Guideline: Management of Anticoagulation in the Anticoagulation Clinics (ACC)

Purpose:

To provide guidance and standardization of clinical practice for the safe and appropriate use of anticoagulation therapy in the Confluence Health (CH) Anticoagulation Clinics. It is not the purpose of this guideline to supersede the clinical judgement of the ACC provider in providing safe management of their anticoagulation patients. The practice of medicine is in constant flux, whereas this guideline is static and consequently should not negate routine reassessment of all relevant recent clinical evidence as it becomes available, especially when treating complicated disease states.

Scope:

Comprehensive outpatient management of patients on oral and injectable anticoagulation therapy for the primary and secondary prevention of thrombosis. The ACC is staffed by Advanced Practice Clinicians (physician assistants, nurse practitioners, and pharmacists), RNs, and clinical staff with the specific knowledge in anticoagulation therapy, under the guidance of the anticoagulation clinic physician director.

Approval:

This document is reviewed and approved through the CH Anticoagulation Steering Committee.

Table of Contents

Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHRE	Atrial high-rate episodes
APS or APLS	Antiphospholipid syndrome
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCD	Chronic coronary disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DOAC	Direct oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban)
DTI	Direct thrombin inhibitor (dabigatran)
DVT	Deep vein thrombosis
FVL	Factor V Leiden mutation
F-Xai	Factor Xa inhibitor (apixaban, edoxaban, rivaroxaban)
ICH	Intracranial hemorrhage
LMWH	Low molecular weight heparin (typically enoxaparin)

OAC	Oral anticoagulant
P2Y12 inhibitor	Class of antiplatelet medications (clopidogrel, prasugrel, ticagrelor)
PAD	Peripheral artery disease (eg, peripheral vascular disease – PVD)
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PTGM	Prothrombin G20210A mutation
Scr	Serum creatinine
SE	Systemic embolism
SIHD	Stable ischemic heart disease
SVT	Superficial venous thrombosis
TE	Thromboembolism
TIA	Transient ischemic attack
TEE	Transesophageal echocardiogram
UFH	Unfractionated heparin
VKA	Vitamin K antagonist (warfarin)
VTE	Venous thromboembolism

Common Indications and Recommendations for Antithrombotic Therapy:

Atrial Fibrillation

Stages of Atrial Fibrillation (AF)	
	Definition
First diagnosed	AF not diagnosed before, irrespective of its duration or the presence /severity of AF-related symptoms
Paroxysmal	AF that is intermittent and terminates within 7 days of onset
Persistent	AF that is continuously sustained > 7 days and requires intervention (if after intervention is paroxysmal, should still be defined as persistent as this reflects original pattern and is more useful to predict outcomes.
Long-standing Persistent	AF that is continuous for >12 months duration
Permanent	Term that is used when patient and clinician make joint decision to stop further attempts to restore/maintain sinus rhythm. Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF
Atrial High-rate Episodes (AHRE)	Atrial events exceeding the programmed detection rate limit set by device. Recorded by implanted devices but require visual inspection to confirm AF and exclude other arrhythmias or artifact

Atrial Fibrillation (NVAF) Decision to Anticoagulate		
Indication	**Risk and Therapeutic Recommendation**	**Duration of Treatment**
CHA_2DS_2-VASc 0	**low:** reasonable to omit anticoagulation	n/a
CHA_2DS_2-VASc 1	**low (female sex):** reasonable to omit anticoagulation **intermediate (male sex):** consider anticoagulation[1]	extended
CHA_2DS_2-VASc 2	**high (male sex**): anticoagulate **intermediate (female sex):** consider anticoagulation[1]	extended
CHA_2DS_2-VASc ≥ 3	**high:** anticoagulate	extended
AF w/bioprosthetic heart valves	**high:** anticoagulate	extended
pre-cardioversion/ablation (AF > 48 hrs)	**mod-high:** anticoagulate	at least 3 weeks prior to procedure
post-cardioversion/ablation	**mod-high:** anticoagulate	at least 4 weeks post procedure
AHRE	Lasting ≥ 24 hr in CHA_2DS_2-VASc ≥ 2: consider AC	extended
	Lasting 5 min - 24 hr in CHA_2DS_2-VASc ≥ 3: consider AC	extended

[1] Patients at intermediate annual risk of thromboembolic events who remain uncertain about benefit of AC, may benefit from consideration of factors that modify their risk of stroke to help inform the decision (see thromboembolic risk tools).

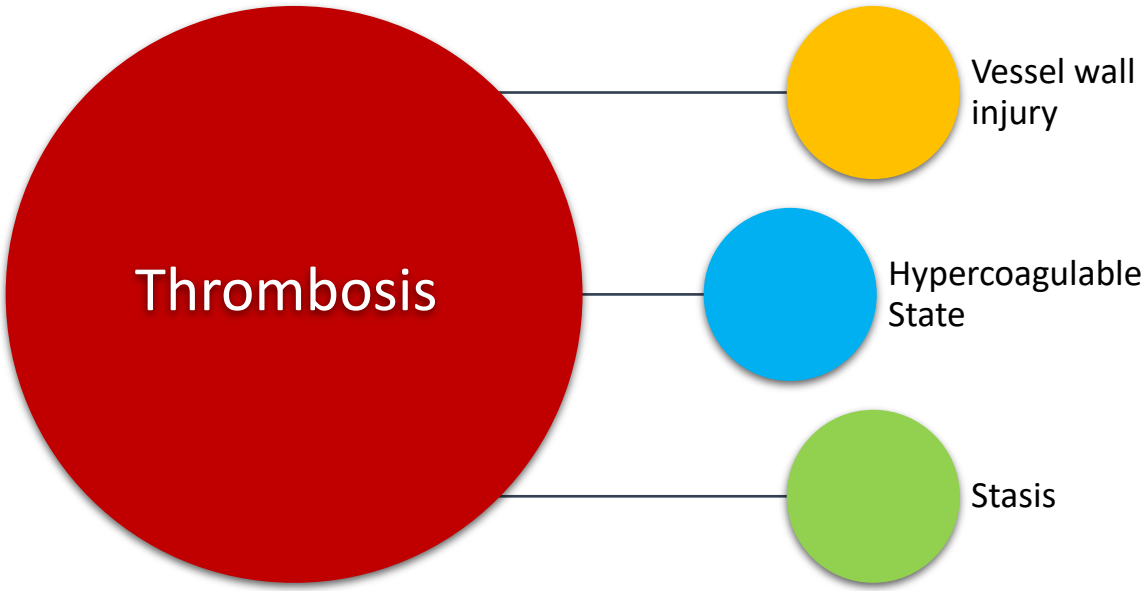
Anticoagulant Considerations in Atrial Fibrillation[2,3]					
	Dosing	**Renal Adjustment**	**Hepatic Adjustment**	**Older Adult**	**Contraindication**
apixaban/Eliquis	5 mg twice daily	2.5 mg twice daily if 2 of the following: body weight ≤ 60 kg, Scr ≥ 1.5mg/dL, age ≥ 80 yrs	Use not recommended in Child-Turcotte-Pugh Class C	Likely safe in older adults, but increased bleed risk versus younger patients.	• Moderate to severe mitral stenosis • Recent bioprosthetic valve replacement (within 1-2 months) • Mechanical valve prosthesis in any position • Antiphospholipid syndrome • Some drug-drug interactions
dabigatran/Pradaxa	150 mg twice daily	•CrCl 15 to ≤ 30 mL/min: 75 mg twice daily if •CrCl < 15 mL/min: Do not use if	No dosage adjustments provided	Increased bleed risk. Use with extreme caution or consider other treatment in patients ≥ 75 years of age.	
edoxaban/Savaysa	60 mg once daily	•CrCl >95 mL/min: Do not use •CrCl 15-50 mL/min: 30 mg once daily •CrCl < 15 mL/min: Do not use	Use not recommended in Child-Turcotte-Pugh Class C	Likely safe in older adults but increased bleed risk versus younger patients.	
rivaroxaban/ Xarelto	20 mg once daily	•CrCl 15-50 mL/min: 15 mg once daily if •CrCl < 15 mL/min: Do not use	Use not recommended in Child-Turcotte-Pugh Class B or C	Mean AUC 41% greater in patients >75 years of age. Similarly, the T½ was extended to 11-13 hours (from 5-9 hr in non-elderly).	
warfarin	Target INR 2.0-3.0 (if mechanical valve present 2.5-3.5)	No dosage adjustments provided	Response to warfarin will be markedly enhanced. Baseline INR elevation can confound results	Increased bleed risk versus DOAC	Recent data suggests no benefit when used in patients on dialysis.[4]

[2] DOACs are now recommended over warfarin in DOAC-eligible patients. When DOAC trials are considered as a group, DOACs were at least non-inferior and, in some trials, superior to VKA for preventing stroke and systemic embolism and were associated with lower risk of serious bleeding.

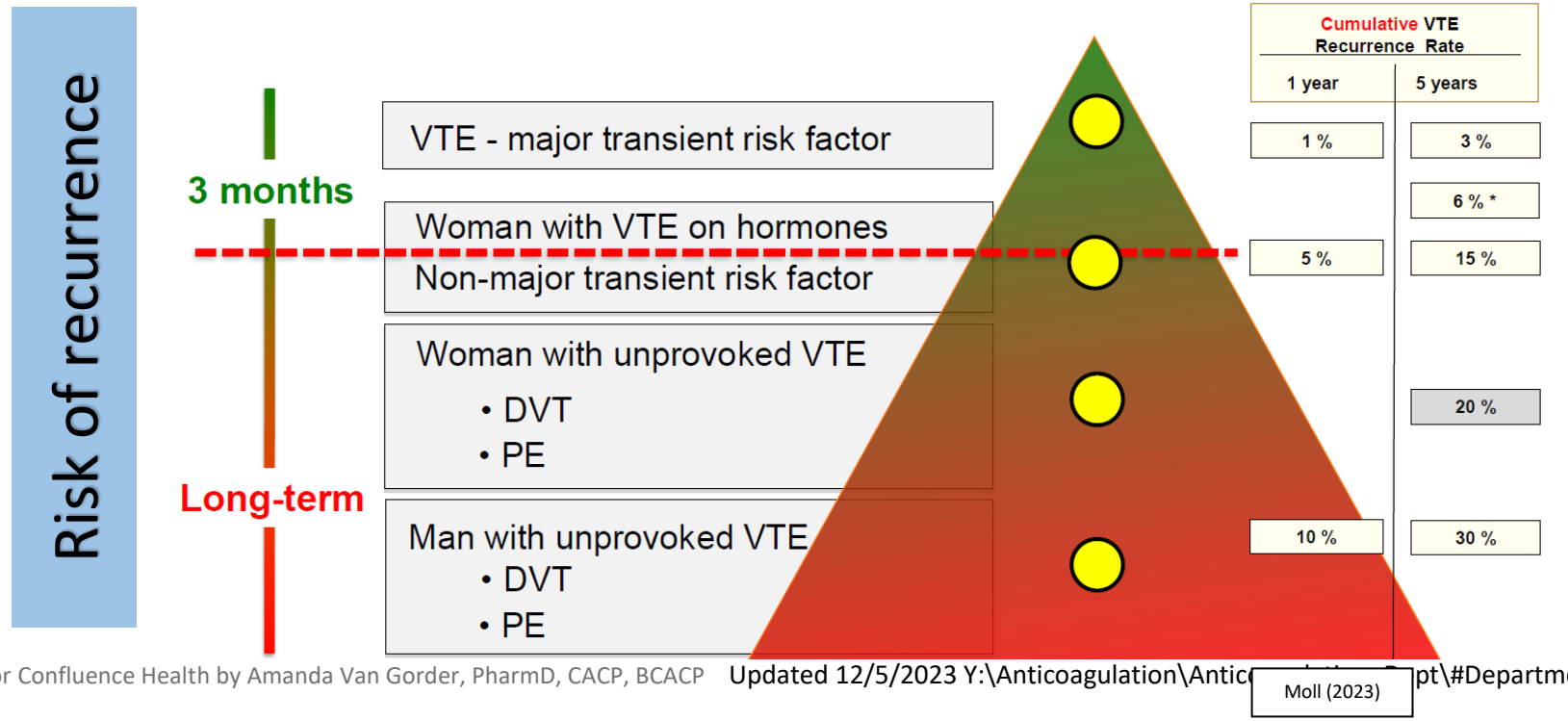
[3] Aspirin alone or in combination with another antiplatelet (e.g., clopidogrel) is no longer recommended for stroke prevention in atrial fibrillation.

[4] Recent studies have demonstrated a lack of thrombotic benefit and increased bleed risk when warfarin is used in patients on dialysis. Similar studies have demonstrated improved safety with apixaban use over warfarin in dialysis, however significant benefit was also not demonstrated. It is reasonable to consider not utilizing anticoagulation in high bleed risk patients on dialysis. If anticoagulation must be used, apixaban is recommended.

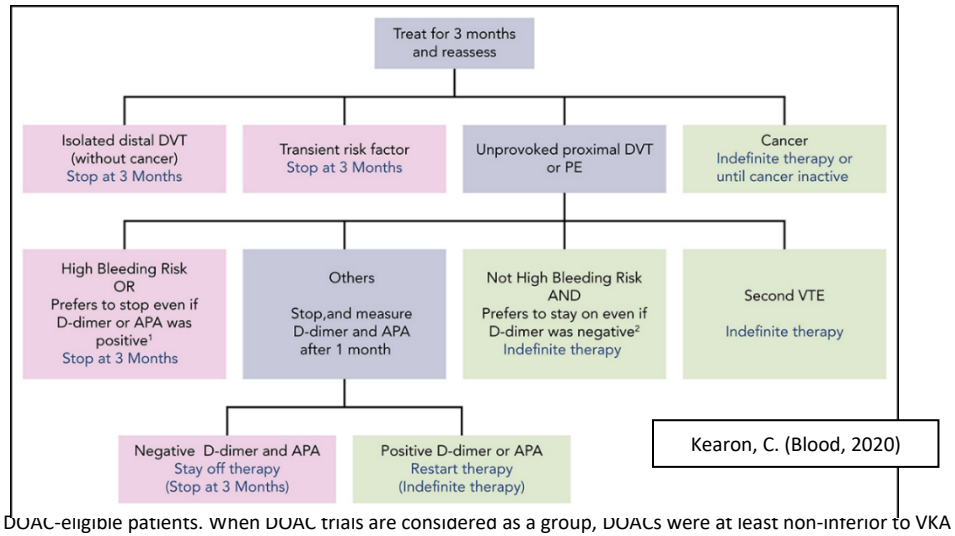
Phases of Anticoagulation		
Phase	**Timeline**	**Explanation**
Initiation Phase	5-21 days	Describes the initial provision of anticoagulants following VTE diagnosis. Consists of parenteral or high-dose oral anticoagulation.
Treatment Phase	3 months	Describes the period after initiation, following which treatment is completed for the acute VTE event. It consists of anticoagulants used at standard therapeutic doses. This phase is considered complete following 12 weeks of anticoagulation.
Extended Phase	> 3 months No pre-planned stop date	Describes the use of anticoagulants, at full or reduced dose, for the goal of secondary prevention. The decision to continue extended-phase anticoagulation should be periodically re-evaluated (annually). It should be noted that studies of extended-phase anticoagulation reported outcomes of therapy over periods from about 2-4 years. Although anticoagulants were generally not stopped in participants, the balance of risks and benefits of longer durations of treatment is uncertain.



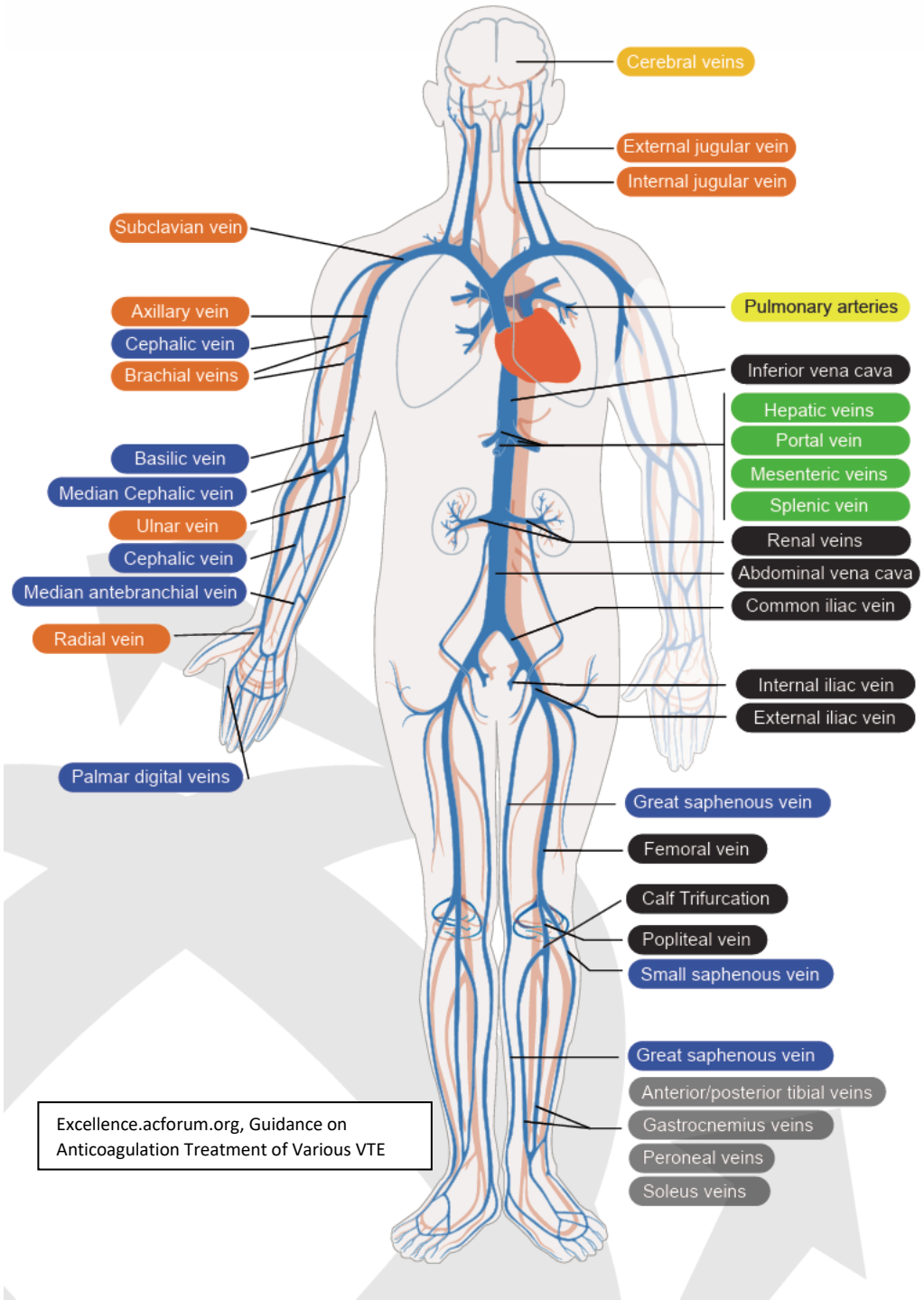
Precipitating Risk Factors for VTE		
Transient risk factors (resolve after they have provoked VTE)		
Major Transient Risk Factor (occur within 3 months of VTE diagnosis)	• Surgery w/general anesthesia for >30 min • Confinement to bed in hospital (only "bathroom privileges") for at least 3 days with an acute illness	• Cesarean section • Major trauma
Minor Transient Risk Factor (occur within 2 months of VTE diagnosis)	• Surgery with general anesthesia for <30 min • Admission to hospital for less than 3 days with an illness • Estrogen therapy • Pregnancy and puerperium	• Confinement to bed out of hospital for at least 3 days with an acute illness • Leg injury associated with reduced mobility for at least 3 days
Chronic (persistent) risk factors (persist after development of VTE)		
Acquired	• Active cancer (ongoing chemotherapy; recurrent or progressive disease) • Inflammatory bowel disease	• Autoimmune disorders (e.g., antiphospholipid syndrome, RA) • Chronic infections • Chronic immobility (e.g., spinal cord injury)
Other risk factors (low or variable relative risk) that may be useful for evaluation in combination with above risk factors	• Hereditary thrombophilia • Older age • Male sex	• Obesity • Varicose veins • Laparoscopic surgery
Unprovoked VTE	Absence of transient risk factor, no cancer	



Venous Thromboembolism (DVT/PE)		
Indication	**Therapeutic Recommendation[5]**	**Duration of Treatment**
Provoked proximal DVT/PE	DOAC or warfarin (INR goal 2-3)	3-6 months (assuming transient risk factor resolved)
First unprovoked proximal DVT or PE with high bleed risk	DOAC or warfarin (INR goal 2-3)	3-6 months
First unprovoked proximal DVT or PE with low bleed risk	DOAC or warfarin (INR goal 2-3)	Extended
Acute isolated distal DVT of leg[6]	DOAC or warfarin (INR goal 2-3)	3 months
Unprovoked recurrent DVT or PE	DOAC or warfarin (INR goal 2-3)	Extended
Breakthrough DVT/PE during therapeutic VKA treatment[7]	LMWH over DOAC	Extended
Any VTE with active cancer[8]	DOAC or LMWH	Extended or until malignancy is resolved (at least 6 months)
Acute superficial venous thrombosis (SVT) of lower extremities[9]	Fondaparinux 2.5 mg daily or rivaroxaban 10 mg daily	45 days
Cerebral venous thrombosis	DOAC or LMWH	At least 3 months
Splanchnic vein thrombosis	DOAC or LMWH	At least 3 months



[5] DOACs are now recommended over VKA or LMWH in DOAC-eligible patients. When DOAC trials are considered as a group, DOACs were at least non-inferior to VKA and were associated with lower risk of serious bleeding.
[6] Without severe symptoms or risk factors for extension, guidelines recommend serial imaging for 2 weeks with anticoagulation advised if thrombus propagation. AC favored in pt who place high value on avoiding inconvenience of repeat imaging and low value on inconvenience of treatment. (ref 30)
[7] 2020 ASH guidelines conditional recommendation based on very low certainty of evidence. Patients who present with new VTE event during therapeutic VKA treatment should be further investigated to identify potential underlying causes. This recommendation **does not** apply to patients who develop breakthrough VTE in the setting of poor INR control, in whom a DOAC may be a reasonable option (ref 22)
[8] 2021 NCCN guidelines endorse apixaban, edoxaban, rivaroxaban over LMWH for patients without gastric or gastroesophageal lesions (LMWH preferred in patients with gastric or gastroesophageal lesions). Dabigatran would be acceptable when other DOAC or LMWH are not appropriate or unavailable. (ref 31)
[9] AC favored if extensive SVT, involvement above the knee particularly if close to saphenofemoral junction, severe symptoms, involvement of greater saphenous vein, hx VTE or SVT, active cancer, recent surgery. AC not typically used in SVT associated with IV infusion. (ref 30)



Excellence.acforum.org, Guidance on Anticoagulation Treatment of Various VTE

Clot Locations

- Upper Extremity DVT
- Cerebral Vein Thrombosis
- Splanchnic Thrombosis
- Pulmonary Embolism
- Superficial Vein Thrombosis
- Proximal DVT
- Isolated Distal DVT

Anticoagulant Considerations in VTE Treatment and Prevention						
	Indication	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**Older Adult**	**Contraindication**
apixaban/ Eliquis	VTE treatment	10 mg BID x7 days, then 5 mg BID	No dosage adjustment recommended	Child-Turcotte-Pugh Class C: Use not recommended	Likely safe in older adults, but increased bleed risk versus younger patients.	• Mechanical valve prosthesis in any position • Antiphospholipid antibody syndrome • Some drug-drug interactions
	Secondary thromboprophylaxis	5 mg BID (can consider 2.5 mg BID after 6 mos of treatment if full dose anticoagulation is not indicated)[10]				
	Periop (TKA, THA) thromboprophylaxis	2.5 mg BID (TKA x10-14 days, THA x30-35 days)				
dabigatran/ Pradaxa	VTE treatment	150 mg twice daily (after 5-10 days of parenteral therapy)	•CrCl > 30 mL/min: No adjustment •CrCl ≤ 30 mL/min: Do not use	No dosage adjustments provided	Increased bleed risk. Use with extreme caution or consider other treatment in patients ≥ 75 years of age.	
	Periop (THA) thromboprophylaxis	110 mg day 1, then 220 mg daily x10-35 days				
edoxaban/ Savaysa	VTE treatment	Weight > 60kg: 60 mg once daily Weight ≤ 60 kg: 30 mg once daily	•CrCl >95 mL/min: Do not use •CrCl 15-50 mL/min: 30 mg once daily •CrCl < 15 mL/min: Do not use	Child-Turcotte-Pugh Class C: Use not recommended	Likely safe in older adults but increased bleed risk versus younger patients.	
rivaroxaban/ Xarelto	VTE treatment	15 mg BID with food x21 days, then 20 mg QD with food	•CrCl ≥ 30 mL/min: No adjustment •CrCl < 15 mL/min: Avoid use	Child-Turcotte-Pugh Class B or C: Use not recommended	Increased bleed risk. Use with caution in older adults (≥ 75 years of age).	
	Secondary thromboprophylaxis	20 mg QD with food (can consider 10 mg QD after 6 mos of treatment if full dose anticoagulation is not indicated)[10]				
	Periop (TKA, THA) thromboprophylaxis	10 mg daily (TKA x10-14 days, THA x30-35 days)				
	SVT treatment	10 mg daily x45 days				

[10] Based on limited data; consider patient's thrombotic risk before reducing dose. (ref 3, 9)

Anticoagulant Considerations in VTE Treatment and Prevention							
	Indication	**Dosing**		**Renal Adjustment**	**Hepatic Adjustment**	**Older Adult**	**Contraindication**
dalteparin/ Fragmin	VTE treatment	200 units/kg SQ QD or 100 units/kg SQ BID		•CrCl > 30 mL/min: No dose adj •CrCl < 30 mL/min: Use not recommended	No dosage adjustments provided		**Do not use in:** • hx of HIT • hypersensitivity to pork • Dialysis
	Periop bridging						
	VTE prophylaxis	TKA	5000 units SQ QD				
		THA	5000 units SQ QD				
		Medically ill	5000 units SQ QD				
enoxaparin/ Lovenox	VTE treatment	1 mg/kg SQ BID or 1.5 mg/kg SQ QD		•CrCl < 30 mL/min: 1 mg/kg SQ QD •Avoid use in dialysis if possible	No dosage adjustments provided (has not been studied – use with caution)	Increased incidence of bleeding with therapeutic dose, especially if <45 kg body weight.	**Do not use in:** • hx of HIT • hypersensitivity to pork **Caution in:** • Dialysis: avoid if possible
	Periop bridging						
	VTE prophylaxis	TKA	30 mg SQ BID	•CrCl < 30 mL/min: 30 mg SQ QD •Avoid use in dialysis if possible			
		THA	40 mg SQ QD				
		Abdominal surgery					
		Medically ill					
fondaparinux/ Arixtra	VTE treatment	<50 kg: 5 mg SQ QD 50-100 kg: 7.5 mg SQ QD >100 kg: 10 mg SQ QD		•CrCl ≥ 30 mL/min: No dose adj however, use caution in CrCl <50 mL/min – consider alternative therapy	Child-Turcotte-Pugh class A and B: No dosage adjustments provided. Child-Turcotte-Pugh class C: Has not been studied – use with caution		• CrCl < 30 mL/min
	VTE prophylaxis	2.5 mg SQ QD Do not use in pt <50 kg					
	SVT treatment	2.5 mg SQ QD x45 days					
unfractionated heparin	VTE treatment	333 units/kg SQ followed by 250 units/kg SQ BID		Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)	Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)	>60 yo may have higher serum levels and longer aPTTs	**Do not use in:** • hx of HIT • hypersensitivity to pork
	Periop bridging	IV infusion in patient					
	VTE prophylaxis	5000 units SQ Q8-12 hours					
warfarin		Target INR 2.0-3.0		No dosage adjustments provided	Response to warfarin will be markedly enhanced. Baseline INR elevation can confound results	Increased bleed risk versus DOAC	Recent data suggests increased bleeding compared to apixaban when used in patients on dialysis.[11]

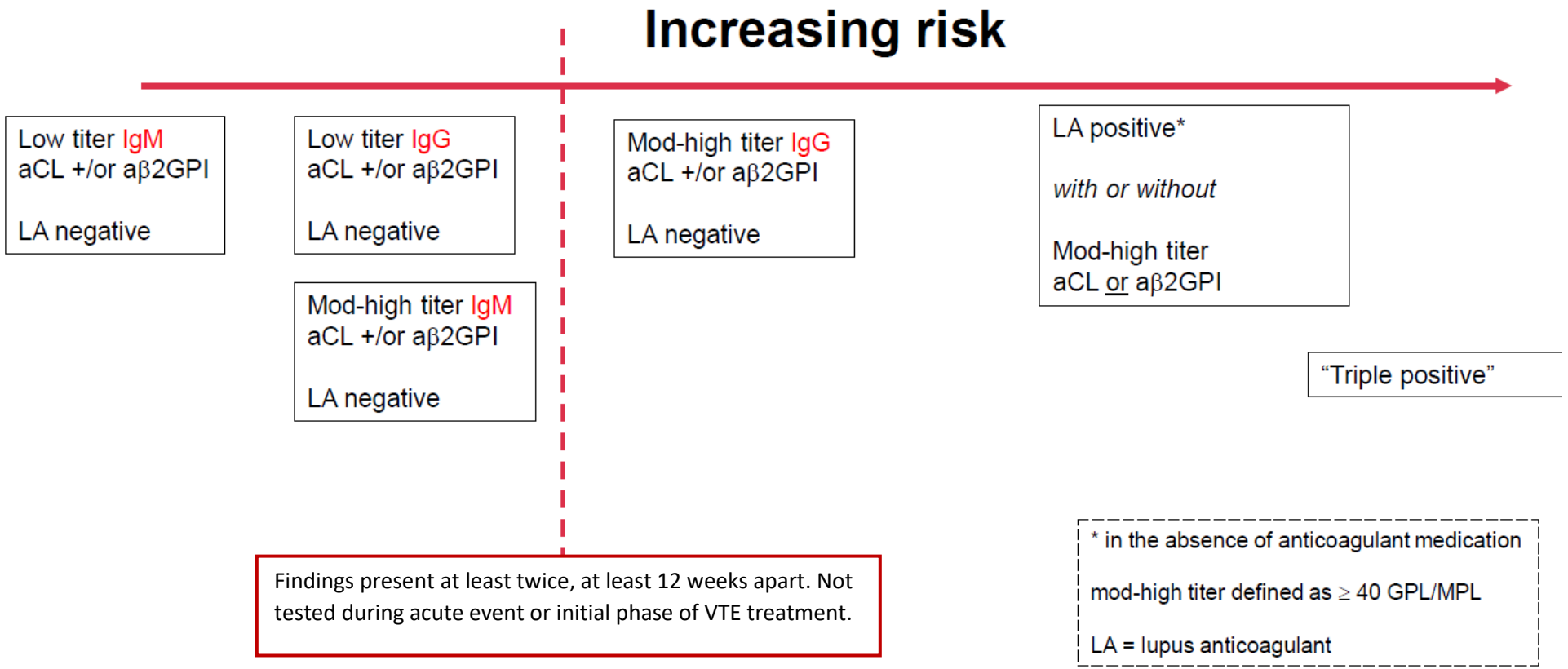
[11] Recent studies have demonstrated increased bleed risk when warfarin is used in patients on dialysis. Similar studies have demonstrated improved safety with apixaban use over warfarin in dialysis.

Thrombophilia Associated VTE

Thrombophilia				
Category	**Thrombophilia**	**Basic Information**	**Laboratory Testing**	**Comments**
Increased level or function of natural procoagulants	Activated protein C resistance (APC)	FVa resistant to inactivation by activated protein C. 90-95% is caused by FVL mutation.	Abnormal APC resistance assay suggests FVL mutation	Results may be impacted by acute thrombotic event, presence of lupus anticoagulant (LA), use of warfarin, heparins, DOACs
	Factor V Leiden (FLV)	Genetic mutation that results in FV resistance to inactivation by PC. Heterozygous: low risk Homozygous: high risk Combined FVL and PTGM = high risk	Factor V Leiden genetic test	Results generally reliable. Test could miss small % of pt with APC resistance not due to FVL.
	Prothrombin G20210A mutation (PTGM)	Elevated circulating levels of prothrombin. Heterozygous: low risk Homozygous: high risk Combined FVL and PTGM = high risk	Factor II G20210A mutation genetic test	Results generally reliable.
	Elevated levels of otherwise normal factors (FVIII, IX, XI)	Cause unknown, may be genetic.	Functional or antigenic tests available.	-
Deficiencies of natural anticoagulants	Antithrombin deficiency	Inhibits FIIa, FXa, and other factors. Decreased activity leads to increased risk of thrombosis. Should be confirmed with repeat tests.	Antithrombin activity	Results may be impacted by acute thrombotic event, conditions that result in loss of protein (nephrotic syndrome, DIC, etc.), factor or PS deficiency, use of UFH or FXai.
	Protein C deficiency	Activated protein C with cofactor protein S inhibit FVa and VIIIa. Decreased activity of either/both results in increased risk of thrombosis. Should be confirmed with repeat tests.	Protein C activity	Results may be impacted by acute thrombotic event, vit K deficiency, liver disease, use of warfarin, DOACs
	Protein S deficiency		Protein S activity	Results may be impacted by acute thrombotic event, vit K deficiency, liver disease, use of combined oral contraceptives or warfarin
Antiphospholipid syndrome	Lupus Anticoagulant (LA)	Tends to occur with other rheumatological and autoimmune disorders. Clinical features include thrombosis, pregnancy morbidity, thrombocytopenia, livedo racemose (or reticularis), cardiac valvulopathy.		Often false positive while pt on AC or in acute thrombotic event. Repeat test 12 weeks later. (+) LA: POC/Lab INRs may be falsely elevated.[12]
	Anti-cardiolipin antibodies (aCL)		IgG >> IgM >>>> IgA	False positive possible in acute thrombotic event. Not conclusive alone, should be checked with aβ2GP. Repeat test 12 weeks later.
	Anti-β_2-glycoprotein antibodies (aβ2GP)		IgG >> IgM >>>> IgA	False positive possible in acute thrombotic event. Repeat test 12 weeks later.

[12] In the event of unexpected/unexplainable supratherapeutic INR, it is reasonable to order concurrent lab INR and chromogenic factor X for evaluating true level of anticoagulation in patients with lupus anticoagulant.

Thrombophilia Prevalence and Associated VTE risk					
Thrombophilia		**Prevalence in General Population**	**Relative Risk for 1st VTE**	**Relative Risk for Recurrent VTE**	**Risk Category**
Antithrombin deficiency		0.02%	5-10%	1.9-2.6%	High
Protein C deficiency		0.2%	4-6.5%	1.4-1.85	High
Protein S deficiency		0.03 to 0.13%	1-10%	1-1.4%	High
Factor V Leiden		3-7%	3-5%	1.4%	Heterozygous: Low Homozygous: High
Prothrombin G20210A mutation		0.7-4%	2-3%	1.4%	Heterozygous: Low Homozygous: High
Antiphospholipid Syndrome	Lupus Anticoagulant	1-8%	3-10%	2-6%	High
	Anti-cardiolipin antibodies	5%	0.7%	1-6%	
	Anti-β_2-glycoprotein antibodies	3.4%	2.4%		



Garcia, (2023)

VTE Associated with Thrombophilia			
Thrombophilia		**Therapeutic Recommendation**	**Duration of Treatment**
Factor V Leiden	provoked by other transient risk factor	DOAC or warfarin (INR goal 2-3)	3-6 months (Assuming transient risk factor resolved)
	recurrence or unprovoked	DOAC or warfarin (INR goal 2-3)	Extended
Prothrombin G20210A mutation	provoked by other transient risk factor	DOAC or warfarin (INR goal 2-3)	3-6 months (Assuming transient risk factor resolved)
	recurrence or unprovoked	DOAC or warfarin (INR goal 2-3)	Extended
Protein C/S deficiency		DOAC or warfarin (INR goal 2-3)	Extended
Antithrombin deficiency		DOAC or warfarin (INR goal 2-3) Generally, should not use LMWH or fondaparinux as they rely on antithrombin for their activity.	Extended
Antiphospholipid antibody syndrome		VKA (INR goal 2-3) or LMWH[13]	Extended

[13] Data from clinical trials have demonstrated increased risk of arterial thrombosis in patients with antiphospholipid syndrome treated with DOACs. [15, 25]

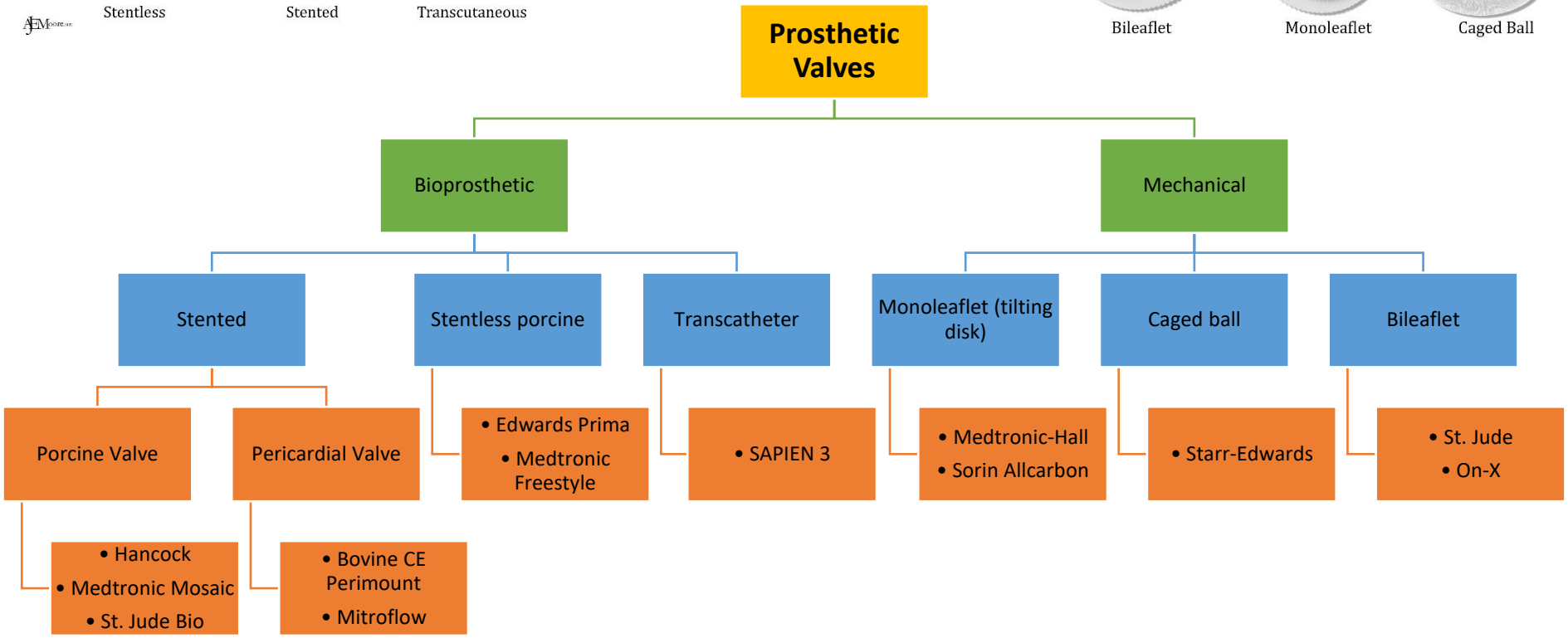
Anticoagulant Considerations in VTE Associated with Thrombophilia						
	Indication	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**Older Adult**	**Contraindication**
apixaban / Eliquis	VTE treatment	10 mg BID x7 days, then 5 mg BID	No dosage adjustment recommended	Use not recommended in Child-Turcotte-Pugh Class C	Likely safe in older adults, but increased bleed risk versus younger patients.	• Antiphospholipid antibody syndrome • Mechanical valve prosthesis in any position • Some drug-drug interactions
	Secondary thromboprophylaxis	5 mg BID (May consider 2.5 mg BID after 6 mos of treatment if full dose anticoagulation is not indicated)[14]				
dabigatran / Pradaxa	VTE treatment	150 mg twice daily (after 5-10 days of parenteral therapy)	•CrCl > 30 mL/min: No adjustment for •CrCl ≤ 30 mL/min: Do not use	No dosage adjustments provided	Increased bleed risk. Use with extreme caution or consider other treatment in patients ≥ 75 years of age.	
edoxaban / Savaysa	VTE treatment	Weight > 60kg: 60 mg once daily Weight ≤ 60 kg: 30 mg once daily	•CrCl >95 mL/min: Do not use •CrCl 15-50 mL/min: 30 mg once daily •CrCl < 15 mL/min: Do not use	Use not recommended in Child-Turcotte-Pugh Class C	Likely safe in older adults but increased bleed risk versus younger patients.	
rivaroxaban / Xarelto	VTE treatment	15 mg BID with food x21 days, then 20 mg QD with food	•CrCl ≥ 30 mL/min: No adjustment •CrCl < 15 mL/min: Avoid use	Use not recommended in Child-Turcotte-Pugh Class B or C	Increased bleed risk. Use with caution in older adults (≥ 75 years of age).	
	Secondary thromboprophylaxis	20 mg QD with food (May consider 10 mg QD after 6 mos of treatment if full dose anticoagulation is not indicated)[14]				

[14] Based on limited data; consider patient's thrombotic risk before reducing dose. (ref 3, 9)

Anticoagulant Considerations in VTE Associated with Thrombophilia (continued)						
	Indication	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**Older Adult**	**Contraindication**
dalteparin/ Fragmin	VTE treatment Bridging	200 units/kg SQ QD or 100 units/kg SQ BID	•CrCl > 30 mL/min: No dose adj •CrCl < 30 mL/min: Use not recommended	No dosage adjustments provided		• hx of HIT • hypersensitivity to pork • Dialysis
enoxaparin / Lovenox	VTE treatment Bridging	1 mg/kg SQ BID or 1.5 mg/kg SQ QD	•CrCl < 30 mL/min: 1 mg/kg SQ QD Avoid use in dialysis if possible	No dosage adjustments provided (has not been studied – use with caution)	Increased incidence of bleeding with therapeutic dose, especially if <45 kg body weight.	
fondaparinux / Arixtra	VTE treatment	<50 kg: 5 mg SQ QD 50-100 kg: 7.5 mg SQ QD >100 kg: 10 mg SQ QD	•CrCl ≥ 30 mL/min: No adjustment however, use caution in CrCl <50 mL/min – consider alternative therapy	No dosage adjustments provided for Child-Turcotte-Pugh class A and B. Has not been studied in Child-Turcotte-Pugh class C – use with caution)		• Antiphospholipid antibody syndrome • CrCl < 30 mL/min
unfractionated heparin	VTE treatment Periop bridging VTE prophylaxis	333 units/kg SQ followed by 250 units/kg SQ BID IV infusion in patient 5000 units SQ Q8-12 hours	Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)	Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)	>60 yo may have higher serum levels and longer aPTTs	
warfarin		Target INR 2.0-3.0	No dosage adjustments provided	Response to warfarin will be markedly enhanced. Baseline INR elevation can confound results	Increased bleed risk versus DOAC	Recent data suggests increased bleeding compared to apixaban when used in patients on dialysis.[15]

[15] Recent studies have demonstrated increased bleed risk when warfarin is used in patients on dialysis. Similar studies have demonstrated improved safety with apixaban use over warfarin in dialysis.

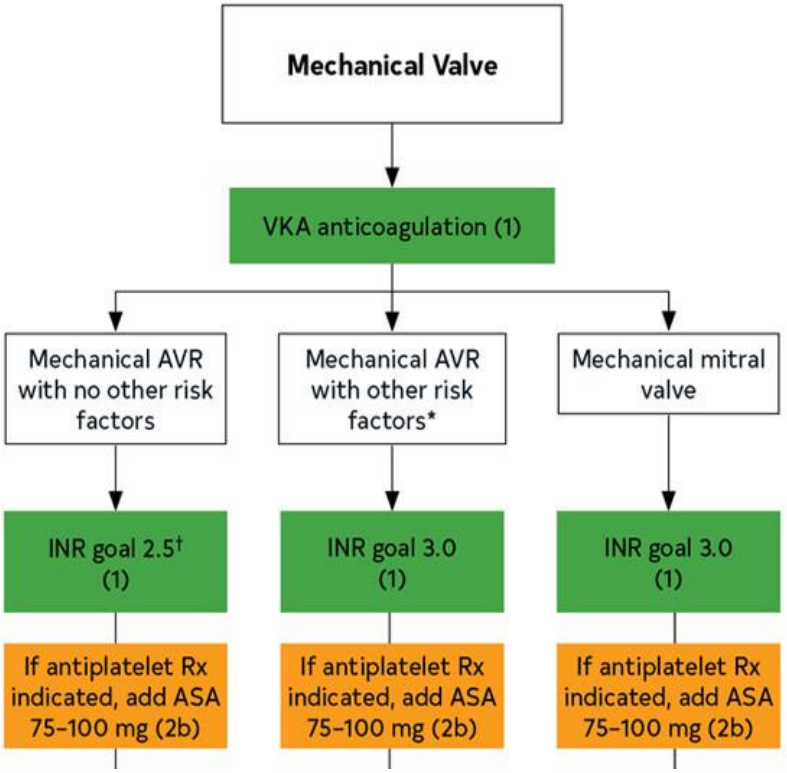
Valvular Heart Disease

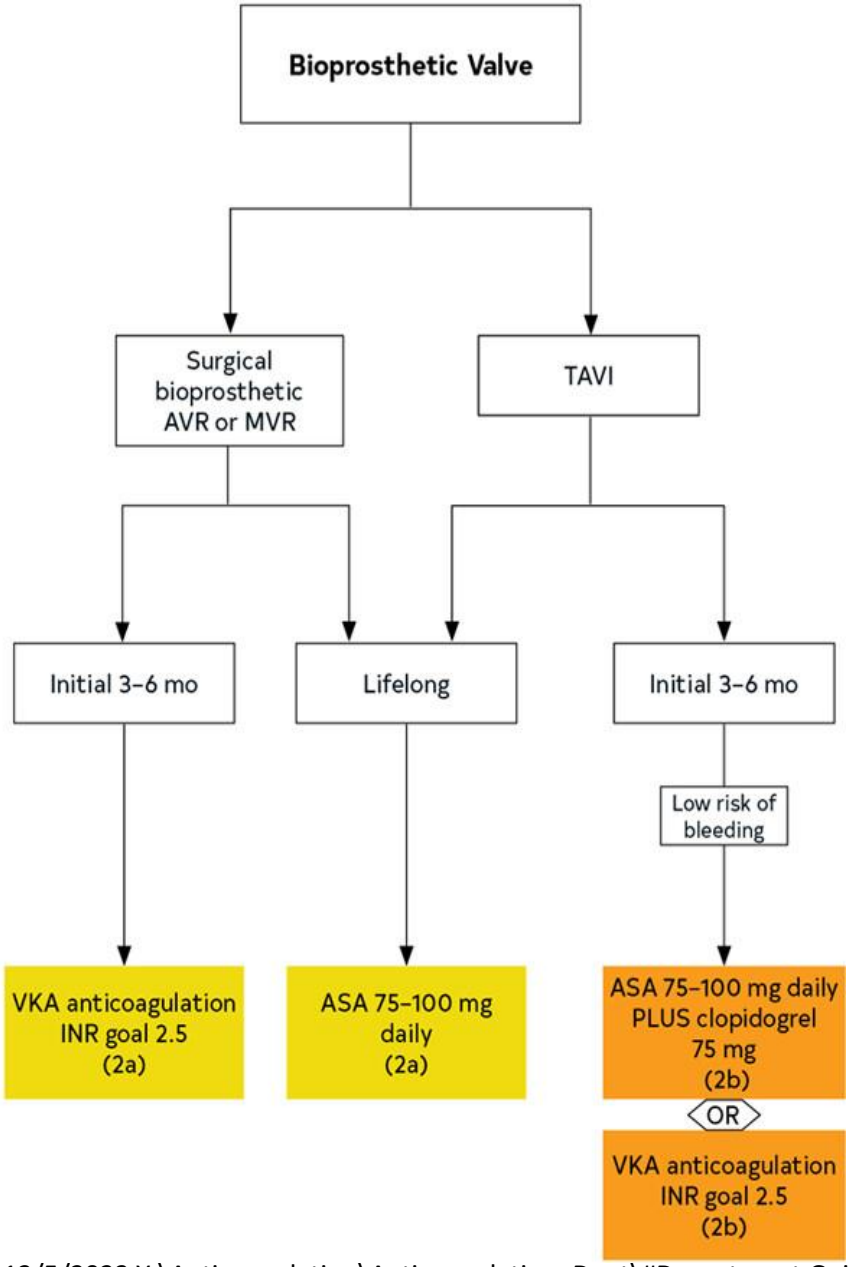


Valvular Atrial Fibrillation		
Indication	**Therapeutic Recommendation**	**Duration of Treatment**
Mitral valve stenosis (mild)	DOAC or VKA (INR 2-3)	Extended
Mitral valve stenosis (moderate to severe)	VKA (INR 2-3)	
Aortic valve disease Tricuspid valve disease Mitral valve regurgitation	DOAC or VKA (INR 2-3)	
Mixed valve disease (minus mod-sev MS)	DOAC or VKA (INR 2-3)	
Prosthetic Valve Replacement		
Indication	**Therapeutic Recommendation**	**Duration of Treatment**
Bioprosthetic mitral valve	Low risk of bleeding: VKA (INR 2-3) or DOAC [16] OR ASA 75-100 mg daily alone	3-6 months then ASA 81 mg indefinitely (If indication for long-term anticoag, may consider continuation of pre-op therapy)
Bioprosthetic aortic valve		
Mechanical aortic valve	VKA (INR 2-3)[17]	Extended Consider ASA 81 mg daily if low risk of bleeding
Mechanical aortic valve with additional risk factors: AF, LV dysfunction, previous thromboembolism, hypercoagulable state, older-generation valve (eg ball-in-cage)	VKA (INR 2.5-3.5)[17]	Extended Consider ASA 81 mg daily if low risk of bleeding
Mechanical mitral valve		
Dual mechanical valve (mitral + aortic)		
On-X mitral valve		
On-X aortic valve	VKA (INR 2.0-3.0) 1st 3 months VKA (INR 1.5-2.0) thereafter if no thromboembolic risk factors[17]	Extended + ASA 81 mg indefinitely
TAVR (transcatheter aortic valve replacement)	ASA 81 mg daily alone OR Low risk of bleeding: DAPT with ASA + clopidogrel for first 3-6 months OR VKA (INR 2.0-3.0) for at least 3 months Indication for long-term OAC: may continue current OAC	ASA 81 mg indefinitely

[16] Data supporting the use of DOAC over VKA in first 3 months post bioprosthetic mitral/aortic valve replacement has increased in recent years, however the studies were small which warrants further investigation in larger trials.

[17] For patients with a mechanical valve prosthesis, the use of direct oral anticoagulants (DOAC) is not recommended.





Catherine M. Otto. ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the ACC/AHA Joint Committee on Clinical Practice Guidelines. Circulation. 2020

Peripheral Artery Disease (PAD) / Coronary Artery Disease (CAD)

Peripheral Artery Disease		
Indication	**Clarification**	**Therapeutic recommendation**
Asymptomatic lower extremity PAD	Low ABI but no clinical symptoms or previous vascular intervention	Do not use anticoagulation unless other atherosclerotic (coronary, cerebrovascular) disease
Chronic symptomatic lower extremity PAD	Low ABI with clinical symptoms (intermittent claudication, ischemic rest pain, ischemic ulceration, functional limitations) without recent revascularization	If low bleed risk: rivaroxaban 2.5 mg twice daily plus ASA 81 mg once daily If high bleed risk: SAPT
Lower extremity PAD after revascularization	Endovascular revascularization	rivaroxaban 2.5 mg twice daily plus ASA 81 mg once daily with or without short term clopidogrel[18]
	Open revascularization	rivaroxaban 2.5 mg twice daily plus ASA 81 mg once daily
Coronary Artery Disease		
Indication	**Clarification**	**Therapeutic recommendation**
Chronic Coronary Disease (CCD)	Without indication for OAC	ASA 81 mg daily
	s/p PCI	DAPT x6 months, then SAPT
	s/p PCI with drug eluting stent (DES)	DAPT x1-3 months, then P2Y12
	s/p PCI with indication for OAC	Triple therapy for 1-4 weeks, then clopidogrel x6 months plus OAC
	Without indication for therapeutic OAC or DAPT and with high risk of recurrent ischemic event	rivaroxaban 2.5 mg twice daily plus ASA 81 mg once daily
Hx Acute Coronary Syndrome (ACS)	s/p PCI with DES or BMS	In select patients, at least 12 months DAPT
	+/- PCI with indication for OAC	OAC plus P2Y12 until 12 mo post ACS, then OAC alone
	s/p CABG	In select patients, 12 months DAPT, then ASA 100-325 mg daily indefinitely
	s/p CABG with indication for OAC	OAC plus ASA 81 mg daily until 12 mo post CABG, then OAC alone

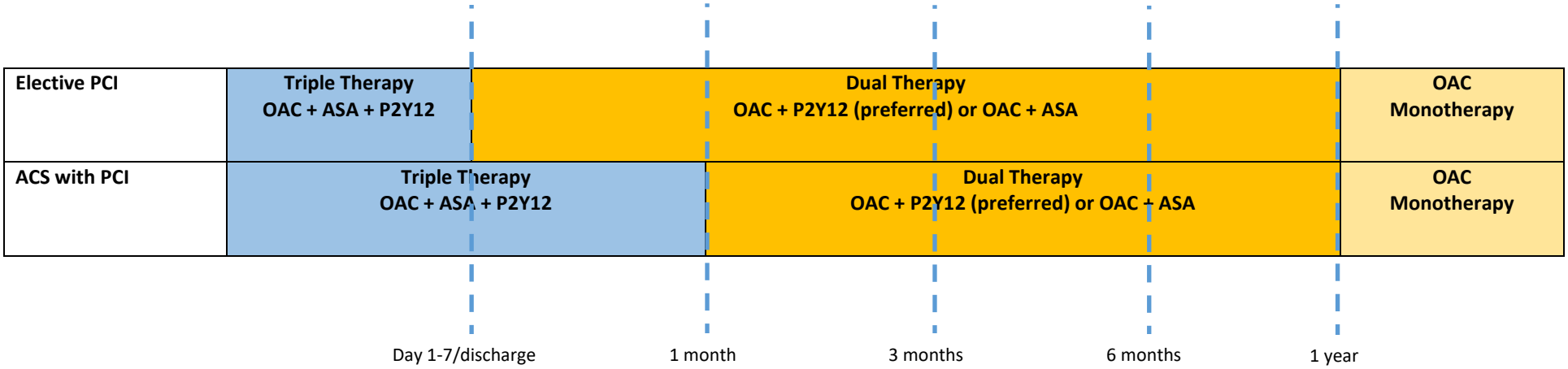
- Dual pathway inhibition (DPI) with aspirin and rivaroxaban 2.5 mg BID has shown benefit by blocking platelet activation via two mechanisms and thereby reducing thrombotic risk.

[18] Full dose anticoagulation plus SAPT may be considered after urgent revascularization.

- The addition of antiplatelet agents to oral anticoagulants may reduce the incidence of thromboembolism at the cost of bleeding. Therefore, addition of antiplatelets to OACs should be reserved for patients at very high risk of thromboembolism where advantages clearly outweigh the risks and continued only for the requisite duration based on individual bleeding risk.

Antiplatelet considerations

Combination Therapy	
Indication	**Information**
Primary CVD prevention	According to 2019 AHA/ACC guidelines, aspirin should now only be considered in patients with the highest ASCVD risk and no increased bleeding risk (eg. concomitant use of anticoagulants) due to lack of a clear net benefit.
Secondary CV event prevention in stable CAD/PAD without other indication for OAC	Dual pathway inhibition (aspirin plus rivaroxaban 2.5 mg BID) is recommended for select group of patients (see CAD/PAD) based on VOYAGER-PAD and COMPASS trials.
First 12 mos post ACS or PCI in pt needing concomitant OAC	DOAC preferred over VKA. Triple therapy for 1-4 weeks, then dual therapy with P2Y12 + DOAC for 6 mos to 1 year, then OAC monotherapy.
Prosthetic valves	Mechanical valves: warfarin alone is recommended. Aspirin (75-100mg) daily may be considered if clear indication for antiplatelet and pt has low bleed risk.
	On-X valve: aspirin (75-100mg) daily recommended in combination with warfarin
	Bioprosthetic valve: aspirin is not recommended in combination with oral anticoagulation. Aspirin (75-100mg) daily is reasonable if pt has no other indication for OAC.



Reasons to Shorten Duration of Combination Therapy[19]	Reasons to Prolong Duration of Combination Therapy[18]
Major Bleeding Risk	**High Thrombotic Risk (early events)**

• Severe or end-stage CKD (eGFR <30 mL/min)
• Hemoglobin <11 g/dL
• Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent
• Moderate or severe baseline thrombocytopenia (platelet count <100x10^9/L)
• Chronic bleeding diathesis
• Liver cirrhosis with portal hypertension
• Active malignancy (excluding non-melanoma skin cancer) within the past 12 months
• Previous spontaneous ICH (at any time)
• Previous traumatic ICH within the past 12 months
• Presence of a brain arteriovenous malformation
• Moderate or severe ischemic stroke within the past 6 months
• Nondeferrable major surgery on DAPT
• Major surgery or major trauma within 30 days before PCI
	• ACS
	• Previous stent thrombosis while on antiplatelet therapy
	• PCI complexity
	  ○ 3 vessels treated
	  ○ ≥ 3 stents implanted
	  ○ ≥ 3 lesions treated
	  ○ Bifurcation with 2 stents implanted
	  ○ Total stent length > 60 mm
	  ○ Surgical bypass graft PCI
	  ○ Chronic total occlusion PCI
	  ○ Atherectomy device use
	  ○ Left main PCI

Minor Bleeding Risk:	**High Ischemic Risk (long-term events)**
• Age 75 or older • Moderate CKD (eGFR 30 to 59 mL/min) • Hemoglobin 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women • Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting a major criterion • Long-term use of oral NSAIDs or steroids • Any ischemic stroke at any time not meeting a major criterion	• Previous myocardial infarction (MI) • Multivessel coronary artery disease • Polyvascular disease • Diabetes mellitus • Chronic kidney disease • Heart failure

[19] List is not all-inclusive of the various bleeding, thrombotic, or ischemic risk factors to be considered when determining duration of combination therapy. Both bleeding and thrombotic/ischemic risk factors should be considered.(ref 5)

Medication Key

Antiplatelet therapy

- APT = Antiplatelet therapy
- ASA = Aspirin
- $P2Y_{12}i$ = $P2Y_{12}$ inhibitor

Anticoagulant therapy

- OAC = Oral anticoagulant

* See Table 2: Dosing Table for AF.

† ASCVD indicates coronary artery disease cerebrovascular disease/peripheral artery disease.

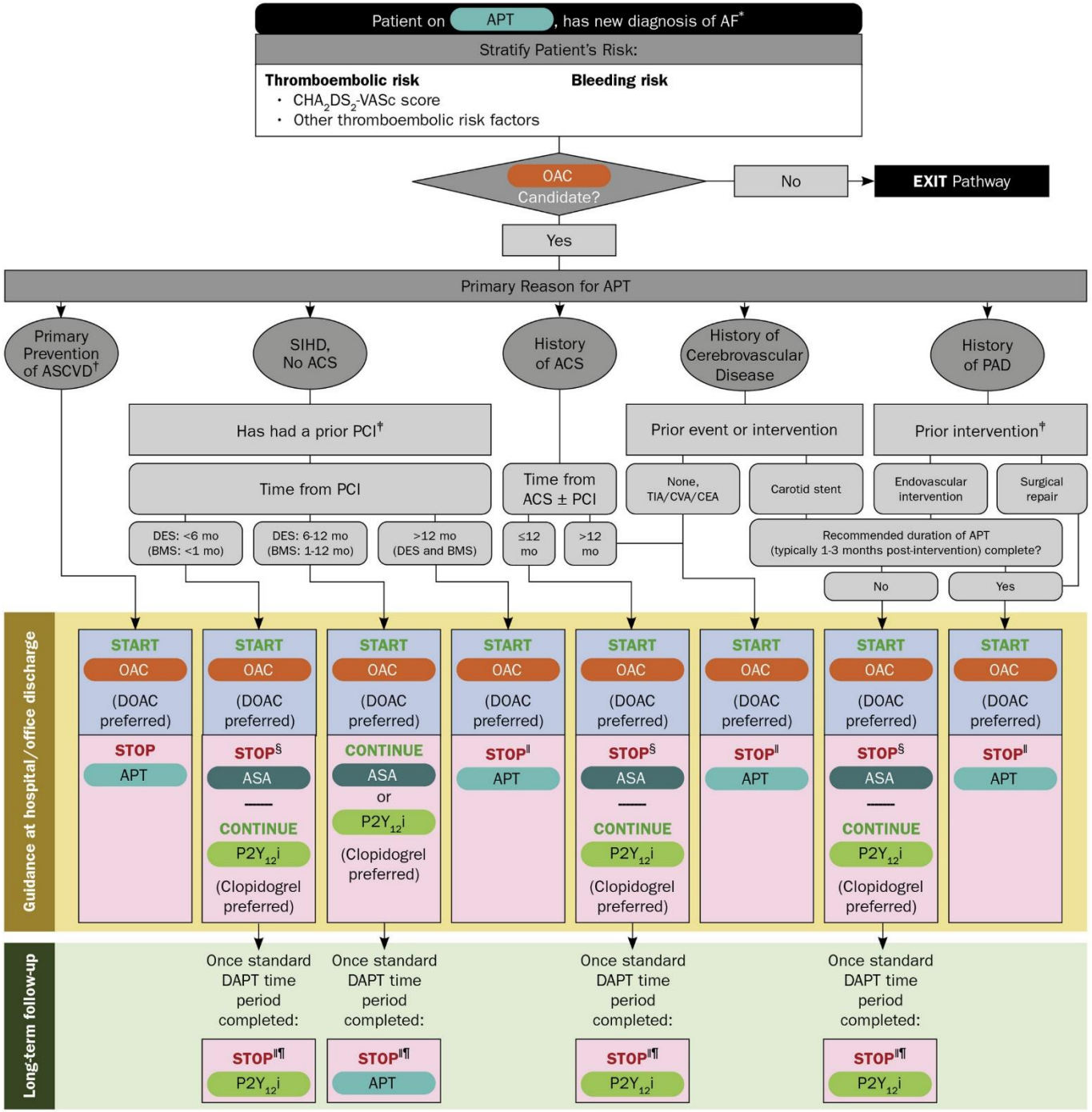
‡ As discussed in the text, for SIHD patients who have undergone prior CABG surgery, time since CABG surgery should be considered once the patient has an indication for an OAC. Continue aspirin (<100 mg daily) if <1 year post-CABG surgery and stop aspirin if >1 year post-CABG surgery. For patients with PAD or SIHD that is medically managed, APT can be stopped once the OAC is started.

§ If thrombotic risk is high and bleeding risk is low, can continue ASA 81 mg daily (as part of triple therapy) for up to 30 days.

‖ Occasionally, in patients felt to be at high thrombotic risk/low bleeding risk who have completed the standard duration of APT, continuation of SAPT with an OAC may be considered.

¶ Resume standard dosing OAC.

AF = atrial fibrillation; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BMS = bare metal stent; CEA = carotid endarterectomy; CVA = cerebrovascular accident; DES = drug-eluting stent; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; TIA = transient ischemic attack.



Kumbhani et al. ***J Am Coll Cardiol 2020;***, *77*(5), 629–658.

Thromboembolic and Bleed Risk Evaluation

Prior to prescribing an anticoagulant, providers should weigh the risk of thrombosis against the risk of bleeding.

Bleeding risk factors	Low thromboembolic risk	Moderate thromboembolic risk	High thromboembolic risk
• Major bleed or ICH < 3 months ago • Platelet abnormality (including antiplatelet use) • High INR • Recent major bleeding or prior major bleed during previous or similar procedure • Prior major bleed during bridging therapy • Age ≥ 65 years • Liver cirrhosis or advanced liver disease • Advanced renal disease • Elevated HASBLED (≥ 3) • Anemia (Hgb < 12, Hct < 35%) • Cancer • Currently on vascular endothelial growth factor (VEGF) inhibitor therapy	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc ≤ 4 and no prior stroke/TIA/SE **Venous Thromboembolism:** • VTE > 12 months ago and no other risk factors **Mechanical Heart Valve:** • Bileaflet aortic prosthesis *without* major stroke risk factors[20]	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc 5-6 **Venous Thromboembolism:** • VTE 3-12 months ago • Non-severe thrombophilia • Recurrent VTE • Active cancer or recent history of cancer **Mechanical Heart Valve:** • Bileaflet aortic prosthesis *with* major stroke risk factors[20] • Bileaflet mitral prosthesis *without* major stroke risk factors[20]	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc ≥ 7 • Stroke/TIA/SE ≤ 3 mos ago • Rhematic valvular heart disease **Venous Thromboembolism:** • VTE < 3 months ago (especially 1 mo) • Severe thrombophilia[21] • Active cancer associated with high VTE risk[22] • Prior perioperative TE **Mechanical Heart Valve:** • Any caged-ball or tilting disc prosthesis • Any mitral prosthesis *with* major stroke risk factors[20] • Stroke or TIA < 3 months

[20] Includes: AF, prior stroke/TIA during anticoagulation interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, age ≥75 years.
[21] Deficiency of protein C, S, or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation; multiple thrombophilia; antiphospholipid antibodies.
[22] Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

Thromboembolic Risk Tools

CHA_2DS_2-VASc Scoring Table for Patients with Atrial Fibrillation		
Risk Factor	**Points**	**Definition**
Congestive heart failure/LV dysfunction	1	Left ventricular dysfunction or symptomatic heart failure
Hypertension	1	More than 140/90mmHg (use of 130-800mmHg is acceptable) or on antihypertensive therapy
Age ≥ 75 years	2	
Diabetes mellitus	1	Fasting blood glucose >126mg/dL, HgA1c >6.5%, or receiving treatment for diabetes
Stroke/TIA or arterial/cardioembolic thromboembolism (prior)	2	Prior history of stroke, TIA, or systemic embolism
Vascular disease	1	CAD, prior MI, PAD, intermittent claudication, aortic plaque, carotid stenosis
Age 65-74 years	1	
Sex **C**ategory (female sex)	1	
Total = (maximum is 9)		

Stroke Risk Stratification for CHA_2DS_2-VASc		
Score	**Unadjusted stroke rate (% per year) if untreated**	**Risk Category**
0	0.2%	Low
1	1.3%	Low
2	2.2%	Low
3	3.2%	Low
4	4.8%	Low
5	7.2%	Moderate
6	9.7%	Moderate
7	11.1%	High
8	10.8%	High
9	12.2%	High

Additional Risk Factors That Increase Risk of Stroke	
Risk Factor	**Notes**
Higher AF burden/long duration	While not included in CHA_2DS_2-VASc, these risk factors should be considered in patients with CHA_2DS_2-VASc of 1 (or 2 in female sex) when interpreting stroke risk score. These additional factors may inform decision-making for patients with lower risk of stroke who remain uncertain about starting OAC or are considering discontinuing OAC.
Persistent/permanent AF vs Paroxysmal	
Obesity (BMI ≥ 30)	
Hypertrophic cardiomyopathy	
Poorly controlled hypertension	
eGFR < 45 mL/hr	
Proteinuria (> 150 mg/24 hr or equivalent)	
Enlarged left atrium volume (≥ 73 mL) or diameter (≥ 4.7 cm)	

HERDOO2 Score for Recurrent VTE[23]	
Criterion	**Points**
Post-thrombotic signs (hyperpigmentation, edema, redness of lower extremity)	1
D-dimer ≥ 250 ng/mL while on anticoagulation	1
BMI ≥ 30 kg/m^2	1
Age ≥ 65 years	1

Clot Risk Stratification for HERDOO2		
Score	**Risk Category**	**Rate of Recurrent VTE 1 yr. Off AC**
0-1	Low	3%
2-4	High	8%

Online VTE Risk Calculator

VTE-PREDICT Score

- Applies to patients with DVT/PE who have completed initial anticoagulation treatment phase and who do not have active cancer
- Estimates risk of recurrent VTE and bleeding with different treatment strategies
- 1 year and 5 year risk estimate available
- Estimates are based on 14 clinical characteristics
- Available at https://vtepredict.com

[23] Applies to women age ≥ 18 years with unprovoked VTE who are on anticoagulation.

Caprini Risk Score for DVT risk in Surgery			
1 Point Per Risk Factor	**2 Point Per Risk Factor**	**3 Point Per Risk Factor**	**5 Point Per Risk Factor**
• Age 41 – 60 years • Minor surgery planned • History of prior major surgery • Varicose veins • History of inflammatory bowel disease • Swollen legs (current) • Obesity (BMI > 30) • Acute MI (< 1 month) • Congestive heart failure (< 1 month) • Sepsis (< 1 month) • COPD • Serious lung disease including pneumonia (< 1 month) • Abnormal pulmonary function • Medical pt currently on bed rest • Other risk factors • Oral contraceptives • Pregnancy or postpartum (< 1 month) • History of unexplained stillborn infant, recurrent spontaneous abortion, premature birth with toxemia or growth-restricted infant	• Age 61 – 74 years • Major surgery (> 60 min) • Arthroscopic surgery (> 60 min) • Laparoscopic surgery (> 60 min) • Immobilizing plaster cast • Patient confined to bed > 72 hrs • Previous malignancy • Central venous access • Morbid obesity (BMI > 40)	• Age over 75 years • Major surgery lasting 2-3 hours • BMI > 50 • History of SVT, DVT/PE • Family history of DVT/PE • Present cancer or chemotherapy • Factor V Leiden • Prothrombin 20210A • Elevated serum homocysteine • Lupus anticoagulant • Elevated anticardiolipin antibodies • Heparin-induced thrombocytopenia • Other thrombophilia	• Elective major lower extremity arthroplasty • Hip, pelvis, or leg fracture (< 1 month) • Stroke (< 1 month) • Multiple trauma (< 1 month) • Acute spinal cord injury (paralysis) (< 1 month) • Major surgery lasting over 3 hrs

Clot Risk Stratification for Caprini			
Caprini Score	**VTE risk category**	**Recommendations**	**Duration**
0	Very low risk	Early ambulation	During hospitalization
1 – 2	Low risk	Intermittent pneumatic compression (IPC) +/- compression stockings	During hospitalization
3 – 4	Moderate risk (0.7%)	IPC +/- compression stockings	During hospitalization
5 – 6	High risk (1.8%)	IPC plus LMWH or low-dose UFH	7 – 10 days total
7 – 8	High risk (4.0%)	IPC plus LMWH or low-dose UFH	7 – 10 days total
≥ 9	High risk (10.7%)	IPC plus LMWH or low-dose UFH	30 days total
Total Joint Replacement			
< 10	Low risk	Early ambulation plus aspirin + IPC	30 days total
> 10	High risk	Early ambulation plus LMWH or fondaparinux or DOAC plus IPC	30 days total

Bleed Risk Tools

HAS-BLED Score[24]		
Risk Factor	**Points**	**Definition**
Hypertension	1	Systolic blood pressure > 160 mmHg
Abnormal renal function	1	Dialysis, transplant, SrCr > 2.26 mg/dL
Abnormal hepatic function	1	Cirrhosis or bilirubin > 2x normal with AST/ALT/AP > 3x normal
Stroke history	1	
Bleeding history or predisposition to bleeding	1	
Labile INR	1	Unstable/high INRs, TTR < 60%
Elderly	1	Age > 65 years
Drugs predisposing to bleed	1	Antiplatelets, NSAIDs
Alcohol	1	≥ 8 drinks per week
Total = (maximum is 9)		

Bleed Risk Stratification for HAS-BLED		
Score	**Major Bleeds / 100 pt yrs[25]**	**Risk Category**
0	1.13	Low
1	1.02	Low
2	1.88	Moderate
3	3.78	High
4	8.70	High
5 to 9	Insufficient data	High

VTE-BLEED Score	
Risk Factor	**Points**
Active cancer	2
Male pt with uncontrolled HTN	1
Anemia	1.5
History of bleeding	1.5
Kidney dysfunction (CrCl 30-60 mL/min)	1.5
Age ≥ 60 years	1.5

Bleed Risk Stratification for VTE-BLEED	
Score	**Risk Category**
0 to 1.5 points	Low
2 or higher	High

[24] HAS-BLED score has only been validated in patients with atrial fibrillation who are on anticoagulation.
[25] Major bleed is defined as: ICH or bleeding resulting in a hospitalization, a hemoglobin drop > 2g/dL, or a blood transfusion.

Bleed Risk Tools (continued)

Child-Turcotte-Pugh Score for Cirrhosis Severity			
Clinical and Lab Criteria	**1 Point**	**2 Points**	**3 Points**
Encephalopathy	None	Mild to mod (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to mod (diuretic responsive)	Severe (diuretic refractory)
Bilirubin	< 2 mg/dL	2 – 3 mg/dL	> 3 mg/dL
Albumin	> 3.5 g/dL	2.8 – 3.5 g/dL	< 2.8 g/dL
INR	< 1.7	1.7 – 2.3	> 2.3

Risk Stratification for Child-Turcotte-Pugh		
Score	**Class**	**Risk Category**
5-6 points	A	Least severe liver disease
7-9 points	B	Moderately severe liver disease
10-15 points	C	Most severe liver disease

SPARCtool – Stroke Prevention in Atrial Fibrillation Risk Tool

This is a risk calculator developed by Peter Loewen, ACPR, PharmD, FCSHP. This tool is useful to clinicians and patients with atrial fibrillation when utilizing shared decision-making to ensure the patient has made an informed decision about whether to use anticoagulation and which anticoagulant to use. The SPARCtool generates patient-specific estimates of stroke and bleed risk for various agents versus no therapy.

Can be found at: SPARCtool.com

Initiation and Maintenance of Anticoagulation Therapy

Warfarin

Prior to starting warfarin check for absolute contraindications to use:

- Pregnancy
- Hemorrhagic tendencies or blood dyscrasias
- Recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces
- Bleeding tendencies associated with certain conditions
- Threatened abortion, eclampsia, and preeclampsia
- Unsupervised patients with potential high levels of non-compliance
- Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding
- Hypersensitivity to warfarin or any component of the product
- Major regional or lumbar block anesthesia
- Malignant hypertension

Consider other patient factors that could impact warfarin safety:

- Possible drug interactions [26]
- Ability of patient/family to comply with monitoring requirements and comprehend warfarin education.
- Alcohol abuse, dementia, depression, unstable diet, other comorbidities
- Discuss treatment options with cardiologist if patient is on duel antiplatelet therapy

Warfarin induction

- The results of clinical trials suggest that initiation doses 5 mg and 10 mg are effective; starting doses of < 5 mg might be appropriate in the elderly, in patients with impaired nutrition, liver disease or congestive heart failure and in patients who are at high risk of bleeding
- 10 mg starting doses should be reserved for patients with lower sensitivity factors (see table below)
- Providers should consider individual patient characteristics and the presence of any sensitizing factors prior to the initiation of warfarin therapy

[26] See warfarin interactions section. Always check via reliable drug information resource (Lexicomp, AC Forum).

Selection of Warfarin Starting Dose	
Higher Sensitivity (consider lower starting dose)	**Lower Sensitivity (consider higher starting dose)**
Baseline INR > 1.2	Baseline INR < 1.2
Advanced age (> 65 years)	Younger age (< 55 years)
Female sex	Male sex
Low body weight (< 50 kg)	Higher body weight (> 90 kg)
Asian ancestry	African American ancestry
Recent surgery and/or blood loss	Diet high in vitamin K
Comorbidities: CHF, renal disease, liver disease, cancer	
Impaired nutritional status	
Alcohol abuse	
Concurrent use of medications that are known to increase INR (amiodarone, metronidazole, etc.)	
Acute illness (diarrhea, fever)	

Induction Dosing

INR Target Range 2.0-3.0		
INR result	**Higher Sensitivity Patients**	**Lower Sensitivity Patients**
	2.5 mg daily	**5 mg daily**
< 1.5	5 mg daily	7.5 mg-10 mg daily
1.5-1.9	2.5 mg daily	5 mg daily
2-3	1.25 mg daily	2.5 mg daily
3.1-4	0.5 mg daily	1.25 mg daily
> 4	Hold until INR <3	Hold until INR <3
Next INR	2-3 days	2-3 days
Next INR (bridging)	1-2 days	1-2 days

INR Target Range 2.5-3.5		
INR result	**Higher Sensitivity Patients**	**Lower Sensitivity Patients**
	2.5 mg daily	5 mg daily
< 1.7	5 mg daily	7.5 mg daily
1.8-2.4	2.5 mg daily	5 mg daily
2.5-3.5	1.25 mg daily	2.5 mg daily
3.6-4.4	0.5 mg daily	1.25 mg daily
> 4.4	Hold	Hold
Next INR	2-3 days	2-3 days
Next INR (bridging)	1-2 days	1-2 days

Cycle is repeated until in-range INR achieved on 2 consecutive measurements

- Once therapeutic INR is obtained on two consecutive measurements, follow up can be extended to every 3-5 days until steady state and stable weekly dosing is established.

Maintenance Dosing

- Maintenance dosing algorithms should be used after the patient has gone through the initiation period and when a weekly maintenance dose has been established.
- Dosing nomograms offer a reasonable starting point for warfarin dose adjustments but should never be used in an "absolute" manner. Thorough patient assessment and clinical judgement are imperative.
- **INRs ≥ 4.5 will be confirmed with reflex Lab PT/INR when possible.**

Target INR 2.5 (Range 2.0-3.0)							
INR	**≤1.5**	**1.51-1.99**	**2.00-3.00**	**3.01-4.00**	**4.01-4.99**	**5.00-10.00**	**>10.00**
Dose Change	Increase 15%	Increase 10%	No change	Decrease 10%	Hold for one day then decrease 10%	Hold until INR therapeutic and then decrease by 15%	Hold until INR therapeutic and then decrease by 25%
Next INR	4-8 days	7-14 days	See follow-up algorithm below	7-14 days	4-8 days	2-3 days	Daily until INR is within target range

Target INR 3.0 (Range 2.5-3.5)							
INR	**≤ 2.00**	**2.01-2.49**	**2.50-3.50**	**3.51-4.50**	**4.51-5.49**	**5.50-10.00**	**>10.00**
Dose Change	Increase 15%	Increase 10%	No change	Decrease 10%	Hold for one day then decrease 10%	Hold until INR therapeutic and then decrease by 15%	Hold until INR therapeutic and then decrease by 25%
Next INR	4-8 days	7-14 days	See follow-up algorithm below	7-14 days	4-8 days	2-3 days	Daily until INR is within target range

Follow Up Intervals for Maintenance Therapy	
Change	**Follow Up[27]**
Dose change today	1-2 weeks
Dose change >2 weeks ago	2-4 weeks
Change in significant interacting medications	3-4 days (following drug interactions guidelines)
Patient self-testers (PST)	Weekly or as prescribed
Hospitalization	Within 1-5 days of discharge or as clinically indicated
Cardioversion/Ablation	Weekly 3 weeks prior; and weekly for 4 weeks after
Bridging	Every 1-3 days until off LMWH

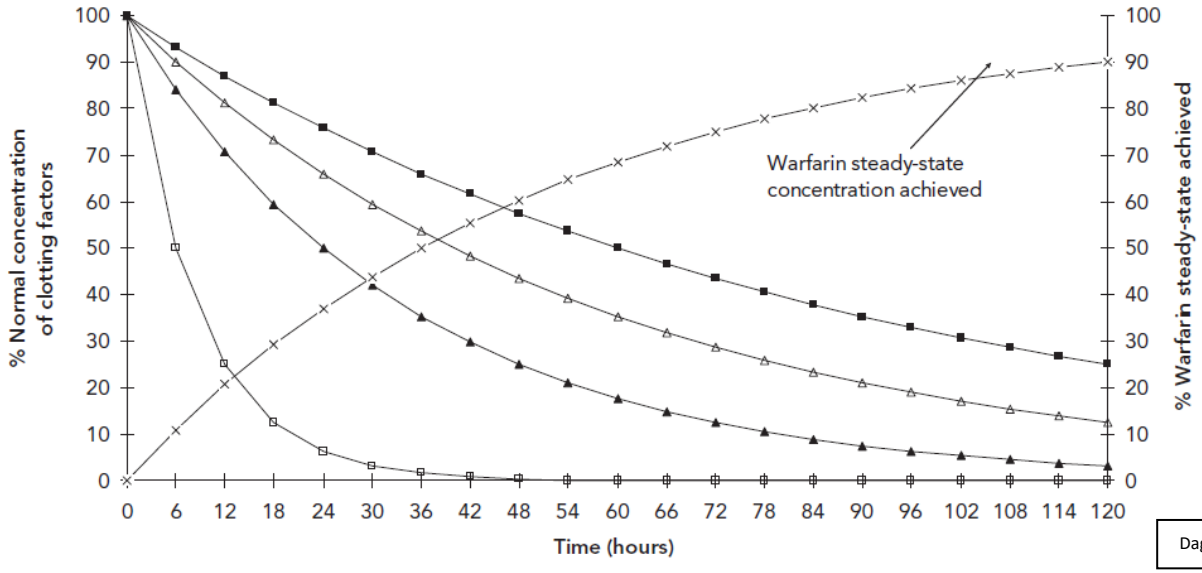
[27] There may be valid clinical reasons to follow up outside of these guideline recommendations. Patient factors may exist that require individual consideration and clinical judgement that may override follow up recommendations. Any deviation from above recommendation will be clearly documented in medical record.

Warfarin Maintenance Continued

- Patients should be seen at least weekly for 2 weeks prior to extending follow-up to two weeks and greater.
- Routine follow up of medically stable and reliable patients is every 4 to 8 weeks. Routine follow up of medically unstable or unreliable patients is every 1 to 2 weeks or sooner as clinical indicated.
- If the patient has had multiple stable INRs and a consistent weekly dose for the past 12-week period, it is reasonable to begin waiting up to 12 weeks for the next INR.
    - 12-week follow up should be reserved for the most stable patients with low bleeding risk.
    - Patients should be reminded of the importance of notifying the clinic of changes in medications, diet, alcohol use, or general health as well as any signs/symptoms of bleeding that would warrant an earlier follow up.
- There may be valid clinical reasons to adjust doses outside of these recommendations (e.g., acute EtOH ingestion, missed doses, patient availability for testing).
- Patient factors may exist that require individual consideration and clinical judgement that will over-ride algorithm recommendations (e.g., patient has INR goal outside those listed above).

Additional Maintenance Dose Considerations

- It may be appropriate to resume prior maintenance dose if a transient factor affected the INR result (e.g., acute EtOH ingestion, missed dose).
- It may be appropriate to continue current dosing if the last 2 INRs have been in range, and if there is no clear explanation for the INR to be out of range, and if the INR does not represent an increased risk of hemorrhage for the patient. Consider resumption of prior maintenance dose if factor causing elevated INR is transient (e.g., acute alcohol consumption).
- If the out-of-range INR is ≤ 0.5 below or above goal INR, and the previous INRs have been stable, it may be appropriate to continue the current dose and retest in 1-2 weeks.
- Other considerations: proximity to bleeding or thromboembolic event, bleeding and thromboembolic risks, stability of the warfarin dose, stability of comorbidities, drug-drug interactions, time of last dose change, status of factors influencing recent dose change.



■ = factor II ; □ = factor VII; ▲= factor IX; △ = factor X ; x = warfarin.

Dager, W.E, et al. (2018)

Managing Patients with High INR Values	
Clinical Situation	**Guidelines**
INRs between 4.5 and 10 ***with no*** evidence of bleeding	Guidelines suggest against the use of vitamin K (grade 2B). Lower the dose or omit the next dose; and resume therapy at a lower dose when the INR is within therapeutic range. If the INR is only slightly above therapeutic range, dose reduction may not be necessary (grade 1C).
INR between 4.5 and 10 ***with*** minor/moderate bleeding	Omit 1-2 doses, monitor INR more frequently and resume therapy at an adjusted dose INR is therapeutic. **Contact PCP/referring provider.**
INR > 5 but < 9: ***no*** signs/symptoms of bleeding	Omit the next 1-2 doses, monitor INR more frequently and resume therapy at an appropriately adjusted dose when the INR is within therapeutic range.
INR > 10 ***with no*** evidence of bleeding	Hold warfarin and suggest oral vitamin K (2.5 – 5 mg) be administered (vitamin K can be ordered as a facility administered medication through EHR). Community pharmacies do not have this readily available. Resume therapy at an appropriately adjusted dose when INR is within therapeutic range. **Contact PCP/referring provider and notify physician director.**
Serious bleeding at any elevation of INR	Hold warfarin and refer patient to ER or other emergency service. **Contact PCP/referring provider.**

Charts to Send to ACC Physician Director
Route Encounter in Epic
• Reversal or complicated peri-procedure plans
• Patients with significant bleeding/thromboembolic symptoms
• All INRs above 10.0 or usage of facility administered vitamin K

Common Warfarin Interactions[28]		
	Potentiation of Effect Increased INR / bleeding risk)	**Diminished Effect (Decreased INR)**
Medications	Acetaminophen (high dose) Antiplatelet medications Allopurinol Amiodarone Azole antifungals Broad-spectrum antibiotics Corticosteroids Fenofibrate Fish oil Fluoroquinolones Fluorouracil (systemic) Gemfibrozil Methotrexate Metronidazole PPIs NSAIDs SSRIs Statins (most) SMZ/TMP Tamoxifen	Azathioprine Barbiturates Carbamazepine Multivitamins Phenytoin Primidone Rifampin Ritonavir St. John's wort Vitamin K
Food	Mango Black licorice Grapefruit (minimal effect)	Green leafy vegetables
Disease State	Acute alcohol ingestion Acute infection/inflammation Cardiac surgery (recent) Diarrhea Fever Heart failure (fluid retention) Hyperthyroidism Liver disease Renal disease	Chronic alcohol ingestion Hypothyroidism Obesity Tobacco smoking Enteral nutrition

[28] List is not comprehensive. Always check via reliable drug information resource (Lexicomp, AC Forum).

ICHECK'D mnemonic for DOAC initiation

- **I = Indication:** Why is the patient receiving the DOAC (Afib, VTE treatment, VTE prophy, prevention of CV events) and is it a valid indication?
- **C = Concomitant medications:** Is the patient receiving any inducers or inhibitors of cytochrome P450 enzyme subtype 3A4 (CYP3A4) or p-glycoprotein (P-gp)?
- **H = History/hepatic function:** Does the patient have a mechanical heart valve, moderate to severe mitral stenosis, history of bariatric or GI surgery, pregnant/nursing, on dialysis, have hepatic impairment (Child-Pugh class B or higher)?
- **E = Education:** Review DOAC patient education booklet with patient/caregiver.
- **C = Compliance:** Missing or skipping doses may increase the risk of a blood clot due to short half-life of DOACs.
- **K = Kidney Function:** Serum creatinine value needed prior to DOAC initiation and while receiving the DOAC in follow up.
  - When creatinine clearance calculation is needed, Cockcroft-Gault formula using actual body weight should be utilized.
- **D = Dose correct for indication:** Monitor for any changes that may be needed based on above
  - NVAF: based on kidney function, age, weight.
  - Acute VTE: based on loading dose followed by maintenance dose.

DOAC Comparison						
	Indication	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**DDI**	**Contraindication/ Caution**
apixaban/ Eliquis	Atrial fibrillation	5 mg twice daily	2.5 mg twice daily If 2 of the following: body weight ≤ 60 kg, Scr ≥ 1.5mg/dL, age ≥ 80 yrs	Use not recommended in Child-Turcotte-Pugh Class C	• P-gp modifiers • CYP3A4 modifiers •Antiplatelet agents • NSAIDs *Always check via a reliable drug reference (Lexicomp, AC Forum)*	**Do not use in:** • Mechanical valve prosthesis in any position • Antiphospholipid antibody syndrome **Caution in:** • Dialysis • bioprosthetic valve replacement (within 1-3 mos)[29]
	VTE treatment	10 mg BID x7 days, then 5 mg BID	No dosage adjustment recommended			
	Secondary thromboprophylaxis	5 mg BID (can consider 2.5 mg BID after 6 mos of treatment if full dose AC not indicated)[30]				
	Periop (TKA, THA) thromboprophylaxis	2.5 mg BID (TKA x10-14 days, THA x30-35 days)				
dabigatran/ Pradaxa	Atrial Fibrillation	150 mg twice daily	•CrCl 15 to ≤ 30 mL/min: 75 mg twice daily •CrCl < 15 mL/min: Do not use if	No dosage adjustments provided	• P-gp modifiers • CYP3A4 modifiers (limited data) •Antiplatelet agents • NSAIDs *Always check via a reliable drug reference (Lexicomp, AC Forum)*	**Do not use in:** • Mechanical valve prosthesis in any position • Antiphospholipid antibody syndrome **Caution in:** • Patients ≥ 75 years of age due to increased bleed risk (consider other treatment) • bioprosthetic valve replacement (within 1-3 mos)[29]
	VTE treatment	150 mg twice daily **(after at least 5 days parenteral therapy)**	•CrCl > 30 mL/min: No adjustment •CrCl ≤ 30 mL/min: Do not use			
	Periop (THA) thromboprophylaxis	110 mg day 1, then 220 mg daily x10-35 days				

[29] Data supporting the use of DOAC over VKA in first 3 months post bioprosthetic mitral/aortic valve replacement has increased in recent years, however the studies were small which warrants further investigation in larger trials.

[30] Based on limited data, consider patient's thrombotic risk before reducing dose. (ref 3, 9)

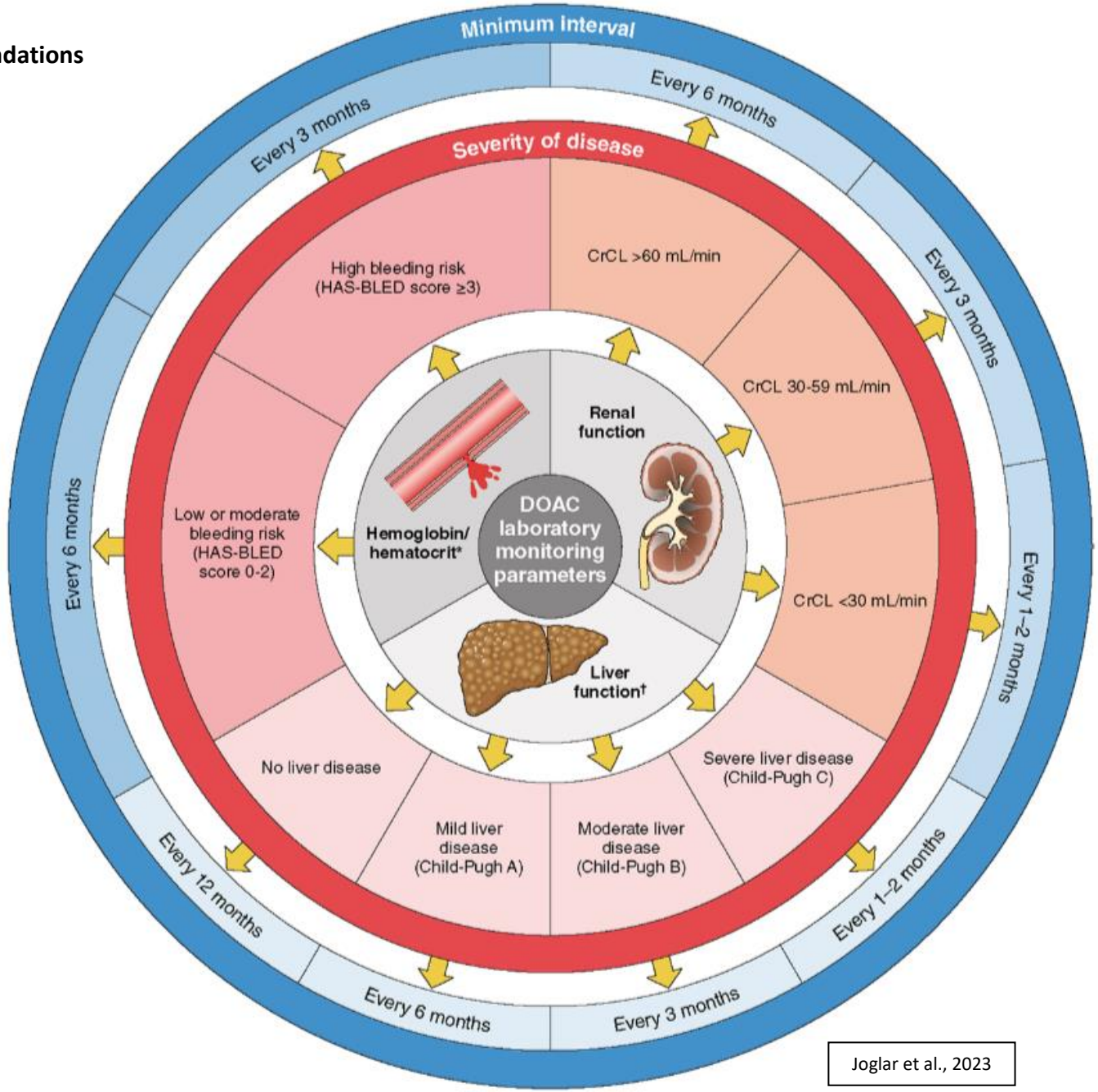
DOAC Comparison						
	Indication	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**DDI**	**Contraindication/ Caution**
edoxaban/ Savaysa	Atrial Fibrillation	60 mg once daily	•CrCl >95 mL/min: Do not use •CrCl 15-50 mL/min: 30 mg once daily •CrCl < 15 mL/min: Do not use	Use not recommended in Child-Turcotte-Pugh Class C	• P-gp modifiers • CYP3A4 modifiers •Antiplatelet agents • NSAIDs *Always check via a reliable drug reference (Lexicomp, AC Forum)*	**Do not use in:** • Mechanical valve prosthesis in any position • Antiphospholipid antibody syndrome • CrCl < 15 mL/min • CrCl > 95 mL/min **Caution in:** • bioprosthetic valve replacement (within 1-3 mos)[31]
	VTE treatment	Weight > 60kg: 60 mg once daily Weight ≤ 60 kg: 30 mg once daily **(after at least 5 days parenteral therapy)**				
rivaroxaban/ Xarelto	Atrial fibrillation	20 mg once daily	•CrCl 15-50 mL/min: 15 mg once daily •CrCl < 15 mL/min: Do not use	Use not recommended in Child-Turcotte-Pugh Class B or C	• P-gp modifiers • CYP3A4 modifiers •Antiplatelet agents • NSAIDs *Always check via a reliable drug reference (Lexicomp, AC Forum)*	**Do not use in:** • bioprosthetic valve replacement (within 1-3 mos) • Mechanical valve prosthesis in any position • Antiphospholipid antibody syndrome • CrCl < 15 mL/min **Caution in:** • older adults (≥ 75 years of age) due to increased bleed risk • bioprosthetic valve replacement (within 1-3 mos)[31]
	VTE treatment	15 mg BID with food x21 days, then 20 mg QD with food	•CrCl ≥ 30 mL/min: No adjustment •CrCl < 15 mL/min: Avoid use			
	Secondary thromboprophylaxis	20 mg QD with food (can consider 10 mg QD after 6 mos of treatment if full dose AC not indicated)[32]				
	Periop (TKA, THA) thromboprophylaxis	10 mg daily (TKA x10-14 days, THA x30-35 days)	No dosage adjustment recommended			
	PAD/CAD	2.5 mg BID with daily 81 mg Aspirin	•CrCl ≥ 15 mL/min: No adjustment •CrCl < 15 mL/min: Avoid use			
	Superficial vein thrombosis	10 mg daily x 45 days	•CrCl ≥ 30 mL/min: No adjustment •CrCl < 30 mL/min: Avoid use			

[31] Data supporting the use of DOAC over VKA in first 3 months post bioprosthetic mitral/aortic valve replacement has increased in recent years, however the studies were small which warrants further investigation in larger trials.

[32] Based on limited data, consider patient's thrombotic risk before reducing dose (ref 3, 9)

DOAC Follow-up Checklist		
Clinical situation	**Interval**	**Notes**
Full DOAC education and counseling	At initiation and highlights at subsequent visits	• DOAC booklet, new patient folder
First 6 months	At 1 week post initiation (VTE treatment, at provider discretion)	• Apixaban for VTE treatment: Dose reduction
	At 3 weeks post initiation (VTE treatment, at provider discretion)	• Rivaroxaban for VTE treatment: Dose reduction
	At 1 month post initiation (at provider discretion)	• Assess tolerance, ability to obtain med, cost, adherence to dosing schedule
	At 3-6 months post initiation	• Assess tolerance, ability to obtain med, cost, adherence to dosing schedule
Routine follow up (after first 6 months)	Every 1-3 months	• High risk patients (older, frail, recent CVA, high risk DDI, severe liver disease, ESRD)
	Every 6 months	• CrCl < 60 mL/min • Advanced age (> 75 years) • Weight < 60 kg
	Every 12 months	• CrCl > 60 mL/min, otherwise healthy patients with reduced thromboembolic/bleed risk
Assess compliance	At every visit	• Reiterate importance of adherence • Discuss barriers to adherence • Discuss methods to overcome barriers to adherence. (pill-boxes, alarms, patient assistance programs, etc.,)
Assess for thromboembolism	At every visit	• Signs/symptoms of stroke • Signs/symptoms of VTE
Assess for bleeding	At every visit	• Management of nuisance bleeds (epistaxis) • Is PPI needed
Medication reconciliation	At every visit	• Update med list • Run med list through Lexicomp.

DOAC Laboratory Monitoring Recommendations



Joglar et al., 2023

Prior to prescribing heparin or enoxaparin use the following checklist to evaluate for risk:

- Hypersensitivity to pork
- History of HIT
- History of thrombocytopenia
- Recent platelet count on file (within 3 weeks)
- Utilization of UFH or LMWH in the last 100 days
    - If yes, get baseline platelet count prior to initiation and 24 hours after
- Check platelet count every 2 to 3 days from day 4 through 14 when initiating UFH or LMWH
    - Then every 1 to 3 months as clinically indicated
- Utilize the 4T Score in patients with thrombocytopenia who are currently or were recently on heparin derived agents

4 T Score for Suspected HIT			
Category	**2 Points**	**1 Point**	**0 Point**
Thrombocytopenia	Plt count fall > 50% AND platelet nadir ≥ 20k AND no surgery within previous 3 days.	• Plt count fall > 50% AND surgery within previous 3 days. • Plt count fall > 30-50% OR platelet nadir 10-19k.	Plt count fall < 30% OR platelet nadir < 10k
Timing of platelet count fall	• Clear onset 5-10 days after heparin • Plt fall ≤ 1 day after heparin (prior heparin exposure within 5-30 days).	• Fall 5-10 days after heparin but unclear (e.g., missing Plt) • Fall ≤ 1 day after heparin (prior heparin exposure within 31-100 days) • Fall after 10 days	Fall ≤ 4 days without recent heparin exposure.
Thrombosis or sequelae	• Confirm new thrombosis • Skin necrosis at inj site • Anaphylactoid reaction to IV heparin bolus • Adrenal hemorrhage.	• Progressive or recurrent thrombosis while on therapeutic anticoagulants • Non-necrotizing skin lesions at heparin inj site • Suspected thrombosis	None
Other causes for thrombocytopenia	No alternative explanation for plt fall	Possible • Sepsis without proven source • Thrombocytopenia associated with initiation of ventilator • Other	Definite • Within 72 hours of surgery • Confirmed bacteremia/sepsis • Chemo/radiation within 20 days • DIC due to non-HIT cause • Drug induced thrombocytopenia

HIT Probability for 4 T Score	
Score	**Risk Category**
≤ 3 points	Low probability for HIT (≤ 5%)
4 – 5 points	Intermediate probability for HIT (approximately 14%)
6 – 8 points	High probability of HIT (approximately 64%)

Parenteral Anticoagulant Comparison						
Agent	**Indication**	**Dosing**	**Renal Adjustment**	**Hepatic Adjustment**	**DDI**	**Contraindication/ Caution**
dalteparin/ Fragmin	VTE treatment Periop bridging	200 units/kg SQ QD or 100 units/kg SQ BID	•CrCl > 30 mL/min: No dose adj •CrCl < 30 mL/min: Use not recommended	No dosage adjustments provided	• Antiplatelet agents • NSAIDs • other anticoagulants *Always check via a reliable drug reference (Lexicomp, AC Forum)*	**Do not use in:** • hx of HIT • hypersensitivity to pork • Dialysis
	VTE prophylaxis	TKA: TKA THA: THA Medically ill: Medically ill				
enoxaparin/ Lovenox	VTE treatment Periop bridging	1 mg/kg SQ BID or 1.5 mg/kg SQ QD *use lower end of dosing range for BMI ≥ 50 *anti-Xa monitoring in extreme BMI (~114) recommended	•CrCl < 30 mL/min: 1 mg/kg SQ QD Avoid use in dialysis if possible	No dosage adjustments provided (has not been studied – use with caution)		**Do not use in:** • hx of HIT • hypersensitivity to pork **Caution in:** • Older adults due to increased incidence of bleeding at therapeutic dose, especially if < 45 kg body weight. • Dialysis: avoid if possible
	VTE prophylaxis	TKA, THA, Abdominal surgery, Medically ill: 30 mg SQ BID or 40 mg SQ QD	•CrCl < 30 mL/min: 30 mg SQ QD Avoid use in dialysis if possible			
	Atrial fibrillation (off label)	1 mg/kg SQ BID or 1.5 mg/kg SQ QD	•CrCl < 30 mL/min: 1 mg/kg SQ QD Avoid use in dialysis if possible			
fondaparinux/ Arixtra	VTE treatment	<50 kg: 5 mg SQ QD 50-100 kg: 7.5 mg SQ QD >100 kg: 10 mg SQ QD	No adjustment for CrCl ≥ 30 mL/min, however, use caution in CrCl < 50 mL/min – consider alternative therapy	No dosage adjustments provided for Child-Turcotte-Pugh class A and B Not studied in Child-Turcotte-Pugh class C – use with caution)		**Do not use in:** • CrCl < 30 mL/min
	VTE prophylaxis	2.5 mg SQ QD Do not use in pt <50 kg				
	SVT treatment	2.5 mg SQ QD x45 days				
unfractionated heparin	VTE treatment	333 units/kg SQ followed by 250 units/kg SQ BID	Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)	Adjust to maintain anticoagulation target (aPTT or anti-Factor Xa)		**Do not use in:** • hx of HIT • hypersensitivity to pork **Caution in:** • >60 yo may have higher serum levels and longer aPTTs
	Periop bridging	IV infusion in patient				
	VTE prophylaxis	5000 units SQ Q8-12 hours				

All creatinine clearance calculations will be performed using he Cockcroft-Gault method via Global RPh (http://www.globalrph.com) using actual body weight.

Therapeutic Enoxaparin Dose Rounding (1 mg/kg)	
Patient Weight	**Enoxaparin Dose (prefilled syringe)**
50 – 69.9 kg	60 mg
70 – 89.9 kg	80 mg
90 – 109.9 kg	100 mg
110 – 134.9 kg	120 mg
135 – 164.9 kg	150 mg
165 – 190 kg	180 mg (150 mg + 30 mg syringes)
Therapeutic Enoxaparin Dose Rounding (1.5 mg/kg)	
Patient Weight	**Enoxaparin Dose (prefilled syringe)**
50 – 59.9 kg	80 mg
60 – 73.3 kg	100 mg
73.4 – 89.9 kg	120 mg
90 – 110 kg	150 mg

Laboratory Monitoring for Anticoagulation Therapy

Required Labs		
Medication	**Lab order**	**Frequency**
warfarin	CBC, CMP, APTT, PT/INR	Baseline
	Hgb, Hct	Every 12 months or as clinically indicated
DOACs	CBC, CMP	Baseline and every 12 months or as clinically indicated
	Scr	Every 3-12 months or as clinically indicated
enoxaparin / Lovenox and unfractionated heparin	CBC, SCr	Baseline and every 12 months or as clinically indicated
	Scr	Every 3 to 6 months or as clinically indicated
	Platelets	24 hours after initiation, then every 2-3 days through day 14, then every 3 to 6 months or as clinically indicated
fondaparinux / Arixtra	CBC, CMP	Baseline and every 12 months or as clinically indicated
	Scr	Every 6 months or as clinically indicated

Conversions of Oral Anticoagulants					
	To warfarin	**To dabigatran**	**To rivaroxaban**	**To apixaban**	**To edoxaban**
From warfarin		Stop warfarin and start dabigatran when INR < 2	Stop warfarin and start rivaroxaban when INR < 3	Stop warfarin and start Apixaban when INR < 2	Stop warfarin and start Edoxaban when INR ≤ 2.5
From dabigatran	CrCl >50 mL/min: start warfarin 3 days before stopping dabigatran CrCl 31-50 mL/min: start warfarin 2 days before stopping dabigatran CrCl 15-30 mL/min: start warfarin 1 day before stopping dabigatran		Stop dabigatran and start rivaroxaban at the next scheduled dosing time	Stop dabigatran and start apixaban at the next scheduled dosing time	Stop dabigatran and start Edoxaban at the next scheduled dosing time
From rivaroxaban	Stop rivaroxaban and start both parenteral AC and warfarin at the time the next dose would be due OR Start warfarin and then stop rivaroxaban 3 days later	Stop rivaroxaban and start dabigatran at the next scheduled dosing time		Stop rivaroxaban and start apixaban at the next scheduled dosing time	Stop rivaroxaban and start Edoxaban at the next scheduled dosing time
From apixaban	Stop apixaban and start both parenteral AC and warfarin at the time the next dose would be due OR Start warfarin and then stop apixaban 3 days later	Stop apixaban and start dabigatran at the next scheduled dosing time	Stop apixaban and start rivaroxaban at the next scheduled dosing time		Stop apixaban and start Edoxaban at the next scheduled dosing time
From edoxaban	Stop edoxaban and start both parenteral AC and warfarin at the time the next dose would be due OR For patients on 60mg reduce the dose to 30 mg and start warfarin. For patients on 30mg, reduce the dose to 15mg and start warfarin. Discontinue edoxaban once INR ≥ 2	Stop edoxaban and start dabigatran at the next scheduled dosing time	Stop edoxaban and start rivaroxaban at the next scheduled dosing time	Stop edoxaban and start apixaban at the next scheduled dosing time	

For patients transitioning from DOAC to VKA for VTE, the 2018 ASH guideline panel suggests overlapping DOAC and VKA therapy until the INR is within range over using LMWH or UFH “bridging therapy”. To minimize DOAC interference with the INR, the ASH guideline panel suggests measuring the INR just before the next DOAC dose if overlapping DOAC therapy is used. Note: Even at trough levels, the INR may still be elevated due to DOAC presence.

Anticoagulation Antidotes for Acute Reversal

Acute reversal of anticoagulation typically occurs in the inpatient setting. However, many patients have concerns about the reversibility of their anticoagulant. This information will facilitate patient education and engagement.

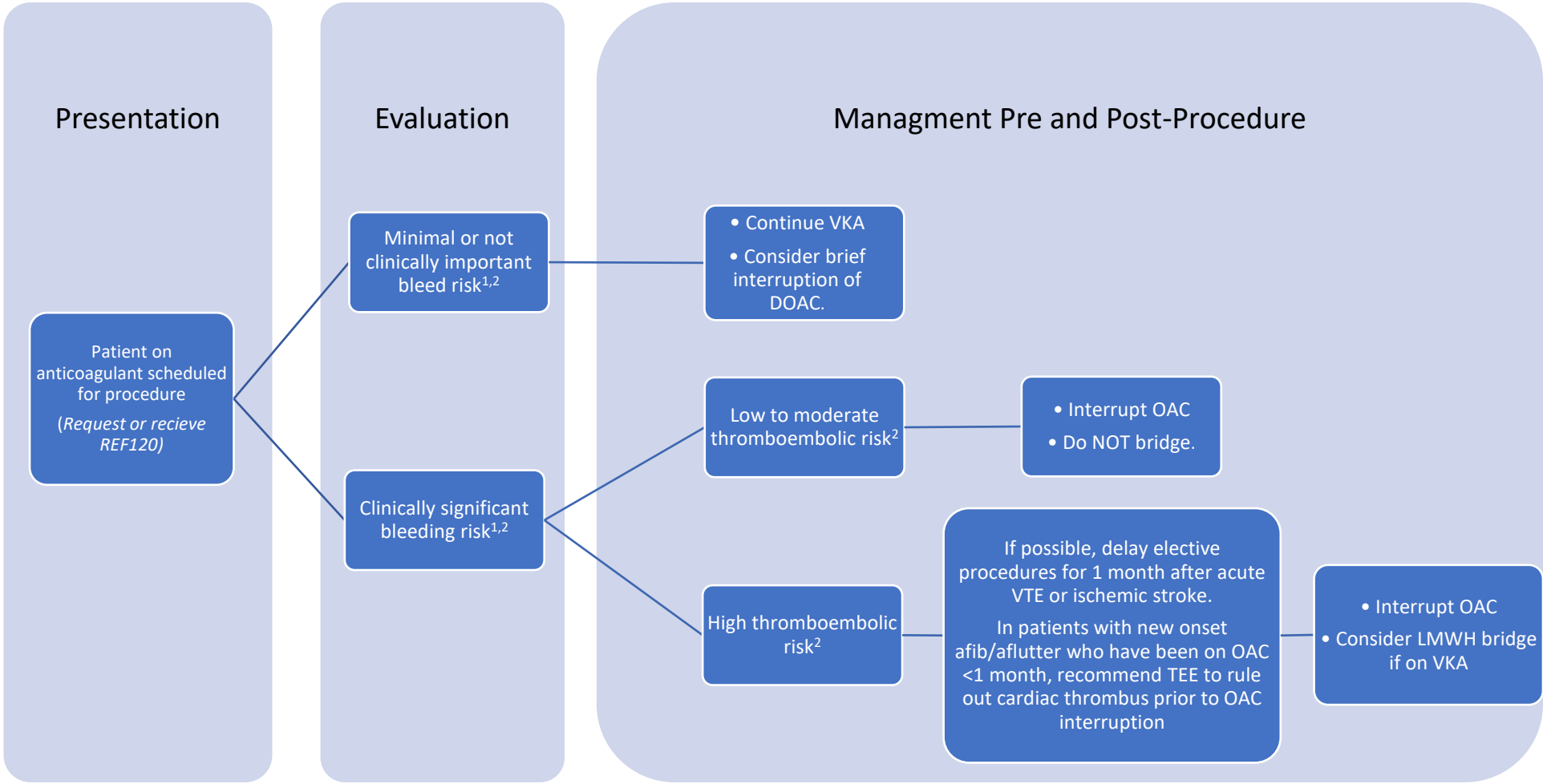
Reversal Agents				
Anticoagulant	**Reversal Agent**	**MOA**	**Onset**	**Notes**
apixaban/Eliquis edoxaban/Savaysa rivaroxaban/Xarelto dabigatran/Pradaxa	Kcentra (4-factor PCC)	Contains factors including II, VII, IX, X	< 30 min	Contains heparin (CI in pt with hx HIT).
	FEIBA (aPCC)	Contains factors including II, VIIa, IX, X	15-30 min	Can be used in pt with hx HIT. Higher thrombotic risk due to activated FVII.
	andexanet alfa/Andexxa	Binds and sequesters factor Xa inhibitors. Also binds and inhibits activity of tissue factor pathway inhibitor (TFPI), which can increase tissue factor-initiated thrombin generation.	Rapid	FDA approved for reversal of apixaban and rivaroxaban only. High expense limits availability.
dabigatran/Pradaxa	idarucizumab/ Praxbind	Binds to both thrombin-bound and free dabigatran with higher affinity than thrombin.	Minutes	Will only reverse dabigatran.
warfarin	phytonadione (vitamin K)	Cofactor for factor II, VII, IX, X	~24 hr (po) 12 hr (IV)	May continue to affect INR for several days after administration.
	Fresh frozen plasma (FFP)	Contains factors II, VII, IX, X, fibrinogen, proteins C and S	2-6 hr	Large volume.
	Kcentra (4-factor PCC)	Contains factors including II, VII, IX, X	<30 min	Contains heparin (CI in pt with hx HIT).
	FEIBA (aPCC)	Contains factors including II, VIIa, IX, X	15-30 min	Can be used in pt with hx HIT. Higher thrombotic risk due to activated FVII.
dalteparin/Fragmin enoxaparin/Lovenox unfractionated heparin	Protamine	Binds heparin molecule to form inactive salt	5-15 min	Fish sourced, caution in pt with fish allergy.
fondaparinux/Arixtra	Kcentra (4-factor PCC)	Contains factors including II, VII, IX, X	< 30 min	Contains heparin (CI in pt with hx HIT).
	FEIBA (aPCC)	Contains factors including II, VIIa, IX, X	15-30 min	Can be used in pt with hx HIT. Higher thrombotic risk due to activated FVII.
	Recombinant factor VIIa (rFVIIa)/ Novoseven	Selective replacement of rFVIIa which activates extrinsic clotting pathway promoting thrombin formation.	5-10 min	Conflicting evidence for use. Significant risk of thrombosis.

References

1. Abbattista, M., Capecchi, M., & Martinelli, I. (2020). Treatment of unusual thrombotic manifestations. *Blood*, *135*(5), 326–334. https://doi.org/10.1182/blood.2019000918
2. Ageno, W., Beyer-Westendorf, J., Garcia, D., Lazo-Langner, A., McBane, R. D., & Paciaroni, M. (2016). Guidance for the management of venous thrombosis in unusual sites. *Journal of Thrombosis and Thrombolysis*, *41*(1), 129–143. https://doi.org/10.1007/s11239-015-1308-1
3. Agnelli, G., Büller, H. R., Cohen, A. T., Curto, M., Gallus, A., Johnson, M., Porcari, A. R., Raskob, G. E., & Weitz, J. I. (2013). Apixaban for extended treatment of venous thromboembolism. *The New England Journal of Medicine*, *368*(8), 699–708. https://doi.org/10.1056/nejmoa1207541
4. Anand, S. S., Bosch, J., Eikelboom, J. W., Connolly, S. J., Diaz, R., Widimský, P., Aboyans, V., Alings, M., Kakkar, A. K., Keltai, K., Maggioni, A. P., Lewis, B. S., Störk, S., Zhu, J., Lopez-Jaramillo, P., O'Donnell, M., Commerford, P., Vinereanu, D., Pogosova, N., . . . Zimmermann, S. (2018). Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet*, *391*(10117), 219–229. https://doi.org/10.1016/s0140-6736(17)32409-1
5. Angiolillo, D. J., Bhatt, D. L., Cannon, C. P., Eikelboom, J. W., Gibson, C. M., Goodman, S. G., Granger, C. B., Holmes, D. R., Lópes, R. D., Mehran, R., Moliterno, D. J., Price, M. J., Saw, J., Tanguay, J. F., & Faxon, D. P. (2021). Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation*, *143*(6), 583–596. https://doi.org/10.1161/circulationaha.120.050438
6. Bonaca, M. P., Bauersachs, R., Anand, S. S., Debus, E. S., Nehler, M. R., Patel, M. R., Fanelli, F., Capell, W. H., Diao, L., Jaeger, N., Hess, C. N., Pap, Á., Kittelson, J. M., Gudz, I., Mátyás, L., Krievins, D., Diaz, R., Brodmann, M., Muehlhofer, E., . . . Hiatt, W. R. (2020a). Rivaroxaban in Peripheral Artery Disease after Revascularization. *The New England Journal of Medicine*, *382*(21), 1994–2004. https://doi.org/10.1056/nejmoa2000052
7. Carnicelli, A. P., Hong, H., Connolly, S. J., Eikelboom, J. W., Giugliano, R. P., Morrow, D. A., Patel, M. R., Wallentin, L., Alexander, J. H., Bahit, M. C., Benz, A. P., Bohula, E. A., Chao, T., Dyal, L., Ezekowitz, M. D., Fox, K. A., Gencer, B., Halperin, J. L., Hijazi, Z., . . . Granger, C. B. (2022). Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. *Circulation*, *145*(4), 242–255. https://doi.org/10.1161/circulationaha.121.056355
8. *Centers of Excellence | Resource Center*. (n.d.). ACE. https://acforum-excellence.org/Resource-Center/resource_files/-2021-10-04-112001.pdf
9. Crowther, M., & Cuker, A. (2017). Reduced-Intensity rivaroxaban for the prevention of recurrent venous thromboembolism. *The New England Journal of Medicine, 376*(13), 1279–1280. https://doi.org/10.1056/nejme1701628
10. Dager, W.E., Gulseth, M.P., & Nutescu, E.A. (2018). *Anticoagulation Therapy: A Clinical Practice Guid.*
11. Garcia, David. (2023, April 1-3). *An update in Antiphospholipid Syndrome* [presentation]. AC Forum 2023: National Conference, San Francisco, CA, United States.
12. Investigators, C. T. (2018). Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet*, *391*(10117), 205–218. https://doi.org/10.1016/s0140-6736(17)32458-3
13. January, C. T., Wann, L. S., Calkins, H., Chen, L. Y., Cigarroa, J. E., Cleveland, J. C., Ellinor, P. T., Ezekowitz, M. D., Field, M. E., Furie, K. L., Heidenreich, P. A., Murray, K. T., Shea, J. B., Tracy, C. M., & Yancy, C. W. (2019). 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*, *140*(2). https://doi.org/10.1161/cir.0000000000000665
14. Joglar, J. A., Chung, M. K., Armbruster, A. L., Benjamin, E. J., Chyou, J. Y., Cronin, E. M., Deswal, A., Eckhardt, L. L., Goldberger, Z. D., Gopinathannair, R., Görenek, B., Hess, P. L., Mark, D. B., Hogan, G., Ibeh, C., Indik, J. H., Kido, K., Kusumoto, F., Link, M. S., . . . Van Wagoner, D. R. (2023). 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. https://doi.org/10.1161/cir.0000000000001193

15. Kearon, C., & Kahn, S. R. (2020a). Long-term treatment of venous thromboembolism. *Blood*, *135*(5), 317–325. https://doi.org/10.1182/blood.2019002364
16. Khairani, C. D., Bejjani, A., Piazza, G., Jiménez, D., Monreal, M., Chatterjee, S., Pengo, V., Woller, S. C., Cortés-Hernández, J., Connors, J. M., Kanthi, Y., Krumholz, H. M., Middeldorp, S., Falanga, A., Cushman, M., Goldhaber, S. Z., Garcia, D., & Bikdeli, B. (2023). Direct Oral Anticoagulants vs Vitamin K Antagonists in Patients With Antiphospholipid Syndromes. *Journal of the American College of Cardiology*, *81*(1), 16–30. https://doi.org/10.1016/j.jacc.2022.10.008
17. Kumbhani, D. J., Cannon, C. P., Beavers, C. J., Bhatt, D. L., Cuker, A., Gluckman, T. J., Marine, J. E., Mehran, R., Messé, S. R., Patel, N. S. A., Peterson, B. E., Rosenfield, K., Spinler, S. A., & Thourani, V. H. (2021a). 2020 ACC Expert Consensus Decision Pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease. *Journal of the American College of Cardiology*, *77*(5), 629–658. https://doi.org/10.1016/j.jacc.2020.09.011
18. Kuno, T., Takagi, H., Ando, T., Sugiyama, T., Miyashita, S., Valentin, N., Shimada, Y. J., Kodaira, M., Numasawa, Y., Briasoulis, A., Burger, A., & Bangalore, S. (2020). Oral anticoagulation for patients with atrial fibrillation on Long-Term dialysis. *Journal of the American College of Cardiology*, *75*(3), 273–285. https://doi.org/10.1016/j.jacc.2019.10.059
19. Lawton, J. S., Lawton, J. S., Tamis-Holland, J. E., Bates, E. R., Bates, E. R., Bischoff, J. M., Bittl, J. A., Cohen, M. G., DiMaio, J. M., Don, C. W., Don, C. W., Gaudino, M., Goldberger, Z. D., Goldberger, Z. D., Jaswal, J. B., Jaswal, J. B., Kurlansky, P., Metkus, T. S., Metkus, T. S., . . . Zwischenberger, B. A. (2022). 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization. *Journal of the American College of Cardiology*, *79*(2), e21–e129. https://doi.org/10.1016/j.jacc.2021.09.006
20. Lip, G. Y., Banerjee, A., Boriani, G., Chiang, C. E., Fargo, R., Freedman, B., Lane, D. A., Ruff, C. T., Turakhia, M. P., Werring, D. J., Patel, S., & Moores, L. K. (2018). Antithrombotic therapy for atrial fibrillation. *Chest*, *154*(5), 1121–1201. https://doi.org/10.1016/j.chest.2018.07.040
21. Moll, S. (2023, April 1-3). *Thrombophilia Testing and Management* [presentation]. AC Forum 2023: National Conference, San Francisco, CA, United States.
22. Niu, J., Song, Y., Li, C., Ren, H., & Zhang, W. (2020). Once-daily vs. twice-daily dosing of enoxaparin for the management of venous thromboembolism: A systematic review and meta-analysis. *Experimental and Therapeutic Medicine*. https://doi.org/10.3892/etm.2020.9036
23. Ortel, T. L., Neumann, I., Ageno, W., Beyth, R. J., Clark, N. P., Cuker, A., Hutten, B. A., Jaff, M. R., Manja, V., Schulman, S., Thurston, C., Vedantham, S., Verhamme, P., Witt, D. M., Florez, I. D., Izcovich, A., Nieuwlaat, R., Ross, S., Schünemann, H. J., . . . Zhang, Y. (2020). American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Advances*, *4*(19), 4693–4738. https://doi.org/10.1182/bloodadvances.2020001830
24. Otto, C. M., Nishimura, R. A., Bonow, R. O., Carabello, B. A., Erwin, J. P., Gentile, F., Jneid, H., Krieger, E. V., Mack, M. J., McLeod, C., O'Gara, P. T., Rigolin, V. H., Sundt, T. M., Thompson, A., & Toly, C. (2021a). 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, *143*(5). https://doi.org/10.1161/cir.0000000000000923
25. Park, H., Yu, H. T., Kim, T. H., Park, J., Park, J., Kang, K., Shim, J., Kim, J. B., Kim, J., Choi, E. K., Park, H. W., Lee, Y. S., & Joung, B. (2023). Oral Anticoagulation Therapy in Atrial Fibrillation Patients with Advanced Chronic Kidney Disease: CODE-AF Registry. *Yonsei Medical Journal*, *64*(1), 18. https://doi.org/10.3349/ymj.2022.0455
26. Pengo, V., Denas, G., Zoppellaro, G., Jose, S. P., Hoxha, A., Ruffatti, A., Andreoli, L., Tincani, A., Cenci, C., Prisco, D., Fierro, T., Gresele, P., Cafolla, A., Micheli, V., Ghirarduzzi, A., Tosetto, A., Falanga, A., Martinelli, I., Testa, S., . . . Banzato, A. (2018). Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*, *132*(13), 1365–1371. https://doi.org/10.1182/blood-2018-04-848333
27. Pokorney, S. D., Chertow, G. M., Al-Khalidi, H. R., Gallup, D., Dignacco, P., Mussina, K., Bansal, N., Gadegbeku, C. A., García, D., Garonzik, S. M., Lópes, R. D., Mahaffey, K. W., Matsuda, K., Middleton, J., Rymer, J. A., Sands, G. H., Thadhani, R., Thomas, K. L., Washam, J. B., . . . Granger, C. B. (2022). Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation*, *146*(23), 1735–1745. https://doi.org/10.1161/circulationaha.121.054990

TABLE OF CONTENTS



[1]See Appendix I for procedural bleeding risk based on type of procedure.
[2]See Appendix A for patient specific bleeding/thromboembolic risk factors.

Definitions and abbreviations

For the purpose of this document the following definitions/clarifications and abbreviations may be useful.

Bridge	The concept of giving a short-acting blood thinner, usually LMWH, at treatment dose around a procedure when warfarin would be interrupted. It is used to maintain therapeutic anticoagulation in patients at very high risk of thromboembolism.		
Drug half-life	Apixaban	12 hours (8-15 hrs)	
	Dabigatran	12-17 hrs	
		Elderly	14-17 hrs
		Mild-mod renal impairment	15-18 hrs
		Severe renal impairment	28 hrs
	Edoxaban	10-14 hours	
	Rivaroxaban	5-9 hours	
		Elderly	11-13 hrs
	Warfarin	20-60 hrs, highly variable	
Pre or Post op thromboprophylaxis	The concept of using lower anticoagulant doses (prophylactic dose) immediately before or after a high thrombotic risk procedure (such as total knee arthroplasty or total hip arthroplasty)		
Reversal Reversal of anticoagulation is dependent on the type of anticoagulant and indication for reversal (i.e., high bleed risk vs low bleed risk procedure).	DOAC	Low bleed risk procedures	Typically requires 2-3 drug half-lives between last dose and procedure. This equates to < 12% - 25% residual anticoagulant effect.
		High bleed risk procedures	Typically requires 4-5 drug half-lives between last dose and procedure. This equates to < 3% - 6% residual anticoagulant effect.
	Warfarin	Reversal is defined as return to baseline INR level or INR ≤ 1.5.	

DOAC	Direct oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban)
DVT	Deep vein thrombosis
ICH	Intracranial hemorrhage
LMWH	Low molecular weight heparin (typically enoxaparin)
OAC	Oral anticoagulant
P2Y12 inhibitor	Class of antiplatelet medications (clopidogrel, prasugrel, ticagrelor)
PE	Pulmonary embolism
REF120	Referral for periprocedural anticoagulation sent to ACC from proceduralist
SE	Systemic embolism
TE	Thromboembolism
TIA	Transient ischemic attack
TEE	Transesophageal echocardiogram
VKA	Vitamin K antagonist (warfarin)
VTE	Venous thromboembolism

Appendix A: Patient Specific Bleeding/Thromboembolic Risk Factors

Bleeding risk factors	Low thromboembolic risk	Moderate thromboembolic risk	High thromboembolic risk
• Major bleed or ICH < 3 months ago • Platelet abnormality (including antiplatelet use) • High INR • Recent major bleeding or prior major bleed during previous or similar procedure • Prior major bleed during bridging therapy • Age ≥ 65 years • Liver cirrhosis or advanced liver disease • Advanced renal disease • Elevated HASBLED (≥ 3) • Anemia (Hgb < 12, Hct < 35%) • Cancer • Currently on vascular endothelial growth factor (VEGF) inhibitor therapy	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc ≤ 4 and no prior stroke/TIA/SE **Venous Thromboembolism:** • VTE > 12 months ago and no other risk factors **Mechanical Heart Valve:** • Bileaflet aortic prosthesis *without* major stroke risk factors[1]	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc 5-6 **Venous Thromboembolism:** • VTE 3-12 months ago • Non-severe thrombophilia • Recurrent VTE • Active cancer or recent history of cancer **Mechanical Heart Valve:** • Bileaflet aortic prosthesis *with* major stroke risk factors[1] • Bileaflet mitral prosthesis *without* major stroke risk factors[1]	**Atrial Fibrillation (afib):** • CHA_2DS_2-VASc ≥ 7 • Stroke/TIA/SE ≤ 3 mos ago • Rhematic valvular heart disease **Venous Thromboembolism:** • VTE < 3 months ago (especially 1 mo) • Severe thrombophilia[2] • Active cancer associated with high VTE risk[3] • Prior perioperative TE **Mechanical Heart Valve:** • Any caged-ball or tilting disc prosthesis • Any mitral prosthesis *with* major stroke risk factors[1] • Stroke or TIA < 3 months

• The type of surgery can affect thromboembolic risk, especially for patients undergoing cardiovascular surgery, such as CABG surgery or carotid endarterectomy, or major orthopedic surgery, in which the risk for stroke or other thromboembolism may be higher irrespective of other patient-related factors.

• Patients' thromboembolic risk may be less important in certain perioperative circumstances. This can occur in patients who are receiving DOAC therapy, irrespective of the clinical indication (atrial fibrillation or VTE). Since the perioperative time period where such patients are not anticoagulated is short (1-3 days), this minimizes the risk for thromboembolism, irrespective of their baseline risk, as reflected by the CHA_2DS_2VASc score or proximity of recent VTE and, similarly, obviates the rationale for administering heparin bridging.

• For patients with elevated bleeding risks consider utilizing management recommendations for high bleeding risk procedures

[1] Includes: AF, prior stroke/TIA during anticoagulation interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, age ≥75 years.
[2] Deficiency of protein C, S, or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation; multiple thrombophilia; antiphospholipid antibodies
[3] Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

Appendix B: Peri-Procedure Management of Direct Oral Anticoagulants (DOACs)

See appendix F for anticoagulation management for gastrointestinal endoscopy procedures.
See appendix G for anticoagulation management for cardiology procedures.

PAUSE	Procedure Bleed Risk[4]	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure (Day 0)	Day +1	Day +2	Day +3
Apixaban CrCl ≥ 25 mL/min Dabigatran CrCl ≥ 50 mL/min Edoxaban CrCl ≥ 30 mL/min Rivaroxaban CrCl ≥ 30 mL/min	Low	-	-	-	-	Hold 1 day prior to procedure		Resume 24 hours after procedure	-	-
	High	-	-	-	Hold 2 days prior to procedure				Resume 48-72 hours after procedure[5]	
	Neuraxial anesthesia in surgery	-	-	Hold 3 days prior to procedure				Resumption timing based on bleed risk of surgical procedure as above.		
Apixaban CrCl < 25 mL/min Edoxaban CrCl < 30 mL/min Rivaroxaban CrCl < 30 mL/min	Low	-	-	-	Hold 2 days prior to procedure			Resume 24 hours after procedure	-	-
	High	-	-	Hold 3 days prior to procedure					Resume 48-72 hours after procedure[5]	
Dabigatran CrCl <50 mL/min	Low	-	-	-	Hold 2 days prior to procedure			Resume 24 hours after procedure	-	-
	High	-	Hold 4 days prior to procedure						Resume 48-72 hours after procedure[5]	
	Neuraxial anesthesia in surgery	Hold 5 days prior to procedure						Resumption timing based on bleed risk of surgical procedure as above.		

- These recommendations for hold strategy are based on current guidelines and estimated half-life of each anticoagulant.
- Moderate risk of bleeding needs 2-3 drug half-lives between the last dose and surgery equating to 36-42 hour interruption interval.
- High risk of bleeding needs 4-5 drug half-lives between the last dose and surgery equating to 60-68 hour interruption interval.
- Procedures with negligible or not clinically important bleed risk can be safely done under full-dose anticoagulation (may consider holding DOAC dose day of procedure to avoid peak anticoagulant effects).
- The rapid offset and rapid onset of action of DOACs obviate the need for heparin bridging with short acting anticoagulants such as UFH or LMWH in a perioperative setting.

[4] See appendix I for procedure bleed risk.
[5] For patients with high risk of thromboembolism (see appendix A), consider resuming anticoagulation earlier if hemostasis can be achieved and approved by proceduralist.

Appendix C: Peri-Procedure Management of Outpatient Parenteral Anticoagulants

See appendix F for anticoagulation management for gastrointestinal endoscopy procedures.

See appendix G for anticoagulation management for cardiology procedures.

	Procedure Bleed Risk[6]	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure (Day 0)	Day +1	Day +2	Day +3
Enoxaparin prophylaxis dose	Low	-	-	-	-	-	Hold 1 day prior to procedure		Resume 24 hours after procedure	-	-
	High	-	-	-	-	-	Hold 1 day prior to procedure		Resume 24 hours after procedure	-	-
Enoxaparin treatment dosing CrCl ≥ 30 mL/min (1 mg/kg every 12 hours)	Low	-	-	-	-	-	50% of daily dose in AM (at least 24 hours pre procedure)		Resume 24 hours after procedure	-	-
	High	-	-	-	-	-				Resume 48-72 hours after procedure[7]	
Enoxaparin treatment dosing CrCl < 30 mL/min (1 mg/kg every 24 hours)	Low	-	-	-	-	-	Hold 1 day prior to procedure		Resume 24 hours after procedure	-	-
	High	-	-	-	-	Hold at least 1 day prior to procedure				Resume 48-72 hours after procedure[7]	
Fondaparinux treatment dosing CrCl ≥ 50 mL/min	Low	-	-	-	-	Hold 2 days prior to procedure			Resume 24 hours after procedure	-	-
	High	-	-	Hold 4 days prior to procedure						Resume 48-72 hours after procedure[7]	
Fondaparinux treatment dosing CrCl < 50 mL/min	Low	-	Hold 5 days prior to procedure						Resume 24 hours after procedure	-	
	High	Hold 6 days prior to procedure								Resume 48-72 hours after procedure[7]	
Unfractionated heparin (SQ)	Low	-	-	-	-	-	Hold 4-6 hours prior to procedure		Resume 12-24 hours after procedure	-	
	High	-	-	-	-	-	Hold 1 day prior to procedure			Resume 48-72 hours after procedure[7]	

[6] See appendix I for procedure bleed risk.

[7] For patients with high risk of thromboembolism (see appendix A), consider resuming anticoagulation earlier if hemostasis can be achieved and approved by proceduralist.

Appendix D: Peri-Procedure Management of Warfarin

See appendix F for anticoagulation management for gastrointestinal endoscopy procedures.
See appendix G for anticoagulation management for cardiology procedures.

Stopping warfarin

Procedure bleed risk[9]	5 – 7 day pre-Procedure INR	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1 (INR 24 hours prior)	Day of Procedure
Reversal needed	Supratherapeutic	Hold ≥ 5 days prior to procedure[11]						Resume night of procedure in most cases
	Therapeutic	-	Hold 5 days prior to procedure[11]					
	Subtherapeutic	-	-	Hold 3-4 days prior to procedure				

Bridging[10]

Pt bleeding risk factors[8]	Procedure bleed risk[9]	Low pt thromboembolic risk[8]	Moderate pt thromboembolic risk[8]	High pt thromboembolic risk[8]
None	negligible	Do Not Interrupt		
	low	Likely interrupt/don't bridge		Interrupt/ likely bridge
	High/uncertain			
Yes	All categories			Interrupt/consider bridge

	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure	Post-procedure	
								Restart	Stop bridge
LMWH twice daily[10]	Last dose of warfarin[11]			Start LMWH when INR falls below therapeutic range or on Day -3	LMWH every 12 hours	50% of daily dose in AM (at least 24 hours pre procedure)	No LMWH	warfarin: within 24 hours LMWH: resume as per appendix C	When INR in range (INR every 3-5 days)
LMWH once daily	Last dose of warfarin[11]			Start LMWH when INR falls below therapeutic range or on Day -3	LMWH every AM		No LMWH		

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[8] See Appendix A for patient specific bleeding/thromboembolic risk factors.
[9] See appendix I for procedure bleed risk.
[10] If history of heparin induced thrombocytopenia (HIT), consider admission for intravenous direct thrombin inhibitor to bridge.
[11] Holding warfarin for more than 5 days may also be indicated in select patient populations (e.g., elderly, liver dysfunction, low warfarin dose requirements, target INR of 3-4)

Appendix E: Peri-Procedure Management of Antiplatelet Medications

	Procedure bleed risk[12]	Day - 7	Day - 6	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure	Day +1
Plavix/clopidogrel	Low	Do not interrupt								
	High	-	-	Hold 5 days prior to procedure						Resume at regular dosing time
Effient/prasugrel	Low	Do not interrupt								
	High	Hold 7 days prior to procedure								Resume at regular dosing time
Pletal/cilostazol, Brillinta/ticagrelor	Low	Do not interrupt								
	High		-	-	-	Hold 3 days prior to procedure				Resume at regular dosing time
aspirin	Low	Do not interrupt								
	High	Do not interrupt								
	High (if interruption needed)	Hold 7 days prior to procedure								Resume at regular dosing time

[12] See appendix I for procedure bleed risk.

Appendix F: Peri-procedure Anticoagulation Management for Outpatient Gastrointestinal Endoscopy Procedures

High Bleed Risk Procedures	Low Bleed Risk Procedures
• Ampullary resection • Biliary or pancreatic sphincterotomy • Colonoscopy (cold snare polypectomy > 10 mm, hot snare polypectomy, EMR) • Cystgastrostomy • Electrohydraulic lithotripsy (EHL) • Endoscopic hemostasis • Endoscopic mucosal or submucosal resection (EMR) (ESD) • Endoscopic retrograde cholangiopancreatography (ERCP) with stent (biliary or pancreatic) removal OR placement with sphincterotomy • Endoscopic ultrasound (EUS) with FNA • Extracorporeal shock wave lithotripsy (ESWL) • Papillary balloon dilation with/without sphincterotomy • Percutaneous endoscopic gastrostomy (PEG) placement • Percutaneous endoscopic jejunostomy (PEJ) • Peroral endoscopic myotomy (POEM) • Pneumatic or bougie dilation • Radiofrequency ablation (RFA) • Therapeutic balloon-assisted enteroscopy • Treatment of varices (including variceal band ligation) • Tumor ablation	• Argon plasma coagulation • Barrett's ablation • Botox injections • Capsule endoscopy (pill cam, video capsule endoscopy) • Colonoscopy (biopsy, cold snare polypectomy < 10 mm, screening, surveillance and unknown) • Diagnostic esophagogastroduodenoscopy (EGD)/flexible sigmoidoscopy including mucosal biopsy • Endoscopic retrograde cholangiopancreatography (ERCP) with stent (biliary or pancreatic) placement (for removal or placement with sphincterotomy see high bleed risk) • Endoscopic ultrasound (EUS) without FNA • Enteral stent deployment • Push enteroscopy and diagnostic balloon-assisted enteroscopy

	Procedure Bleed Risk	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure	Day +1	Day +2	Day +3
Apixaban Edoxaban Rivaroxaban Dabigatran CrCl >50 mL/min	Low	-	-	-	-	Hold 1 day prior to procedure		Resume 24 hours after procedure	-	-
	High	-	-	-	Hold 2 days prior to procedure				Resume 48-72 hours after procedure[13]	
Dabigatran CrCl <50 mL/min	Low	-	-	-	Hold 2 days prior to procedure			Resume 24 hours after procedure	-	-
	High	-	Hold 4 days prior to procedure						Resume 48-72 hours after procedure[13]	
warfarin[14]	Low (target low therapeutic INR)[15]	-	-	-	-	-	Resume within 24 hours	-	-	-
	High (reverse INR)[16]	Hold 5 days prior to procedure						-	-	-
LMWH (enoxaparin)	Low	-	-	-	-	50% of daily dose in AM (at least 24 hours pre procedure)	Resume within 24 hours	-	-	-
	High	-	-	-	-				Resume 48-72 hours after procedure[17]	

[13] For patients with high risk of thromboembolism (see appendix A), consider resuming anticoagulation earlier if hemostasis can be achieved and approved by proceduralist.
[14] See appendix D for LMWH bridging considerations for warfarin reversal in patients with high thromboembolic risk.
[15] Consider holding 1-2 days for procedures involving bowel prep (colonoscopy) to mitigate INR elevation typically seen with bowel prep.
[16] Holding warfarin for more than 5 days may also be indicated in select patient populations (e.g., elderly, liver dysfunction, low warfarin dose requirements, target INR of 3-4)
[17] For patients with high risk of thromboembolism (see appendix A), consider resuming anticoagulation earlier if hemostasis can be achieved and approved by proceduralist.

Appendix G: Peri-procedure Anticoagulation Management for Cardiovascular Procedures

High bleed risk procedures	Diagnostic/Interventional procedures	Electrophysiology procedures
• Intrathoracic surgery • CABG • Surgical valve replacement/repair • TAVR • Other non-coronary cardiac surgery	• Right heart catheterization • Left heart catheterization • Percutaneous coronary intervention (PCI)	• Cardiac ablation (most) • Cardioversion • Internal cardiac defibrillator implantation battery change • Permanent pacemaker implantation battery change • Implantable loop recorder

	Procedure	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure	Day +1	Day +2	Day +3
Apixaban Edoxaban Rivaroxaban Dabigatran	Cardioversion	Do not interrupt								
	Ablation	-	-	-	-	-	Hold AM of procedure	-	-	-
	Device placement	-	-	-	-	-	Hold AM of procedure[18]	-	-	-
Apixaban Edoxaban Rivaroxaban Dabigatran CrCl ≥ 50 mL/min	Diagnostic/ interventional procedures	-	-	-	Hold 2 days prior to procedure			Resume 24 hours after procedure	-	-
	High bleed risk procedures	-	-	-	Hold 2 days prior to procedure				Resume 48-72 hours after procedure[19]	
Dabigatran CrCl ≤ 50 mL/min	Diagnostic/ interventional procedures	-	Hold 4 days prior to procedure					Resume 24 hours after procedure	-	-
	High bleed risk procedures	-	Hold 4 days prior to procedure						Resume 48-72 hours after procedure[19]	

[18] Hold PM prior and AM of procedure for patients taking once daily rivaroxaban/edoxaban with PM administration.

[19] For patients with high risk of thromboembolism (see appendix A), consider resuming anticoagulation earlier if hemostasis can be achieved and approved by proceduralist.

Cardiology procedures continued	Procedure	Day -5	Day -4	Day -3	Day -2	Day -1	Day of Procedure	Day +1	Day +2	Day +3
Warfarin[20]	Cardioversion	Do not interrupt. Maintain therapeutic INR x3 weeks prior and x4 weeks post with weekly INR checks.								
	Ablation	Do not interrupt. Maintain therapeutic INR x3 weeks prior and x4 weeks post with weekly INR checks.								
	Device Placement	Do not interrupt. Maintain therapeutic INR								
	Diagnostic/ interventional procedures	Hold 4-5 days to target INR < 1.5					Resume PM of procedure	-	-	-
	High bleed risk procedures	Hold 4-5 days to target INR < 1.5					Resume PM of procedure	-	-	-

- Antiplatelet recommendations post PCI (in addition to anticoagulation as above for diagnostic/interventional procedures):
  - Aspirin for 1 week post PCI (will be stopped after 1 week only) AND
  - $P2Y_{12}$ antagonist (clopidogrel/Plavix preferred) for 6 months post PCI if stable ischemic heart disease or 12 months post PCI if unstable angina or acute coronary syndrome.

Surgical valve replacement

Valve	Position	Pre-Procedure	Day of Procedure	First 3-6 months post-op[21]	Chronic management	Anti-platelet
Bioprosthetic valve replacement	Aortic position	Reverse any previous anticoagulation as above for high bleed risk procedures	For all surgical valve replacement procedures, start warfarin[21]	VKA with target INR 2.5 (2.0-3.0) for 3-6 months post-op	If continued anticoagulation indicated, may use DOAC or VKA. If no anticoagulation indication, discontinue VKA.	Start/resume aspirin 81 mg daily
	Mitral position					
Mechanical valve replacement	Aortic position (On-X)	Reverse any previous anticoagulation as above for high bleed risk procedures	For all surgical valve replacement procedures, start warfarin	VKA with target INR 2.5 (2.0-3.0) for 3 months post-op	VKA with reduced target INR of 1.5-2.0 thereafter	Start/resume aspirin 81 mg daily
	Aortic position			Target INR 2.5 (2.0-3.0)		Consider addition of aspirin 81 mg daily if bleed risk considered low
	Mitral position (any)			Target INR 3.0 (2.5-3.5), consider LMWH bridge until therapeutic		Consider addition of aspirin 81 mg daily if bleed risk considered low

[20] See appendix D for LMWH bridging considerations for warfarin reversal in patients with high thromboembolic risk.

[21] For patients on a DOAC pre-op, it is reasonable to resume home DOAC within 48-72 hours post-op (limited body of evidence available, very low certainty of evidence, care-team and patient shared decision making required)

Appendix H: Miscellaneous

	Procedure Type[22]	Warfarin	DOAC
Dental procedure nuances - Dental letter is sent instead of REF120	Mod/high bleed risk	• create PPP and interrupt as per appropriate appendix D	• create PPP and interrupt as per appropriate appendix above
	Low bleed risk - flow sheet is sufficient	• no PPP, document management in routine notes targeting therapeutic INR	• Document communication with pt reiterating no interruption (either in telephone encounter or routine visit)
Dermatological procedure nuances	Mohs procedure - flow sheet is sufficient	• no PPP, document management in routine notes targeting therapeutic INR 3-5 days prior to procedure	• Document communication with pt reiterating no interruption (either in telephone encounter or routine visit)
	All other derm procedures - no REF120	• Routine management, no intervention needed	• Routine management, no intervention needed
Ophthalmological procedure nuances	Mod/high bleed risk	• create PPP and interrupt as per appropriate appendix above	• create PPP and interrupt as per appropriate appendix above
	Low bleed risk (cataract, etc) - no REF120	• Routine management, no intervention needed	• Routine management, no intervention needed

[22] See appendix I for procedure bleed risk.

Appendix I: Procedure Bleeding Risk

- For patients with other bleeding risks (see appendix A for patient bleeding risk.) consider utilizing management recommendations for high bleeding risk procedures.
- Low bleed risk procedures can be safely done under full-dose anticoagulation (may consider holding DOAC dose day of procedure to avoid peak anticoagulant effects)

High Bleeding Risk	Low Bleeding Risk	Negligible Bleeding Risk
Breast Radiology and Surgical Procedures		
• Axillary dissection • Lumpectomy w/ or w/o oncoplastic reconstruction • Mastectomy w/or w/o sentinel lymph node biopsy • MRI-guided breast biopsies • Reduction mammoplasty • Stereotactic or 3D-tomosynthesis-guided breast biopsies • All surgical breast procedures	• Duct excision • Excisional breast biopsy • Sentinel lymph node biopsy, alone	• FNA (fine needle aspiration), breast • FNA, axillary node • All magnetic seed placement • All needle localizations • Punch biopsy, skin • Ultrasound guided core needle breast biopsy • Ultrasound guided cyst aspirations
Cardiology Procedures: See appendix G		
-	-	-
Dental Procedures		
• Bone excision • Root removal	• Bone grafting • > 3 dental extractions • Dental implant surgery	(see appendix I) • 1-3 dental extractions • Incision and drainage, intra-oral swellings • Local anesthesia
Dermatologic Procedures (see appendix I)		
N/A	N/A	• Mohs procedures • All other dermatologic procedures
Gastroenterology Procedure: See appendix F		
-	-	-

High Bleeding Risk	Low Bleeding Risk	Negligible Bleeding Risk
Gynecology Procedures		
• Hysterectomy • All other surgical gynecology procedures	• Cervical loop electrosurgical excision procedure (LEEP) • Cervical large loop excision of the transformation zone (LLETZ) • Cold knife conization (CKC)	• Colposcopy • Diagnostic laparoscopy • Dilation and curettage (D&C) • Endometrial biopsy • Exam under anesthesia • Hysteroscopy • Insertion/removal of intrauterine device • Laser ablation of cervix/vulva/vagina • Vulval/vaginal/cervical biopsies
Interventional Radiology Procedures		
• Ablations: complex, solid organ • Biliary interventions: percutaneous transhepatic biliary drainage, cholecystostomy • Deep abscess drainage • Deep biopsy: thoracic (lung), intraperitoneal (liver), retroperitoneal (kidney), pelvic (lymph node), deep/nonpalpable bone) • Diagnostic arteriography, arterial intervention (regardless of catheter size) * • Epidural injection • Gastrostomy, jejunostomy placement • IVC filter placement or retrieval (complex) • Kyphoplasty • Lumbar puncture (including myelography) • Myelogram • Portal vein embolization and stenting • Radiofrequency/microwave ablation: complex, solid organ • Spine procedures: vertebroplasty, kyphoplasty • Transcatheter Arterial Chemoembolization (TACE) • Thyroid CORE biopsy • Transjugular Intrahepatic Porto-systemic Shunt (TIPS) • Urinary intervention: nephrostomy, ureteral dilation, stone removal • Uterine fibroid embolization • Venous embolization and stenting* • Venous thrombolysis (DVT, pulmonary artery, portal vein)		• Central venous line placement/removal • Central venous port placement/removal • Diagnostic venography • Dialysis access interventions • Drainage catheter exchange (gastrostomy, jejunostomy, biliary, nephrostomy, abscess including gastrostomy/gastrojejunostomy conversions) • IVC filter placement or retrieval (1st attempt/simple) • Joint and musculoskeletal injection and/or aspirations (including arthrogram) • Non-tunneled central venous catheter placement or removal • Non-tunneled chest tube placement for pleural effusion • Paracentesis • Peripheral nerve blocks • Sacroiliac join injection and sacral lateral branch blocks • Superficial abscess drainage • Superficial biopsy (lymph node, soft tissue, thyroid FNA, superficial/palpable bone/marrow [e.g., extremities and bone marrow aspiration]) • Thoracentesis • Thoracic and lumbar facet medial branch nerve block (MBNB) and radiofrequency ablation (RFA) • Trigger point injections including piriformis injection

• Vertebroplasty *For arterial revascularization/arterial stents and venous stents: **do not** withhold antiplatelets		•Tunneled venous catheter placement/removal • Tunneled pleural and peritoneal drainage catheter placement/removal • Transjugular liver biopsy • Venous thrombectomy

Interventional Spine and Pain Procedures Including Regional Anesthesia		
• Dorsal root ganglion stimulation • Epidural blood patch • Epidural injections • Epiduroscopy and epidural decompression • Intrathecal catheter and pump implant • Percutaneous decompression laminotomy • Spinal cord stimulation trial and implant • Vertebral augmentation • Cervical facet MBNB and RFA • Cervical intra-articular injections • Interlaminar and transforaminal epidural steroid injections (ESI) • Intradiscal procedures • Sympathetic blocks (stellate, T, splanchnic, celiac, lumbar, hypogastric) • Trigeminal and sphenopalatine ganglia blocks		• Joint and musculoskeletal injection and/or aspirations • Peripheral nerve blocks • Pocket revision and implantable pulse generator/ intrathecal pump replacement • Sacroiliac joint injection and sacral lateral branch blocks • Thoracic and lumbar facet medial branch nerve block (MBNB) and radiofrequency ablation (RFA) • Trigger point injections including piriformis injection
Neurosurgery Procedures - **consult neurosurgery for restart recommendations**		
• Craniectomy • Craniotomy • Deep brain stimulation • Discectomy • intracranial embolization • Laminectomy • Spinal fusion • Spinal cord stimulation		
Ophthalmic Procedures		
• Eye plaque brachytherapy • Major eyelid surgery/lacrimal surgery • Orbital surgery/eye removal/orbital removal • Posterior eye surgery • Scleral buckle	• Conjunctival surgery • Descemet's stripping endothelia keratoplasty (DSEK) • Minor eyelid or periocular surgery • Penetrating keratoplasty	(see appendix I) • Cataract surgery • Intravitreal injection of pharmacologic agent • Vitreoretinal surgery

High Bleeding Risk	Low Bleeding Risk	Negligible Bleeding Risk
Orthopedic Procedures		
• Arthroplasty • All other surgical orthopedic procedures	• Arthroscopy • Major lower extremity fracture ORIF • Moderate hand and upper extremity surgery/cubital tunnel release/ORIF • Shoulder, foot, ankle tendon repair	• Joint or soft tissue injections • Minor hand surgery/carpal tunnel release, trigger finger release
Plastic Surgery Procedures		
• All plastic surgery procedures • Consult plastic surgery for all other non-OR procedures		
Pulmonary Procedures		
• Endobronchial/transbronchial biopsy • Endobronchial ultrasound FNA • Pleural biopsy • Tumor resection	• Bronchial or tracheal stent placement • Chemical pleurodesis • Non-tunneled chest tube placement (pleural space) • Thoracentesis • Tracheostomy • Tunneled pleural catheter placement or removal	• Diagnostic bronchoscopy airway exam without biopsy • Diagnostic bronchoscopy with bronchoalveolar lavage without biopsy

High Bleeding Risk	Low Bleeding Risk	Negligible Bleeding Risk
Thoracic Surgery Procedures		
• Coronary artery bypass graft (CABG) surgery • Pulmonary lobectomy • Pulmonary segmentectomy • Pulmonary wedge resection • Thymectomy • Treatment of aortic aneurysm, dissection • Valve replacement (w/or w/o CABG)	• Pericardial window	
Urology Procedures		
• All OR urology procedures • Prostate biopsy • Solid organ fiducial placement • TURP • TURBT	• Shock wave lithotripsy	• Cystoscopy • Laser lithotripsy • Ureteral stent placement/exchange • Ureteroscopy
Vascular Access/Surgery Procedures		
• Carotid endarterectomy • Complex central line placement • Complex dialysis/apheresis catheter placement • Consult with vascular surgery for peri-operative anticoagulant management	• Arteriovenous (AV) graft angioplasty/stent • AV fistula thrombectomy/stent • AV graft thrombectomy/stent	• Dialysis access interventions • Femoral vein vascular access device placement • Non-tunneled centra venous catheter exchange or removal • Peripherally inserted central catheter (PICC) placement • Venous port removal

References and Related Documents

Ahrar, K., Iliescu, C., Kroll, M., Toale, K., & Zalpour, A. (2022, June 21). *Peri-Procedure Management of Anticoagulants*. MD Anderson Cancer Center. Retrieved February 23, 2023, from https://Visio-clin-management-peri-procedure-anticoagulants-web-algorithm.vsd (mdanderson.org)

Anticoagulation Clinic: Confluence Health Guideline: Outpatient Gastrointestinal Endoscopy Periprocedural Management of Coagulation Status and Hemostasis Risk (2021, December 13)

Anticoagulation Clinic: Confluence Health Guideline: Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-Guided BREAST Interventions (2022, April 28)

Anticoagulation Clinic: Confluence Health Guideline: Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-Guided Interventions

Anticoagulation Clinic: Confluence Health Guideline: Management of Coagulation Status and Hemostasis Risk in Cardiovascular Interventions

Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. *Chest*. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025

Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. *JAMA Intern Med*. 2019;179(11):1469-1478. doi:10.1001/jamainternmed.2019.2431

Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med*. 2015;373(9):823-833. doi:10.1056/NEJMoa1501035

Eliquis. Package insert. Bristol Myers Squibb/Pfizer; 2021. pi_eliquis.pdf (bms.com)

Kovacs MJ, Wells PS, Anderson DR, et al. Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. *BMJ*. 2021;373:n1205. Published 2021 Jun 9. doi:10.1136/bmj.n1205

Pradaxa. Package insert. Boehringer Ingelheim; 2021. pradaxa capsules-us-pi.pdf (boehringer-ingelheim.com)

Savaysa. Package insert. Daiichi-Sankyo; 2021. getPIContent (daiichisankyo.us)

Xarelto. Package insert. Janssen Pharmaceuticals; 2023. XARELTO-pi.pdf (janssenlabels.com)

28. Rodger, M., Gal, G. L., Anderson, D. R., Schmidt, J., Pernod, G., Kahn, S. R., Righini, M., Mismetti, P., Kearon, C., Meyer, G., Elias, A., Ramsay, T., Ortel, T. L., Huisman, M. V., & Kovacs, M. J. (2017). Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. *BMJ*, j1065. https://doi.org/10.1136/bmj.j1065
29. Siontis, K. C., Zhang, X., Eckard, A., Bhave, N. M., Schaubel, D. E., He, K., Tilea, A., Stack, A. G., Balkrishnan, R., Yao, X., Noseworthy, P. A., Shah, N. D., Saran, R., & Nallamothu, B. K. (2018). Outcomes associated with Apixaban use in patients with End-Stage kidney disease and atrial fibrillation in the United States. *Circulation*, *138*(15), 1519–1529. https://doi.org/10.1161/circulationaha.118.035418
30. Steffel, J., Eikelboom, J. W., Anand, S. S., Shestakovska, O., Yusuf, S., & Fox, K. A. (2020). The COMPASS trial. *Circulation*, *142*(1), 40–48. https://doi.org/10.1161/circulationaha.120.046048
31. Stevens, S. M., Woller, S. C., Kreuziger, L. B., Bounameaux, H., Doerschug, K. C., Geersing, G., Huisman, M. V., Kearon, C., King, C. S., Knighton, A. J., Lake, E., Murin, S., Vintch, J., Wells, P. S., & Moores, L. K. (2021a). Antithrombotic therapy for VTE disease. *Chest*, *160*(6), e545–e608. https://doi.org/10.1016/j.chest.2021.07.055
32. Streiff, M. B., Holmstrom, B., Angelini, D. E., Ashrani, A. A., Elshoury, A., Fanikos, J., Fertrin, K. Y., Fogerty, A. E., Gao, S., Goldhaber, S. Z., Gundabolu, K., Ibrahim, I., Kraut, E. H., Leavitt, A. D., Lee, A., Lee, J. T., Lim, M. Y., Mann, J., Martin, K., . . . Nguyen, M. Q. (2021). Cancer-Associated Venous Thromboembolic Disease, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *PubMed*, *19*(10), 1181–1201. https://doi.org/10.6004/jnccn.2021.0047
33. Tomaselli, G. F., Mahaffey, K. W., Cuker, A., Dobesh, P. P., Doherty, J. U., Eikelboom, J. W., Florido, R., Gluckman, T. J., Hucker, W. J., Mehran, R., Messé, S. R., Perino, A. C., Rodríguez, F., Sarode, R., Siegal, D., & Wiggins, B. S. (2020). 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *Journal of the American College of Cardiology*, *76*(5), 594–622. https://doi.org/10.1016/j.jacc.2020.04.053
34. Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S., Bauersachs, J., Capodanno, D., Conradi, L., De Bonis, M., De Paulis, R., Delgado, V., Freemantle, N., Gilard, M., Haugaa, K. H., Jeppsson, A., Jüni, P., Pierard, L., Prendergast, B., Sádaba, J. R., . . . Wojakowski, W. (2022). 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Revista Española De Cardiología*, *75*(6), 524. https://doi.org/10.1016/j.rec.2022.05.006
35. Weitz, J. I., Lensing, A. W. A., Prins, M. H., Bauersachs, R., Beyer-Westendorf, J., Bounameaux, H., Brighton, T., Cohen, A. T., Davidson, B. L., Decousus, H., Freitas, M. C. S., Holberg, G., Kakkar, A. K., Haskell, L., Van Bellen, B., Pap, A. F., Berkowitz, S. D., Verhamme, P., Wells, P. S., & Prandoni, P. (2017). Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *The New England Journal of Medicine*, *376*(13), 1211–1222. https://doi.org/10.1056/nejmoa1700518