing at least two weeks following discontinuation of anticoagulation, when feasible.

C- Factor V and prothrombin gene mutations can be tested at any time if considered.

8- Other testing

A- Homocysteine levels and mutational analysis for methylene tetrahydrofolate reductase (MTHFR), should not be performed since

causal role of hyperhomocysteinemia in thrombosis is unclear. Furthermore, lowering homocysteine levels with folic acid, pyridoxine, and vitamin B12 does not appear to reduce the rate of VTE in patients with hyperhomocysteinemia.

9- Evaluation for occult malignancy
   A- Recommend regular malignancy testing (Pap smear, mammography, colonoscopy, prostatic exam, PSA) based on patient's gender and age.
   B- Consider further testing for malignancy only if there is clinical suspicion for one.

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APPENDIX

Table 1: Risk factors (causes) for the development of venous thrombosis

Inherited thrombophilia
Factor V Leiden mutation
Prothrombin G20210A mutation
Protein S deficiency
Protein C deficiency
Antithrombin (AT) deficiency
Other disorders and risk factors
Malignancy
Presence of a central venous catheter
Surgery, especially orthopedic
Trauma
Pregnancy
Oral contraceptives
Hormone replacement therapy
Certain cancer therapies (eg, tamoxifen, thalidomide, lenalidomide)
Immobilization
Heart failure
Congenital heart disease

Antiphospholipid syndrome
Myeloproliferative neoplasms
Polycythemia vera
Essential thrombocythemia
Paroxysmal nocturnal hemoglobinuria
Inflammatory bowel disease
Nephrotic syndrome

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Table 2: Clinical settings that may interfere with testing for thrombophilia

Hypercoagulable disorder for testing	Confounding factors		
	Acute thrombosis	**Heparin therapy**	**Warfarin therapy**
Antithrombin (deficiency)	Can be lowered*	Lowered	NC; rarely increased
Antiphospholipid antibodies	NC	NC	NC
Factor V Leiden	NC	NC	NC
Factor VIII level	Acute phase reactant. Do not test while inflammation is still present.		
Lupus anticoagulant	NC	Cannot measure¶	False positives possible
Protein C (deficiency)	Can be lowered*	NC	Cannot measure
Protein S (deficiency)	Can be lowered*	NC	Cannot measure
Prothrombin gene mutation	NC	NC	NC
Acquired AT deficiency:			
Neonatal period, pregnancy, liver disease, DIC, nephrotic syndrome, major surgery, acute thrombosis, treatment with L-asparaginase, heparin, or estrogens			
Acquired protein C deficiency:			
Neonatal period, liver disease, DIC, chemotherapy (CMF), inflammation, acute thrombosis, treatment with warfarin or L-asparaginase			
Acquired protein S deficiency:			
Neonatal period, pregnancy, liver disease, DIC, acute thrombosis, treatment with warfarin, L-asparaginase, or estrogens			

NC: not changed; LMW heparin: low molecular weight heparin; AT: antithrombin; DIC: disseminated intravascular coagulation; CMF: cyclophosphamide, methotrexate, 5-fluorouracil.

* Results can be affected by acute thrombosis; it is most cost effective to avoid testing for these deficiencies during the initial presentation. However, if plasma levels are well within the normal range at presentation, deficiency of these proteins is essentially excluded. Common causes for an acquired deficiency of AT, protein C, or protein S are listed.

¶ Some laboratories can test for a lupus anticoagulant in the presence of heparin, but many cannot.

Δ If it is important to measure for these deficiencies while the patient is still anticoagulated, switch the treatment to full-dose heparin or LMW heparin and discontinue Coumadin for at least two weeks before measurement. Comparing protein S or C levels with prothrombin antigen in stable anticoagulated patients is not reliable, as accurate measurement of prothrombin antigen levels is a research assay which is not generally available.

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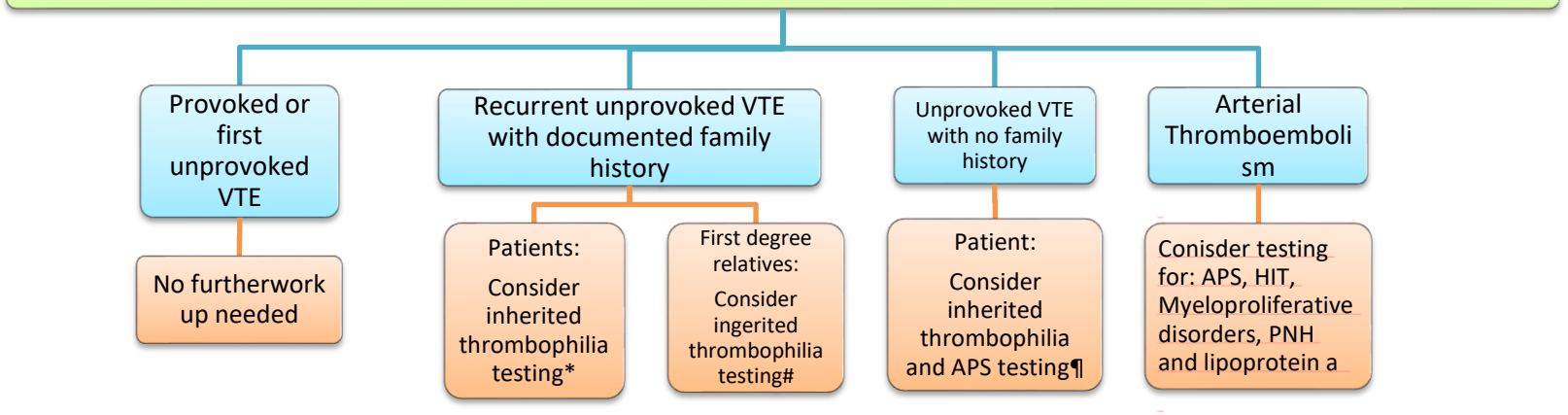
Figure 1: THROMBOPHILIA WORK UP RECOMMENDATION ALGORITHM



APS: Antiphospholipid syndrome, HIT: Heparin-induced thrombocytopenia, PNH: Paroxysmal nocturnal hemoglobinuria, VTE: Venous thromboembolism

***** In patient who is not interested in long-term anticoagulation and is considering hormonal therapy, and/or in patient who is not interested in long-term anticoagulation and is agreeable to aggressive risk lowering recommendations.
# Relatives who are considered for hormonal therapy and/or are agreeable for aggressive risk lowering recommendations.
¶ Young patients (<45 years old), recurrent VTE, unusual location for deep vein thrombosis, or warfarin-induced skin necrosis.

Watchman (Left Atrial Appendage Occluder Device)
Non-Implanter Reference

Anticoagulation and Thrombophilia Clinic, Minneapolis Heart Institute®, Abbott Northwestern Hospital.
Tel: 612-863-6800 | Reviewed August 2016, June 2018, July 2019

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Minneapolis Heart Institute

Allina Health
Abbott Northwestern Hospital

Watchman (Left Atrial Appendage Occluder Device) Non-Implanter Reference

REFERRAL INFORMATION

- Minneapolis Heart Institute Structural Heart Program
  - Tel: 612-863-3588
  - Fax: 612-863-1300

- Minneapolis Heart Institute Cardiac Electrophysiology Program
  - Tel: 855-644-4787 (855-MHI-HRTS)
  - Fax: 612-775-3230

PATIENT INCLUSION CRITERIA

- Non-valvular atrial fibrillation (excludes patients with any mechanical heart valve, or rheumatic mitral stenosis)
- Patient with an appropriate rationale to seek a non-pharmacologic alternative to warfarin/DOAC (history of bleeding, fall risk, previous trauma, labile INR)
  - Consult MHI Anticoagulation/Thrombophilia clinic 612-863-6800 for labile INR patient evaluation
- $CHAD_2S_2$-VASc score ≥ 3
- Suitable for short-term warfarin therapy
  - Per protocol – all patients will be on at least 45 days of warfarin after the Watchman™ implantation before it can be discontinued
- Patient with no alternative indication for long-term warfarin (ex: mechanical AVR/MVR)

RISKS

Risks include but not limited to: infection, bleeding, vessel injury, cardiac perforation at times requiring drainage or surgery, heart failure, migration of the device, emergency surgery, myocardial infarction, stroke and death.

NON-IMPLANTING PROVIDER VISIT

- Use an OAC evidence-based decision tool - see education booklet for patients – “Atrial Fibrillation and Options to Reduce Your Risk of Blood Clots and Stroke”
  - Link:http://akn.allina.com/content1/groups/patient-care/@akn-commprgov/documents/patient_care_documents/278707.pdf
  - Access via AKN, steps to find:
    - Patient Care
    - Patient Education
    - Shared Decision Making folder, click on “Decision Aids”
    - “Atrial Fibrillation and Options to Reduce Your Risk of Blood Clots and Stroke”
  - Copies can be ordered from SMARTworks (ID # 278707)

- Document a formal discussion between non-implanting provider and patient regarding management options and anticoagulation risks/benefits and options
  - The MHI EP/structural heart team developed a smart phrase that can be used to document (see below).
  - Consider consulting with MHI Anticoagulation/Thrombophilia Clinic (612-863-6800)
  - **It does not satisfy CMS requirements if only implanters document discussion with the patient (!)**.

SMART TEXT PHRASE for Discussion/Decision Making Process (.LAAODICTATION):

- *@NAME@ has indication for anticoagulation due to atrial arrhythmias and associated high risk for cardio-embolic stroke. @NAME@ is suitable for short-term warfarin, however, @NAME@ has a relative contraindication for long-term anticoagulation due to ***. I discussed at length the pathophysiology and management strategies of cardio-embolic risk, anticoagulation risks and benefits, and management strategy options with @NAME@. @NAME@ understands that that anticoagulation will be maintained in a variety of forms during the first year.*

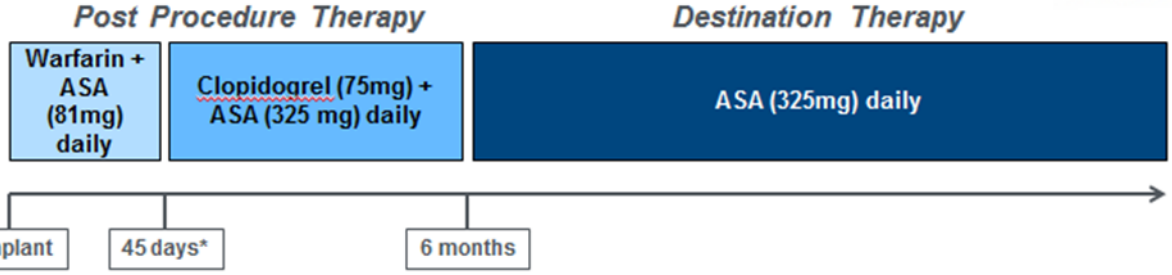
PRE-PROCEDURE ANTITHROMBOTIC THERAPY

- Goal INR for procedure 1.7-2.5
  - INR < 1.7 day of procedure: move forward with procedure
  - INR > 2.5 day of procedure: decision is based on patient's risks and benefits
- High risk patients (CHA_2DS_2-VASc score ≥ 5) that need to transition to warfarin
  - These patients will be given specific recommendations pre-procedure from Watchman implanting team
- ASA 81mg daily, continue uninterrupted
- Plavix (clopidogrel): The implanting provider will give direction for use while on warfarin based on individual patient cardiac interventional history.

PLATELETS

- < 50: EP and Structural Heart nurse clinicians will work with implanting MD for best approach
- > 50: good to go

POST-PROCEDURE ANTITHROMBOTIC THERAPY



G823

- Consider aspirin 81 mg rather than 325 mg (45 days to 6 months) in patients with high risk of bleeding.

For the most recent version, access it online on the AKN at
Abbott Northwestern Hospital > Excellian patient care quick links.

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