MAQI² MICHIGAN ANTICOAGULATION QUALITY IMPROVEMENT INITIATIVE

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Anticoagulation Desktop Reference

(Version 2.2)

A Consortium-Developed Compendium of Anticoagulation Information

This reference was produced by the **Michigan Anticoagulation Quality Improvement Initiative (MAQI²)**, a consortium of anticoagulation clinics and experts from across the state of Michigan. Funding for MAQI² is provided by **Blue Cross Blue Shield of Michigan and Blue Care Network** through the Collaborative Quality Improvement (CQI) program.

The goal of this reference is to provide practitioners with an up-to-date, reliable, and easy to use source of information for anticoagulation. The content is based on the latest available evidence-based guidelines and research, whenever possible. If you are aware of new guidelines or research, or if you have suggestions that can help improve this reference, please email.

What's new in version 2.2?

- Updated DOAC indications, dosing, and contraindication information based on latest package inserts (p.6)
- Updated anticoagulant selection information based on latest guidelines and research (p.14)
- Expanded valve types in warfarin INR and length of treatment table (p.22)
- Replaced the previous DOAC peri-procedural interruption protocol with the more simplified and validated PAUSE trial protocol (p.67)
- Added information on VTE prophylaxis in ambulatory cancer patients (p. 92)

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Bleeding/Clotting Risk Evaluation Tools for Atrial Fibrillation Patients

Before prescribing anticoagulants, providers should weigh the risk of thrombosis against the risk of bleeding. The tools below can be used to help providers and patients make informed decisions about whether or not anticoagulation is warranted.

Stroke Risk Scores

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score is an expansion of the original $CHADS_2$ score to include 3 additional stroke risk factors: age 65-74, female sex, and history of vascular disease. The additional risk factors are believed to more accurately determine stroke risk and the need for anticoagulation in patients with $CHADS_2$ scores of 0 or 1. **The CHA_2DS_2-VASc is recommended over $CHADS_2$ since the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines.[1]**

CHA_2DS_2-VASc Scoring Tool[2]	
Condition	**Points**
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA or thromboembolism (prior)	2
Vascular disease (MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Sex Category (Female)	1
Total score=	

Score	Risk	AHA/ACC/HRS Guidelines[1]
≥3	High	Anticoagulate (men and women)
2	High (men) Intermediate (women)	Anticoagulate (men) Consider anticoagulation (women)
1	Intermediate (men) Low (women)	Consider anticoagulation (men) Reasonable to omit anticoag. (women)
0	Low	Reasonable to omit anticoagulation

Aspirin alone or in combination with another antiplatelet (eg. clopidogrel) is no longer recommended for stroke prevention in atrial fibrillation alone.[5]

CHA_2DS_2-VASc Score	Yearly Stroke Risk (%)		
	No Warfarin	With Aspirin[4]	With Warfarin[4]
0	0	0	0
1	1.3	1.0	0.5
2	2.2	1.8	0.8
3	3.2	2.6	1.1
4	4.0	3.2	1.4
5	6.7	5.4	2.3
6	9.8	7.8	3.4

[1] January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019;139:e000–e000. DOI: 10.1161/CIR.0000000000000665

[2] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72. doi: 10.1378/chest.09-1584.

[3] Camm, AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart Journal (2012)33, 2719–2747. doi: 10.1093/eurheartj/ehs253

[4] Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;146:857-8673. doi:10.7326/0003-4819-146-12-200706190-00007

[5] Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

Bleeding Risk Scores

Bleeding risk should be assessed at each patient contact and should initially focus on potentially modifiable risk factors. The HAS-BLED tool can be used to identify modifiable risk factors (in red). Patients with scores indicating high bleed risk (≥3) should be followed more closely.[1]

HAS-BLED Score (warfarin in atrial fibrillation patients)[2]

Estimates risk of major bleeding for patients on **warfarin** for **atrial fibrillation**.

	Condition	Points
H	Hypertension	1
A	Abnormal renal/liver function (1 pt each)	1 or 2
S	Stroke	1
B	Bleeding history or disposition	1
L	Labile INRs	1
E	Elderly	1
D	Current drugs (medication) or alcohol use (1pt each)	1 or 2
	TOTAL POINTS	

Total Points	Annual Major bleed risk (%)	Intracranial bleeds per 100-pt-yrs[3]	Major bleed risk category
0	1.13		Low
1	1.02		Low
2	1.88	0.6	Intermediate
3	3.74	0.7	High
4	8.7	1.0	High
5	12.5	1.2	High

Modifiable risk factors in red.

When evaluating the risk/benefit of anticoagulation in atrial fibrillation, it is important to consider the risks of ischemic stroke, intracranial hemorrhage and extracranial hemorrhage independently.

Condition	Definition
Hypertension	Systolic Blood Pressure >160
Abnormal renal function	Chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or CrCl<50
Abnormal liver function	Chronic hepatic disease/biochemical evidence of hepatic derangement (eg, bilirubin >2× upper limit of normal, with AST/ALT/Alk Phos >3× upper limit normal)
Stroke	Any previous history of Stroke
Bleeding history or disposition	Bleeding event history (defined below), genetic predisposition, anemia.
Labile INRs	<60% of time spent in therapeutic INR range (INR 2-3)
Elderly	Age ≥ 65 years
Current medication or alcohol use	Concomitant use of antiplatelet agent/aspirin, NSAIDs, or alcohol >16 beers/week, >10 glasses wine/week or equivalent
Bleeding event	Bleeding requiring hospitalization and/or causing a decrease in Hgb>2g/dL and/or requiring ≥2 unit blood transfusion.

[1]Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

[2]Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093-100. doi: 10.1378/chest

[3]Friberg L, Rosenqvist M, Lip G. Net Clinical Benefit in Patients With Atrial Fibrillation: A Report From the Swedish Atrial Fibrillation Cohort Study. Circulation. 2012; 125: 2298-2307. Doi: 10:1161/CIRCULATIONAHA.111.055079

RIETE Predictive Score for bleeding (warfarin in acute venous thromboembolism)

Estimates risk of major bleeding for patients on **warfarin** for **acute venous thromboembolism**.

Condition	Points
Recent major bleeding (<15 days prior to VTE)	2
Creatinine >1.2 mg/dl	1.5
Anemia (Hgb <13 g/dl in men or <12 g/dl in women)	1.5
Cancer	1
Clinically overt Pulmonary Embolism	1
Age >75 years	1
TOTAL POINTS	

Total Points	Major bleeding (%)	Risk level
0	0.1	Low
1	1.4	Moderate
1.5-2	2.2	
2.5-3	4.4	
3.5-4	4.2	
4.5-5	4.9	High
5.5-6	11	
>6	20	

Ruíz-Giménez et al. Thromb Haemost. 2008 Jul;100(1):26-31. doi: 10.1160/TH08-03-0193

Other Bleeding Risk Models

General bleeding Risk

IMPROVE: Factors at Admission Associated With Bleeding Risk in Medical Patients. Chest. 2011;139(1):69-79.

VTE treatment

Outpatient Bleeding Risk Index: The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. Arch Intern Med. 2003 Apr 28;163(8):917-20.

Kuijer: Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999; 159: 457–60.

Kearon: Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003 Aug 14;349(7):631-9.

AF treatment

ATRIA: A New Risk Scheme to Predict Warfarin-Associated Hemorrhage. The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401.

HEMORR$_2$HAGES: Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151:713–9.

Online risk calculators and apps

http://www.mdcalc.com/chads2-score-for-atrial-fibrillation-stroke-risk/
$CHADS_2$ calculator

http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/
CHA_2DS_2-VASc calculator

http://www.sparctool.com/
Combination tool that calculates $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores and provides detailed risk estimates for various anticoagulants based on these scores.

https://itunes.apple.com/us/app/anticoagevaluator/id609795286?mt=8
ACC AnticoagEvaluator: The American College of Cardiology's AnticoagEvaluator is an easy and fast way to assess stroke and bleeding risk and the benefits and risks of antithrombotic therapy in patients with chronic atrial fibrillation.

Warfarin Information

Generic (Trade Name)	FDA approved indications	Warnings and Additional Info
Warfarin (Coumadin®, Jantoven®)[1]	• Prophylaxis and treatment of venous thromboembolism (VTE)* • Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation* and/or cardiac valve replacement • Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction *DOACs now recommended over warfarin in patients with DVT of the leg or PE (in non-cancer patients) and atrial fibrillation (except in patients with moderate-to-severe mitral stenosis or a mechanical heart valve)	Dosage customized so that INR is in therapeutic range. See INR target range table for recommended INR target ranges. Available pill strengths: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg In patients on warfarin with consistently low time in INR therapeutic range (eg, TTR < 65%), CHEST guidelines recommend considering interventions to improve TTR or switching to a DOAC. Possible interventions include: more regular INR tests, review medication adherence, address other factors known to influence INR control, education/counselling[2]

[1] Coumadin® package insert

[5]Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

DOAC Information

(updated from latest US FDA Package Inserts on 11/4/19)

	Apixaban (Eliquis®)[1]	Betrixaban (Bevyxxa®)[2]	Dabigatran (Pradaxa®)[3]	Edoxaban (Savaysa®)[4]	Rivaroxaban (Xarelto®)[5]
General information for all indications	• Not recommended in patients with severe (Child-Pugh C) hepatic impairment, prosthetic heart valves, or pregnancy • If pt receiving 5 mg or 10 mg BID, dose should be reduced by 50% when given with strong dual inhibitors of CYP3A4 and P-gp* • If receiving 2.5 mg BID, avoid giving with strong dual inhibitors of CYP3A4 and P-gp* *conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, voriconazole • Avoid giving with strong dual inducers of CYP3A4 and P-gp: carbamazepine, phenytoin, rifampin, St. John's wort • Limited data available for use in patients with end stage renal impairment on dialysis. • Not recommended patients with triple-positive antiphospholipid syndrome (APS)	• Safety and effectiveness have not been established in patients with prosthetic heart valves • Not recommended in patients with hepatic impairment •	• Contraindicated in patients with mechanical prosthetic heart valves • Not recommended in patients with bioprosthetic heart valves. • There is limited data on dabigatran in pregnancy, so drug-associated risks cannot be determined • Concomitant use with P-gp inducers should generally be avoided: carbamazepine, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir • Not recommended patients with triple-positive antiphospholipid syndrome (APS)	• Not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) • Not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis. • Avoid concomitant use with rifampin, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, desvenlafaxine, duloxetine, venlafaxine, venlafaxine XR, milnacipran, levomilnacipran • Use with caution in pregnant women. Edoxaban has not been adequately studied in this population.	• Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C or associated coagulopathy), prosthetic heart valves, or pregnancy • Avoid concomitant use with combined P-gp and strong CYP3A4 inhibitors: conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, ritonavir, voriconazole • Avoid in patients with CrCl 15 to <80 mL/min and receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (eg. diltiazem, dronedarone, erythromycin, and verapamil) unless benefit exceeds risk. • Avoid concomitant use with drugs that are combined P-gp and strong CYP3A4 inducers: carbamazepine, phenytoin, rifampin, St. John's wort • No data available for use in patients with end stage renal impairment on dialysis. • Not recommended patients with triple-positive antiphospholipid syndrome (APS)

	Apixaban (Eliquis®)[1]	Betrixaban (Bevyxxa®)[2]	Dabigatran (Pradaxa®)[3]	Edoxaban (Savaysa®)[4]	Rivaroxaban (Xarelto®)[5]
Non-valvular Afib	**Dose: 5 mg BID** • If **at least 2** of the following characteristics are present: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose of is **2.5 mg BID**	Not FDA approved for this indication	**Dose: 150 mg BID** • Avoid if CrCl <15 mL/min or on dialysis • Reduce dose to **75 mg BID** if CrCl 15-30 mL/min • Reduce dose to **75 mg BID** if CrCl 30-50 mL/min and concomitant use of P-gp inhibitors dronedarone or systemic ketoconazole • Avoid co-administration with P-gp inhibitors* if CrCl <30 mL/min *** P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil**	**Dose: 60 mg QD** • Avoid if CrCl >95 mL/min • Reduce dose to **30 mg QD** if CrCl is 15-50 mL/min	**Dose: 20 mg QD with evening meal** • Reduce dose to **15 mg QD** with the evening meal if CrCl ≤50 mL/min
VTE treatment	**Dose: 10 mg BID x 7 days, then 5 mg BID**	Not FDA approved for this indication	**Dose: 150 mg BID after 5-10 days of parenteral lead in** • Avoid if CrCl ≤30 mL/min or on dialysis • Avoid co-administration with P-gp inhibitors* if CrCl <50 mL/min	**Dose: 60 mg QD after 5-10 days of parenteral lead in** • **Reduce dose to 30 mg QD** if CrCl is 15-50 mL/min or body weight ≤60 kg or using certain P-gp	**Dose: 15 mg BID x 21 days then switch to 20 mg QD** • Take with food • Avoid if CrCl <15 mL/min

	Apixaban (Eliquis®)[1]	Betrixaban (Bevyxxa®)[2]	Dabigatran (Pradaxa®)[3]	Edoxaban (Savaysa®)[4]	Rivaroxaban (Xarelto®)[5]
			* P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	inhibitors: verapamil or quinidine; or short term use of azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole	
Secondary risk reduction of VTE following initial therapy	**Dose: 2.5 mg BID after 6 months of initial treatment**	Not FDA approved for this indication	**Dose: 150 mg BID after initial treatment** • Avoid if CrCl ≤30 mL/min or on dialysis • Avoid co-administration with P-gp inhibitors* if CrCl <50 mL/min * P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	Not FDA approved for this indication	**Dose: 10 mg QD after 6 months of standard treatment** • Avoid if CrCl <15 mL/min
VTE Prophy after hip/knee replacement	**Dose: 2.5 mg BID for 12 days (knee) or 35 days (hip)** • Give first dose 12-24 hrs after surgery	Not FDA approved for this indication	**Dose: 110 mg day 1 then 220 mg QD for 28-35 days (for hip replacement only)** • Not FDA approved for knee replacement	Not FDA approved for this indication	**Dose: 10 mg QD for 12 days (knee) or 35 days (hip)** • Avoid if CrCl <15 mL/min

	Apixaban (Eliquis®)[1]	Betrixaban (Bevyxxa®)[2]	Dabigatran (Pradaxa®)[3]	Edoxaban (Savaysa®)[4]	Rivaroxaban (Xarelto®)[5]
			• Avoid if CrCl ≤30 mL/min or on dialysis • Avoid co-administration with P-gp inhibitors* if CrCl <50 mL/min * P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil		
VTE prophylaxis in adult patients hospitalized for acute illness	Not FDA approved for this indication	In patients who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE: **Dose: Initial single dose of 160 mg, followed by 80 mg once daily for 35 to 42 days** • If severe renal impairment (CrCl ≥ 15 to < 30 mL/min), **initial single dose of 80 mg followed by 40 mg once daily** • If concurrent use of P-gp inhibitors*, **use initial single dose of 80 mg followed by 40 mg once daily** * eg. e.g., amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin	Not FDA approved for this indication	Not FDA approved for this indication	In patients who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and NOT at high risk of bleeding (Patients with bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) **Dose: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days** • Avoid if CrCl <15 mL/min

	Apixaban (Eliquis®)[1]	Betrixaban (Bevyxxa®)[2]	Dabigatran (Pradaxa®)[3]	Edoxaban (Savaysa®)[4]	Rivaroxaban (Xarelto®)[5]
CV event reduction in stable CAD or PAD	Not FDA approved for this indication	Not FDA approved for this indication	Not FDA approved for this indication	Not FDA approved for this indication	2.5 mg twice daily with aspirin (75-100 mg) once daily

[1]Eliquis® package insert [2] Bevyxxa® package insert [3] Pradaxa® package insert [4]Savaysa® package insert [5] Xarelto® package insert

- **CrCl should be based on the Cockcroft-Gault formula and actual body weight: https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc**
- **See ICHECK'd mnemonic to help with DOAC prescribing**

Nonvalvular Atrial Fibrillation Definitions

- There is some confusion around the definition of *nonvalvular* as it relates to the use of DOACs in stroke prevention in atrial fibrillation.
- DOAC clinical trials defined *nonvalvular* differently; and therefore, had different exclusion criteria.[1]
- All trials excluded patients with mechanical valves or moderate to severe (hemodynamically significant) mitral stenosis.[1]
- **The 2019 ACC guidelines for atrial fibrillation recommend warfarin over DOACs in patients with mechanical valves or mod/severe mitral stenosis.[2]**

DOAC Trial Exclusion Criteria[1]

	Mechanical Valve Replacement	Bioprosthetic Valve Replacement	Mitral Stenosis	Mitral Regurgitation	Aortic Valve Disease	Valve Repair
RE-LY (dabigatran)	Excluded	Excluded	Excluded (H.S.)	Excluded (H.S.)	Excluded (H.S.)	
ROCKET-AF (rivaroxaban)	Excluded	Excluded	Excluded (H.S.)			
ARISTOTLE (apixaban)	Excluded	Not an exclusion criteria, but very few patients*	Excluded (mod-severe)			
ENGAGE AF-TIMI (edoxaban)	Excluded		Excluded (mod-severe)			

H.S.-hemodynamically significant

* 251 (1.4%) of patients enrolled in ARISTOTLE had prior valve surgery. It is unknown how many of these had bioprosthetic valves. Avezum et al. Apixaban Compared with Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the ARISTOTLE TrialCirculation. 2015 Aug 25;132(8):624-32. doi: 10.1161/CIRCULATIONAHA.114.014807. Epub 2015 Jun 23.

[1]Breithardt et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. European Heart Journal. doi:10.1093/eurheartj/ehu305

[2] January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019;139:e000–e000. DOI: 10.1161/CIR.0000000000000665

Comparison of Anticoagulants

Basic Characteristics of Warfarin and DOACs

	Warfarin	DOACs
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	Rivaroxaban should be taken with largest meal of the day, otherwise no known food effects for DOACs
Medication interactions	Many	Few*
Therapeutic monitoring required	Yes	No
Offset	Long	Shorter

*Apixaban is contraindicated if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) AND is taking a strong dual CYP3A4 and P-gp inhibitor.

Safety, Efficacy, and Pharmacology

	Warfarin[a]	Rivaroxaban[a]	Apixaban[a]	Dabigatran[a]	Edoxaban[b]

FDA approved indications	• AF
	• VTE
	  ○ treatment
	  ○ secondary prevention
	  ○ prophylaxis
	• Valve replacement
	• MI
		• AF (non-valvular only)
		• VTE
		  ○ treatment
		  ○ secondary prevention
		  ○ prophylaxis[1]
		• CV event reduction in stable CAD or PAD
		• VTE prophy in acutely ill medical patients
			• AF (non-valvular only)
			• VTE
			  ○ treatment
			  ○ secondary prevention
			  ○ prophylaxis[1]
				• AF (non-valvular only)
				• VTE
				  ○ Treatment[3]
				  ○ secondary prevention
				  ○ prophylaxis[2]
					• AF (non-valvular only)
					• VTE
					  ○ Treatment[3]

Administration	• Once daily with or without food	• Once or twice daily with largest meal of day[4]	• Twice daily with or without food	• Twice daily with or without food • Must be kept in original packaging • Can't be crushed	• Once daily with or without food
Safety in non-valvular atrial fibrillation	• Higher risk of intracranial hemorrhage compared to DOACs	• Higher risk of GI bleeding compared to warfarin	• Lower risk of major bleeding compared to warfarin	• Higher risk of GI bleeding compared to warfarin • Small increase in risk of MI compared to warfarin	• Lower risk of major bleeding compared to warfarin • Higher risk of GI bleeding (60mg dose)compared to warfarin
Efficacy in non-valvular atrial fibrillation[5]		• Non-inferior to warfarin	• Reduced all-cause mortality	• Lower risk of ischemic stroke (150mg dose only) • Trend towards reduced all-cause mortality	• Non-inferior to warfarin
Safety in VTE	• Increased risk of intracranial hemorrhage[d]	• Lower risk of major bleeding than warfarin[c] • May have higher risk of GI bleeding than warfarin[d]	• Potentially lower risk of major bleeding than warfarin, LMWH/dabigatran, and LMWH/edoxaban[c]	• May have higher risk of GI bleeding than warfarin[d]	• May have higher risk of GI bleeding than warfarin[d]
Efficacy in VTE	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]	Similar reduction in risk of recurrence[c]
Initial parenteral	Yes	No	No	Yes	Yes

	Warfarin[a]	Rivaroxaban[a]	Apixaban[a]	Dabigatran[a]	Edoxaban[b]
therapy needed for VTE treatment?					
Drug interactions	Multiple	3A4/P-gp	3A4/P-gp	P-gp	P-gp
Target	VKORC1	Factor Xa	Factor Xa	Thrombin	Factor Xa
Prodrug	No	No	No	Yes	No
Bioavailability	100%	60%-80%[6]	60%	6%	62%
Time to peak effect	4-5 days	2-4 hours	1-2 hours	1-3 hours	1-2 hours
Half-life	40 hours	7-11 hours	12 hours	8-15 hours	10-14 hours
Renal clearance	None	33%	25%	80%	50%

[1]Approved for VTE prophylaxis following knee or hip surgery only.
[2]Approved for VTE prophylaxis following hip surgery only.
[3]After 5-10 days of parental anticoagulant treatment only
[4]Twice daily for first 21 days of VTE treatment. Once daily for other indications.
[5]All are considered effective for stroke reduction in non-valvular AF
[6]Bioavailability of rivaroxaban decreases as the dose is increased. With once daily doses of 20 and 10 mg, bioavailabilities are 60% and 80%, respectively

[a]Adapted from: Weitz JI, Gross PL. New oral anticoagulants: which one should my patient use? Hematology Am Soc Hematol Educ Program. 2012;2012:536-40. doi: 10.1182/asheducation-2012.1.536.
[b]U.S. edoxaban package insert
[c]Castellucci LA. JAMA. 2014;312(11):1122-1135
[d]Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016. doi:10.1016/j.chest.2015.11.026.

For more details on the individual trials comparing warfarin with each of the DOACs/DOACs see:
Rivaroxaban (ROCKET-AF) DOI: 10.1056/NEJMoa1009638
Apixaban (ARISTOTLE) DOI: 10.1056/NEJMoa1107039
Dabigatran (RE-LY) DOI: 10.1056/NEJMoa0905561
Edoxaban (ENGAGE AF) DOI: 10.1056/NEJMoa1310907

Choice of Anticoagulant in AF Based on Patient Characteristics*

Patient Characteristic	Drug Choice	Rationale
Mechanical Heart Valve (valvular AF)	warfarin	Dabigatran inferior to warfarin and contraindicated in this group; other DOACs not studied in this patient population
Mod/severe mitral stenosis (valvular AF)	warfarin	There is limited data with DOAC therapy in this group. ACC/AHA guidelines recommend warfarin as first line in these patients.[1]
Moderate hepatic impairment (Child-Pugh B)	warfarin	Rivaroxaban and edoxaban are contraindicated in patients with moderate or severe hepatic impairment. Patients with significant liver impairment were excluded from the RE-LY trial for dabigatran. Apixaban should be used with caution in patients with moderate liver dysfunction per package insert.
Severe hepatic impairment (Child-Pugh C)	warfarin	Rivaroxan, apixaban, and edoxaban are contraindicated in patients with severe hepatic impairment. Patients with significant liver impairment were excluded from the RE-LY trial for dabigatran.
Antiphospholipid Syndrome (APS)	warfarin	For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin antibody, and anti-beta 2-glycoprotein I antibody]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.
Stable on warfarin†	warfarin or DOAC	Patients on warfarin should be informed about DOACs so they can make an informed decision on preferred anticoagulant
CrCl <30 mL/min	Warfarin or apixaban‡	Very few patients with CrCl<30 were included in the DOAC trials. The 2019 AHA/ACC AF guidelines do support the use of apixaban in end-stage renal disease patients with CHA_2DS_2-VASc scores ≥3 (men) or ≥2 (women).[1]
Dyspepsia or upper gastrointestinal symptoms	warfarin, rivaroxaban, apixaban, or edoxaban	Dyspepsia in up to 10% of patients taking dabigatran.
Bariatric surgery (gastric-bypass, lap band surgery, or gastrectomy)	warfarin	Due to possible altered absorption and lack of data on efficacy, DOACs are not recommended in patients that have had bariatric surgery.[2]
Recent gastrointestinal bleed	Warfarin or apixaban	More GI bleeds with dabigatran (150mg), rivaroxaban, or edoxaban (60mg) than with warfarin. Warfarin easier to reverse if there is further bleeding.
Prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding[3]	Apixaban, Edoxaban, dabigatran 110mg	All of these options demonstrate significantly less major bleeding compared with warfarin.[3]
Requirement for compliance aid such as medication planner/pill box	warfarin, rivaroxaban, apixaban, or edoxaban	Dabigatran capsules must be kept in their original container.

Stroke prevention in AF patients with CrCl > 95 mL/min	warfarin, dabigatran, rivaroxaban, or apixaban	Edoxaban inferior to warfarin in these patients based on post hoc analysis and contraindicated by FDA.

*Based on MAQI[2] expert consensus unless otherwise referenced.

†Warfarin dose has been stable and INRs have mostly been in therapeutic range.

‡ Apixaban reasonable choice if CHA_2DS_2-VASc scores ≥3 (men) or ≥2 (women).[1]

[1] January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019;139:e000–e000. DOI: 10.1161/CIR.0000000000000665

[2]Am J Med. 2017 May;130(5):517-524. doi: 10.1016/j.amjmed.2016.12.033. Epub 2017 Feb

[3]Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

The choice of anticoagulant in AF should be a shared decision; however, American, Canadian, and European guidelines now recommend DOACs over warfarin in patient with AF (except in patients with moderate-to-severe mitral stenosis or a mechanical heart valve).

The Society of Vascular Medicine has developed an online shared decision making tool for providers to use with their patients and families. The tool is available at: http://www.mybloodclots.org/

Choice of Anticoagulant in VTE Based on Patient Characteristics[1]

Patient Characteristic	Drug Choice	Remarks
DVT of Leg or PE in non-cancer patients	DOAC (2B recommendation over warfarin)	Trials have shown DOACs to be as effective at preventing VTE recurrence as warfarin with lower risk of bleeding.
DVT of Leg or PE in patients with cancer	LMWH, edoxaban[5], or rivaroxaban[6]	Recommendation for LMWH is stronger if: VTE was just diagnosed, extensive, metastatic cancer, very symptomatic; vomiting; on chemotherapy[1] or if high bleed risk (ex. GI/GU cancers or GI ulcers, colitis or other mucosal abnormalities).[7] Edoxaban or rivaroxaban suggested if patient has low bleed risk and no known drug interactions.[7]
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	DOACs contraindicated if elevated baseline INR due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30ml/min	warfarin	DOACs and LMWH contraindicated with severe renal impairment. DOAC dosing is unique for each medication and level of renal function.
Coronary artery disease	warfarin, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban,	Dabigatran can cause dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Bariatric surgery (gastric-bypass, lap band surgery, or gastrectomy)	warfarin	Due to possible altered absorption and lack of data on efficacy, DOACs are not recommended in patients that have had bariatric surgery.[4]
Poor compliance	warfarin	INR monitoring can help to detect problems. However, some patients may be more compliant with a DOAC because it is less complex.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Breast feeding[2]	LMWH or warfarin	It is unknown if DOACs are excreted in breast milk.
Extremes of weight (eg <50kg or >120kg)[2] or BMI >40[3]	warfarin	Patients at extremes of weight represented a very small proportion of the patients in DOAC VTE trials.
Antiphospholipid Syndrome[2]	warfarin	There have been recent case reports of possible failure of rivaroxaban and dabigatran to prevent thrombosis in antiphospholipid syndrome patients.
Cost, coverage, licensing	Varies among regions and with individual circumstances	

[1]Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016. doi:10.1016/j.chest.2015.11.026.

[2] Burnett et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *Journal of Thrombosis and Thrombolysis*, 2016, Volume 41, Number 1, Page 206

[3]Martin et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*, 14: 1308–1313. DOI: 10.1111/jth.13323

[4]Am J Med. 2017 May;130(5):517-524. doi: 10.1016/j.amjmed.2016.12.033. Epub 2017 Feb 1

[5] Edoxaban non-inferior to LMWH for treatment of CA-associated VTE. Hokusai VTE Cancer trial. N Engl J Med 2018; 378:615-624 DOI: 10.1056/NEJMoa1711948

[6]SELECT-D Pilot study found low VTE recurrence, similar major bleeds, but more clinically relevant non-major bleeds with rivaroxaban compared to LMWH. Blood, 130(Suppl 1), 625. 10.1200/JCO.2018.78.8034

[7] Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis,16: 1891–1894

Identifying Patients Appropriate for Direct Oral Anticoagulants (DOACs)

With the FDA approval of direct oral anticoagulants (DOACs), such as dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®), clinicians have alternatives to warfarin for stroke prevention in non-valvular A-Fib and the prevention/treatment of VTE. Although their safety and efficacy are comparable or better than warfarin and they are easier to manage, DOACs may not be the best choice for all patients. Clinicians must weigh individual patient factors to determine whether a DOAC or warfarin is most appropriate. The criteria and pros and cons below can help providers and patients make an informed decision.

Criteria for Good DOAC Candidates*

Criteria	Rationale
FDA approved indication	DOACs are currently only approved for non-valvular atrial fibrillation and treatment/prevention of VTE. Review prescribing information for DOACs for updated FDA approval information. DOACs are contraindicated in mechanical valve patients.
Adequate renal function	Since DOACs rely on renal function for elimination, they should be used with caution in patients with significant renal disease. DOAC dosing is adjusted according to renal function.
History of compliance with medical regimen	Since DOACs have a short half-life compared to warfarin and do not require monitoring, compliance may be a more important concern.
Frequent medication, diet, or health status changes that make warfarin management difficult.	Unlike warfarin, DOACs have few medication interactions. In addition, the only food-related factor with DOACs is that rivaroxaban should be taken with food.
Barriers to patient/family education	While DOAC education is still important, warfarin education is more involved due to the difficulty of management and number of topics needing to be covered.
Barriers to frequent monitoring (lack of transportation, mobility issues)	Unlike warfarin, frequent blood draws are not necessary with DOACs. Most follow-up monitoring can occur at regularly scheduled medical appointments.
Not taking medications known to interact with DOACs	While DOACs interact with fewer medications, there are still medications that increase or decrease drug exposure depending on the DOAC being used, including P-glycoprotein (Pgp) and strong CYP3A4 inducers and inhibitors (rifampin, ketoconazole, dronedarone, and itraconazole). Prescribing information should be reviewed for complete drug-drug interaction information.
Financial resources or adequate insurance coverage to pay out-of-pocket expense	DOACs may require higher out-of-pocket expenses based on insurance coverage.
History of labile INRs while on warfarin in spite of good compliance and efforts to improve INR stability.	In patients unable to maintain therapeutic INR levels, the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines recommend switching patients to a DOAC (Class IC rec.)[1]
Documented warfarin failure	DOACs should be considered if a patient has a thromboembolic event while on warfarin, especially if the patient's INR was therapeutic at time of event.

Criteria	Rationale
Patient understands and accepts that DOACs are not monitored and cannot accurately be measured	Patients need to be part of the decision-making process, which includes informing them about some of the key differences between warfarin and DOACs.

*Based on MAQI[2] expert consensus unless otherwise noted.

[1] January C, Wann L, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014. Doi: 10.1016/j.jacc.2014.03.022

Pros and Cons of DOACs*

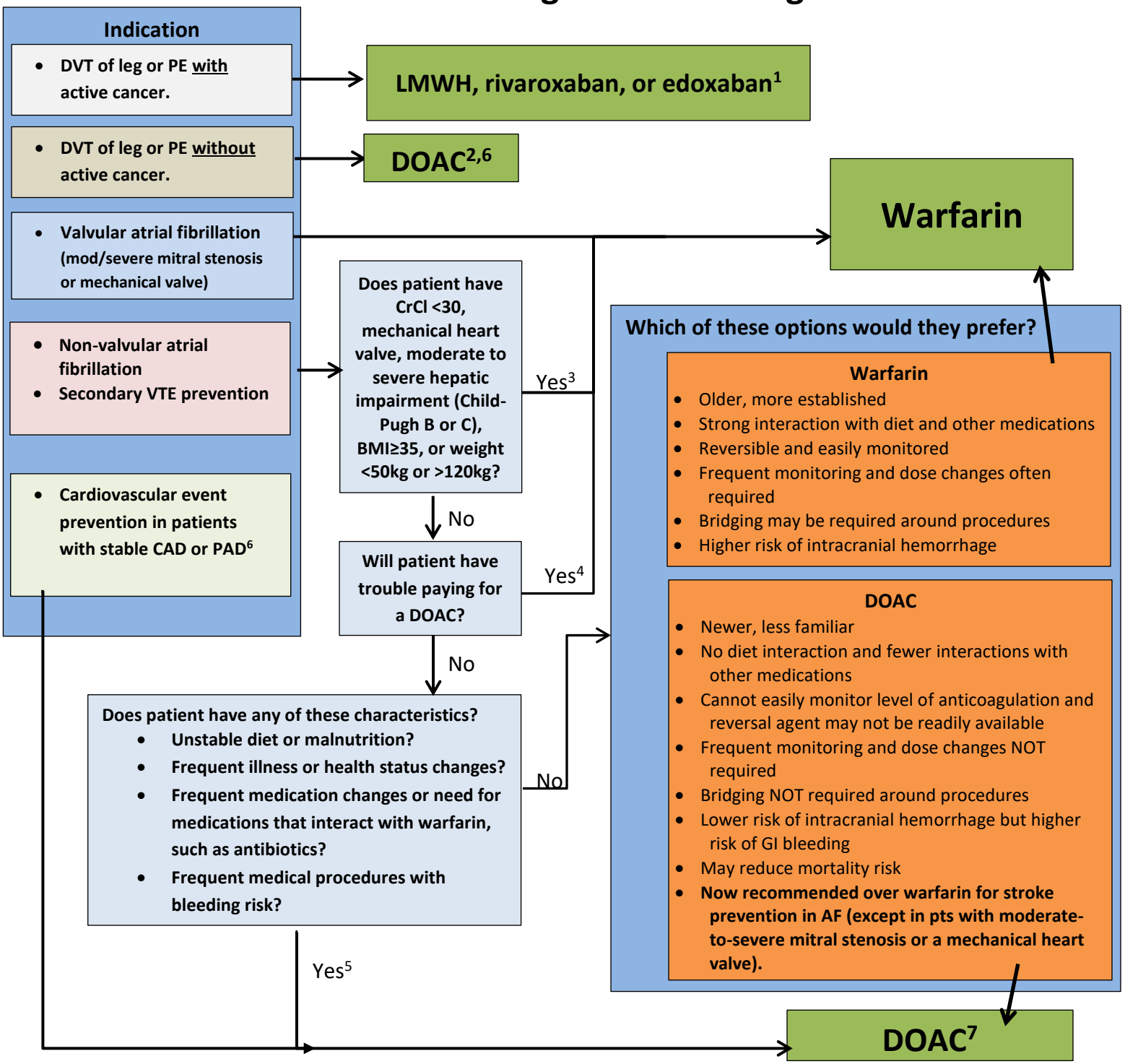
PROS
Lower incident of intracranial hemorrhage compared to warfarin
Reduced risk of ischemic stroke compared to warfarin (apixaban and dabigatran 150mg)
Lower risk of major bleeding compared to warfarin in AF (apixaban and edoxaban) (rivaroxaban had less major bleeding in pulmonary embolism patients[1])
Lower overall risk of mortality compared to warfarin (apixaban and dabigatran 150mg)
No INR monitoring required
Bridging/induction therapy likely not needed (except for dabigatran and edoxaban which require 5-10 days of parenteral anticoagulation for treatment of VTE)
Short half-life allows easier perioperative management
Convenient for rural patients or those with other barriers to INR monitoring
Fewer drug/diet/co-morbidity interactions
Less complex patient/family education
Follow up can likely be performed by community providers as well as specialty clinics

CONS
DOACs with BID dosing (dabigatran and apixaban) and rivaroxaban's requirement to take with food may have a negative impact on compliance.
No specific monitoring parameter
Higher incidence of GI side effects and discontinuation rate (dabigatran only)
Possible increased incidence of certain adverse events (e.g. MI, GI bleed, etc.) depending on DOAC
Lack of monitoring may result in non-compliance and an increased chance that patient may not report bleeding
Renal monitoring and dose adjustment required
Higher out-of-pocket costs and copays
New medications with only short history of use outside clinical trials

*Based on MAQI[2] expert consensus

[1] EINSTEIN-PE trial: N Engl J Med 2012; 366:1287-1297April 5, 2012 DOI: 10.1056/NEJMoa1113572

First Choice of Long-Term Anticoagulant



1. LMWH recommended if VTE was just diagnosed or extensive/very symptomatic; pt has metastatic CA, vomiting, on chemo (ACCP guidelines) or is high bleed risk (ex. GI or GU cancer or GI ulcers/abnormalities (2018 ISTH guidance). Rivaroxaban or edoxaban recommended if patient is low bleed-risk and has no drug interactions (2018 ISTH guidance)
2. DOACs recommended over warfarin in treatment of DVT of leg or PE in patients without active CA (ACCP guidelines).
3. Few patients in clinical trials had CrCl < 30. DOACs are either contraindicated or to be used cautiously in patients with significant hepatic disease or mechanical valves. ISTH does not recommend DOACs in pts with BMI>40 or wt >120 kg because of limited clinical data. AC Forum advises against DOACs if wt <50kg or >120kg or BMI ≥35.
4. DOACs have much higher co-pays compared to warfarin.
5. Warfarin is affected by diet and general health status, has many medication interactions, and may require bridging around certain medical procedures.
6. Rivaroxaban (+ low dose ASA) FDA approved for this indication.
7. Each DOAC is only approved for certain indications and may have warnings about use in specific populations (ex. levels of renal/hepatic failure) and with certain concurrent medications (pgp/CYP3A4 inducers or inhibitors). Review the package insert to ensure the selected DOAC is appropriate.

Things to Consider when Starting Warfarin

1. **Ensure that patient doesn't have any of these absolute contraindication for warfarin**[1]
    - Pregnancy, except in women with mechanical heart valves
    - 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

2. **Weigh risk of clotting with risk of bleeding**
    - In a-fib patients, calculate the patient's stroke risk using $CHADS_2$ or CHA_2DS_2-VASc scores and bleeding risk using the HAS-BLED score.
    - In VTE patients, calculate the patient's bleeding risk using the RIETE bleeding risk score.

3. **Consider other patient factors that could impact warfarin safety**
    - Possible drug interactions (drug interaction table)
    - Ability of patient/family to comply with monitoring and dose changes and comprehend warfarin education
    - Alcohol abuse, dementia, depression, unstable diet, co-morbidities
    - Discuss treatment options with cardiologist if patient is also on dual antiplatelet medications

4. **Select appropriate target INR range**
    - Selecting appropriate target range

5. **Select appropriate treatment duration**
    - Selecting appropriate duration

6. **Select appropriate starting dose**
    - Select starting dose based on factors affecting bleeding risk and warfarin sensitivity such as age, co-morbidities, and interacting drugs.

[1] Coumadin® package insert: http://packageinserts.bms.com/pi/pi_coumadin.pdf

Warfarin Target INR Range and Length of Treatment

Table 1. Recommendations for Target INR Range and Duration of Treatment			
Indication	**Target INR Range**	**Duration and additional information**	**Grade of Recommendation**
DVT and PE[1]			
PE or DVT of leg provoked by surgery or transient/reversible risk factor	2-3	3 months	1B
PE or DVT of leg unprovoked by surgery or transient/reversible risk factor	2-3	At least 3 months (over shorter period), then evaluate for risk-benefit of extended therapy (see flowchart below) In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a low or moderate bleeding risk, use extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B). If high bleeding risk, use 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).	1B
PE or DVT of leg in patients with active cancer	2-3	Extended (>3 months) Suggest use of LMWH over warfarin in PE or DVT of leg	1B (2B if high-risk for bleed) 2B
Non valvular atrial fibrillation and/or flutter[2]			
Low risk (CHA_2DS_2-VASc =0)	N/A	Reasonable to omit antithrombotic therapy	2A
Intermediate risk (CHA_2DS_2-VASc =1)	2-3	No antithrombotic therapy or long-term treatment with an oral anticoagulant or aspirin may be considered	2B
High risk (CHA_2DS_2-VASc $\geq$ 2)	2-3	Long-term	1A recommendation for warfarin 1B recommendation for dabigatran, rivaroxaban, or apixaban*
Cardioversion	2-3	At least 3 weeks prior to and at least 4 weeks after regardless of CHA_2DS_2-VASc score or method of cardioversion.	1B

Valvular Disease[3]			
Mechanical aortic valve replacement (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism	2-3	Long-term Thromboembolism risk factors: AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions ASA 75mg-100mg daily in addition to warfarin	1B 1A
Mechanical Aortic valve and additional risk factors for thromboembolic events or an older-generation mechanical AVR (such as ball-in-cage)	2.5-3.5	Long-term Thromboembolism risk factors: AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions ASA 75mg-100mg daily in addition to warfarin	1B 1A
Mechanical mitral valve replacement	2.5-3.5	Long-term ASA 75mg-100mg daily in addition to warfarin	1B 1A
Bioprosthetic mitral or aortic valve replacement[4]	2.0-3.0	3-6 months (+/- aspirin) (in patients at low risk for bleeding) followed with aspirin	2A
On-X® mechanical aortic valve replacement[4]	2.0-3.0 → 1.5-2.5 →	first 3 months after 3 months (with 81mg ASA) in patients with no thromboembolic risk factors	2B
Transcatheter aortic valve replacement (TAVR)[5]	2.0-3.0	May be reasonable for at least 3 months (in addition to aspirin) if patient is at risk for atrial fibrillation and low risk for bleeding	2B
Post-op VTE prophylaxis[6]* **			
Total hip replacement	2.0-3.0	At least 10 to 14 days Suggestion to extend up to 35 days	1B 2B
Total knee replacement	2.0-3.0	At least 10 to 14 days Suggestion to extend up to 35 days	1B 2B
Hip fracture surgery	2.0-3.0	At least 10 to 14 days Suggestion to extend up to 35 days	1B 2B

*Edoxaban not FDA approved at time of writing of 2014 AHA/ACC guidelines.
**+/- aspirin while on warfarin followed with aspirin upon warfarin discontinuation
***LMWH is recommended over warfarin for post-op VTE prophylaxis (Grade 2C)[5]

[1] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016. doi:10.1016/j.chest.2015.11.026.
[2] 2014 AHA/ACC Guideline for the Management of Patients With Atrial Fibrillation. doi:10.1016/j.jacc.2014.03.022
[3] 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. doi:10.1161/CIR.0000000000000031/-/DC1

[4]2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Circulation. 2017;135:e1159–e1195. DOI: 10.1161/CIR.0000000000000503

[5]2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis. J Am Coll Cardiol. 2017 Mar, 69 (10) 1313-1346. doi.org/10.1016/j.jacc.2016.12.006

[6] Prevention of VTE in Orthopedic Surgery Patients Antithrombotic Therapy and Prevention of Thrombosis,9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e278S–e325S

Length of Anticoagulation Treatment in VTE[1]

Type of VTE	Recommendation
Provoked proximal DVT of leg or PE	3 months
Provoked isolated distal DVT of leg	3 months
Unprovoked DVT of leg (isolated distal or proximal) or PE	At least 3 months[2] (1B recommendation over shorter duration)
1st VTE that is unprovoked proximal DVT of leg or PE and low/moderate bleed risk pt.	Extended[3,4]
1st VTE that is unprovoked proximal DVT of leg or PE and high bleed risk	3 months
2nd unprovoked VTE in low/moderate bleed risk pt.	Extended[4]
2nd unprovoked VTE in high bleed risk pt.	3 months
DVT of the leg or PE and active CA	Extended[4]

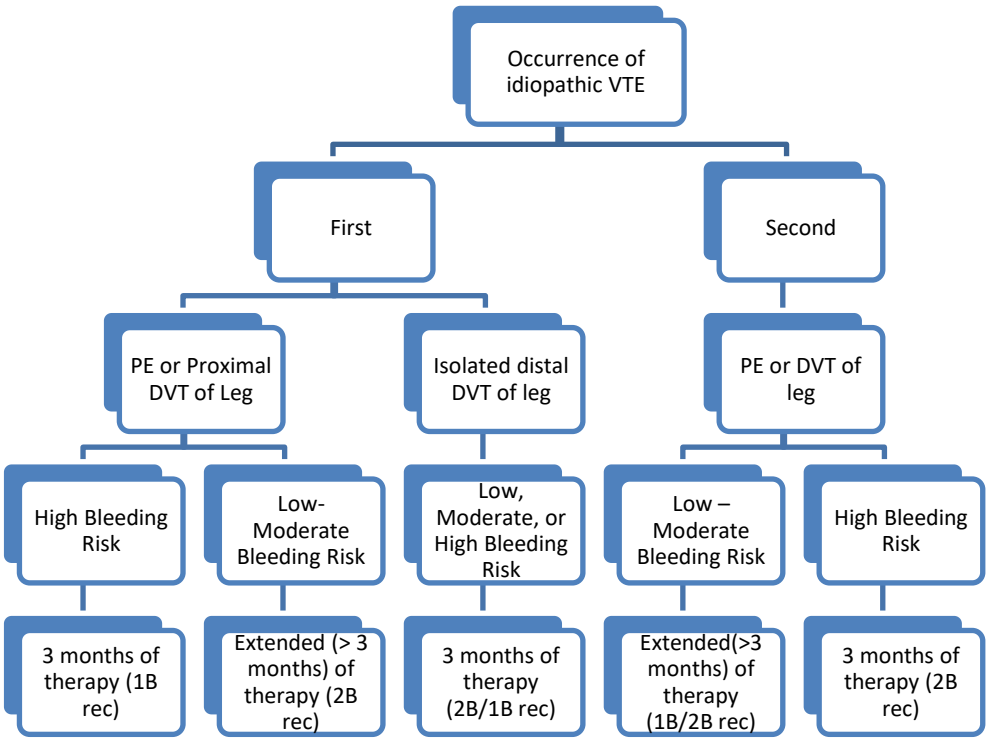
[1]Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: Chest Guideline Published online January 07, 2016. doi:10.1016/j.chest.2015.11.026.

[2]After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy.

[3]Patient sex and D-dimer level measured about one month after stopping anticoagulant therapy can help to further stratify the risk of recurrent VTE. Men have about a 75% higher risk of recurrence compared to women, while patients with a positive D-dimer result have about double the risk of recurrence compared to those with a negative D-dimer. The risk of recurrence in women with a negative post treatment D-dimer appears to be similar to the risk for patients with a proximal DVT or PE that was provoked by a minor transient risk factor (~15% recurrence at 5 years); consequently, the argument for extended anticoagulation in these women is not strong, suggesting that D-dimer testing will often influence a woman's decision. The risk of recurrence in men with a negative dimer is not much less than the overall risk of recurrence that we have estimated for patients with an unprovoked proximal DVT or PE (~25% compared to ~30% recurrence at 5 years); consequently, the argument for extended anticoagulation in these men is still substantial, suggesting that D-dimer testing will often not influence a male's decision.

[4]In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

Length of treatment recommendations for idiopathic (unprovoked) VTE[1]



[1]Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi:10.1378/chest.11-2301

Return to Things to Consider when Starting Patients on Warfarin

Selection of Warfarin Starting Dose

Patient population	Initial dose
Most patients *Follow 5mg initiation nomogram after first two 5mg doses.*	• 5mg
Patients with acute VTE being treated in the outpatient setting and are low to moderate risk for bleeding[1] *Follow 10 mg initiation nomogram after first two 10mg doses.*	• 10mg *Loading dose of 10mg daily for 2 days and then dosing based on INR measurements is a 2C recommendation in the latest ACCP guidelines for patients sufficiently health to be treated as outpatients where rapid attainment of therapeutic INR is required and considered safe[3]*
High bleeding risk patients (ex. elderly, malnourished, CHF, hepatic dysfunction, interacting drugs such as amiodarone)	• Consider 2.5mg*

*MAQI[2] expert consensus

Selecting the initial starting dose involves assessing the patient's bleeding risk, need for rapid anticoagulation, and treatment environment. Two small randomized trials have compared 5mg and 10mg starting doses.

Study	Patient population	Methods	Results
Kovacs[1]	Acute VTE, outpatient setting, concurrent LMWH treatment, 25% had CA, mean age 55 Patients excluded: baseline INR>1.4, thrombocytopenia, <18 years old, required hospitalization, high-risk for bleeding	201 patients randomized to receive either 5mg or 10mg initial dosing.	**10mg superior to 5mg** Patients with 10mg initial dosing reached first in-range INRs 1.4 days sooner and had similar rates of bleeding AEs and supratherapeutic INRs as patients started on 5mg.
Crowther[2]	Acute VTE, inpatient setting, most had concurrent heparin treatment, 1/3 had CA, mean age 66	53 patients randomized to receive either 5mg or 10mg initial dosing.	**5mg just as good and possibly safer** 5mg initial dosing resulted in therapeutic INRs as quickly as 10mg dosing with a trend toward less over-anticoagulation

An INR should be obtained within 3-5 days after starting warfarin to assess initial response

[1]Kovacs M J et al. Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism. Ann Intern Med. 2003;138:714-719.

[2]Crowther MA et al. A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses. Arch Intern Med. 1999;159:46-8.

[3] Holbrook. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi: 10.1378/chest.11-2295

Return to Things to Consider when Starting Patients on Warfarin

Factors Increasing or Decreasing Warfarin Sensitivity

When determining the appropriate starting dose of warfarin and making dose adjustments, it is important to consider if the patient may have increased or decreased sensitivity to warfarin.

Higher Sensitivity (Consider lower starting dose)	Lower Sensitivity (Consider higher starting dose)
Baseline INR >1.2	Baseline INR < 1.2
Advanced age (>65)	Younger age (<55)[1]
Female gender[2]	Male gender[2]
Low body weight (<110 pounds)	>200 pounds[2]
Asian ancestry[3]	African American ancestry[2]
Recent surgery and blood loss[2]	Diet high in Vitamin K[2]
Comorbidities: CHF, renal disease, liver disease, and cancer[4]	
Impaired nutritional status	
Alcohol abuse[4]	
Concurrent use of medications known to increase INR, including amiodarone, acetaminophen, and many antibiotics and antifungals	
Acute illness (diarrhea, fever)[4]	

[1]Crowther MA et al. A Randomized Trial Comparing 5-mg and 10-mg Warfarin Loading Doses. Arch Intern Med. 1999;159:46-8.
[2] Absher. Patient-specific factors predictive of warfarin dosage requirements. Ann Pharmacother. 2002 Oct;36(10):1512-7.
[3] Dang. The influence of ethnicity on warfarin dosage requirement. Ann Pharmacother. 2005 Jun;39(6):1008-12. Epub 2005 Apr 26. doi: 10.1345/aph.1E566
[4] White. Patient factors that influence warfarin dose response. J Pharm Pract. 2010 Jun;23(3):194-204. doi: 10.1177/0897190010362177. Epub 2010 May 6. doi: 10.1177/0897190010362177

Warfarin Initiation Nomograms

Warfarin Initiation Nomogram (5mg starting dose, target INR range 2-3)[1]

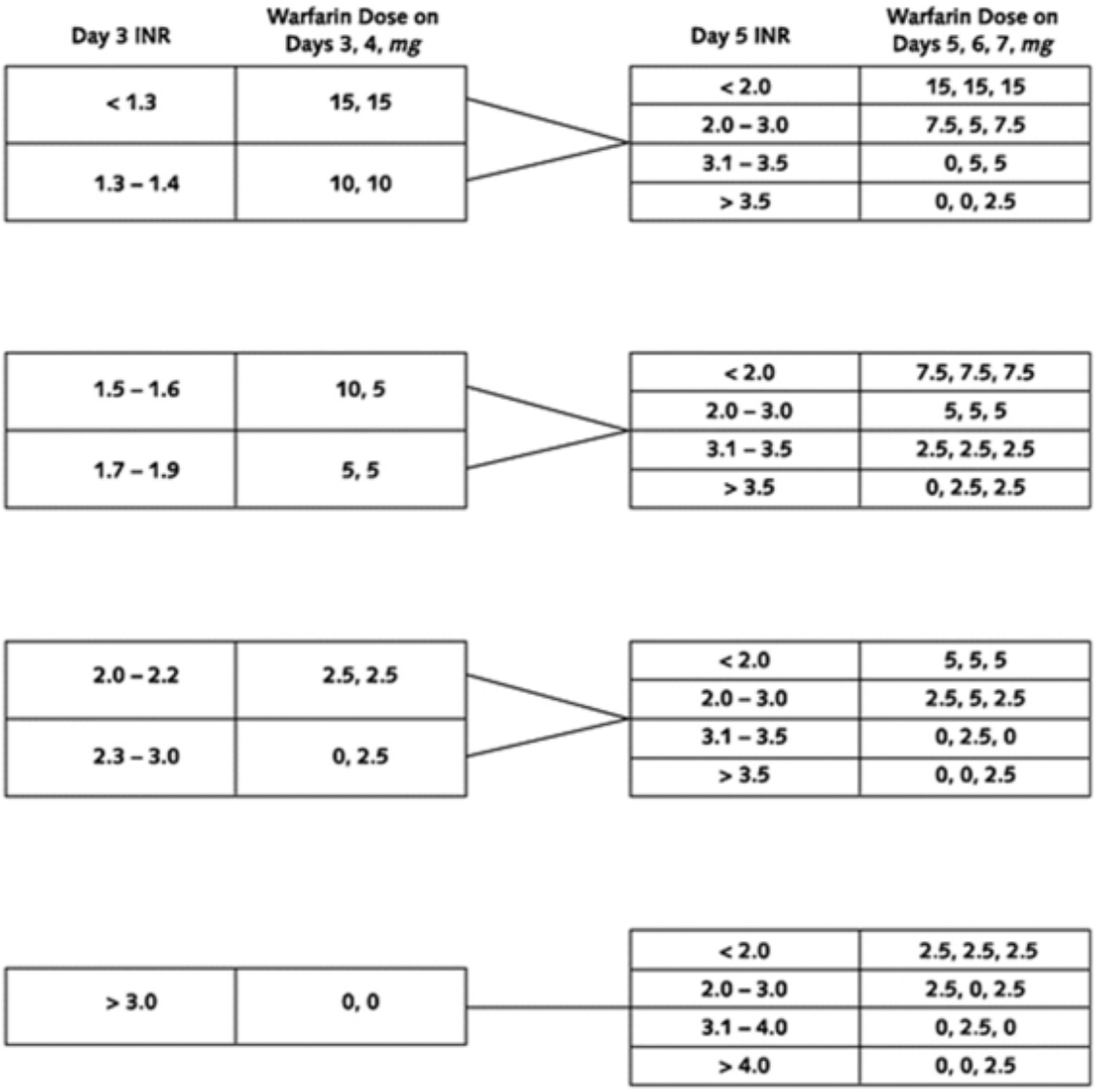
This algorithm was developed for in-patients started on **5mg with an INR target range of 2-3** and monitored with daily INRs. It may not be applicable to outpatient use in which daily INRs are not practical.

	INR	Dose
DAY 1		5 mg
DAY 2	<1.5 1.5 - 1.9 2.0 - 2.5 > 2.5	5 mg 2.5 mg 1 – 2.5 mg 0 mg
DAY 3	<1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	5 - 10 mg 2.5 - 5 mg 0 - 2.5 mg 0 mg
DAY 4	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	10 mg 5 -7.5 mg 0 - 5 mg 0
DAY 5	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	10 mg 7.5 - 10 mg 0 - 5 mg 0
DAY 6	< 1.5 1.5 - 1.9 2.0 - 3.0 > 3.0	7.5 - 12.5 mg 5 - 10 mg 0 - 7.5 mg 0

[1]Crowther.Ann Int Med, 127:333, 1997

Warfarin Initiation Nomogram (10mg starting dose, INR target range 2-3)[2]

This algorithm was developed and validated in acute VTE patients treated in the outpatient setting and receiving 10mg of warfarin for the first two days of treatment. Patients included in the study were deemed to not be high-risk for bleeds.[3] Use in other patient populations, such as atrial fibrillation, has not been validated.



Day 3 INR	Warfarin Dose on Days 3, 4, *mg*	Day 5 INR	Warfarin Dose on Days 5, 6, 7, *mg*
< 1.3	15, 15	< 2.0	15, 15, 15
		2.0 – 3.0	7.5, 5, 7.5
1.3 – 1.4	10, 10	3.1 – 3.5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 – 1.6	10, 5	< 2.0	7.5, 7.5, 7.5
		2.0 – 3.0	5, 5, 5
1.7 – 1.9	5, 5	3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2.0 – 2.2	2.5, 2.5	< 2.0	5, 5, 5
		2.0 – 3.0	2.5, 5, 2.5
2.3 – 3.0	0, 2.5	3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
> 3.0	0, 0	< 2.0	2.5, 2.5, 2.5
		2.0 – 3.0	2.5, 0, 2.5
		3.1 – 4.0	0, 2.5, 0
		> 4.0	0, 0, 2.5

[2]Kovacs M J et al. Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism. Ann Intern Med. 2003;138:714-719.3

Patients excluded from study: baseline INR>1.4, platelet count <50 K/uL, age < 18 years, required hospitalizations, considered high-risk for major bleeding (including interacting medications)

Initial VTE Treatment Setting (Hospital vs Home)

Guidelines recommend initial home treatment (or early discharge) of VTE patients if both clinical and home environment criteria are met.

Type/Location	Clinical criteria for initial treatment in home	Home environment criteria for initial treatment in home
Low-risk PE[1]	• Clinically stable with good cardiopulmonary reserve, including: ○ age ≤80 ○ no hx of CA or chronic cardiopulmonary disease ○ HR <110, SBP ≥100 mm Hg, and O2 ≥90% • No contraindications such as recent bleeding, severe liver/kidney disease, or thrombocytopenia	• Well-maintained living conditions • Strong support network • Ready access to medical care • Expected to be compliant • Access to phone
Acute DVT of leg[2]	• No severe leg symptoms or important comorbidities	

[1]Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. CHEST 2016; 149(2):315-352

[2]Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians, Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(2)(Suppl):e419S–e494S

Another tool that can be used to determine the safety of outpatient treatment for PE is the scoring tool used in the HESTIA Study.

Criteria	Additional information for criteria
Is the patient hemodynamically unstable?	SBP <100mmHg with HR >100 bpm; condition requiring admission to an intensive care unit
Is thrombolysis or embolectomy necessary?	
Active bleeding or high risk of bleeding?	GI bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count <75 × 10^9/L), uncontrolled hypertension (SBP >180 mmHg or DBP >110 mmHg).
More than 24h of oxygen supply to maintain oxygen saturation >90%	
Is pulmonary embolism diagnosed during anticoagulant treatment?	
Severe pain needing intravenous pain medication for more than 24h?	
Medical or social reason for treatment in the hospital for more than 24h (infection, malignancy, no support system)?	
Does the patient have a creatinine clearance of <30mL/min?	
Does the patient have severe liver impairment?	
Is the patient pregnant?	
Does the patient have a documented history of heparin-induced thrombocytopenia?	

If all of the answers were "no" (HESTIA score=0), patients were eligible for outpatient treatment.

J Thromb Haemost. 2011 Aug;9(8):1500-7. doi: 10.1111/j.1538-7836.2011.04388.x

Conversion from DOACs to Warfarin (Coumadin®)

Generic (Trade Name)	Package Insert Instructions (see below for 2018 ASH VTE guidelines+ on transitioning)

Dabigatran (Pradaxa®)[1]	• Adjust the starting time of warfarin based on creatinine clearance* as follows:
	  ○ For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing dabigatran.
	  ○ For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing dabigatran.
	  ○ For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing dabigatran.
	  ○ For CrCl <15 mL/min, no recommendations can be made.
	
	**CrCl determined using Cockcroft-Gault formula and actual body weight: http://touchcalc.com/calculators/cg*
	• Because dabigatran can increase INR, the INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days

Apixaban (Eliquis®)[2]	• Apixaban affects INR, so initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue apixaban and begin warfarin with a concomitant parenteral anticoagulant when the next dose of apixaban would have been due, discontinuing the parenteral anticoagulant when INR reaches goal range.+
Rivaroxaban (Xarelto®)[3]	• No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. • Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.+
Edoxaban (Savaysa®)[4]	• For patients on 60 mg of edoxaban, reduce dose to 30 mg and begin warfarin concomitantly. • For patients on 30 mg of edoxaban, reduce dose to 15 mg and begin warfarin concomitantly. • During transition, INR should be done at least weekly just prior to daily dose of edoxaban (to minimize influence on INR). • Discontinue edoxaban once a stable INR ≥ 2.0 is achieved.

+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. [5] Note: Even at trough levels, the INR may still be elevated due to DOAC presence.

[1]Pradaxa package insert (updated 12/2013): http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf

[2] Eliquis® package insert (updated 1/2014): http://packageinserts.bms.com/pi/pi_eliquis.pdf

[3] Xarelto package insert (updated 1/2014): http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100

[4] Savaysa® package insert: http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true

[5]Witt DM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 Nov 27; 2(22): 3257–3291. doi: 10.1182/bloodadvances.2018024893

Most Clinically Relevant Warfarin-Drug Interactions	
Potentiation of Drug Effect (Increased INR or increased bleed risk)	**Inhibition of Drug Effect (Decreased INR)**
Acetaminophen	Barbiturates
Allopurinol	Bosentan
Amiodarone	Carbamazepine
Amoxicillin	Cigarette Smoking
Aspirin	Chlordiazepoxide
Azithromycin	Ginseng
Bactrim(TMP-SMX)	Griseofulvin
Cimetadine	Mercaptopurine
Ciprofloxacin	Multivitamin Supplement
Citalopram	Nafcillin
Clarithromycin	Phenobarbital
Clopidogrel	Ribavarin
Cotrimoxazole	Rifampin
Diltiazem	Secobarbital
Entacapone	St. John's wort
Erythromycin	Phenytoin
Fenofibrate	
Fish Oil	
Fluconazole	
Fluvastatin	
Gemcitabine	
Gemfibrozil	
Levofloxacin	
Lovastatin	
Metronidazole	
Miconazole (Suppository and Gel)	
Omeprazole	
Propafenone	
Propanolol	
Simvastatin	
SSRI's	
Tamoxifen	
Tetracycline	
Tramadol	

For a more comprehensive list of potential drug, food, and dietary supplement interactions see Ageno et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines http://journal.publications.chestnet.org/article.aspx?articleid=1159432

Sources:

- Holbrook AM, et al. Systematic Overview of warfarin and its drug and food interactions. Arch Intern Med. 2005 May 23;165(10):1095-106. doi:10.1001/archinte.165.10.1095
- Badyal DK, Dadhich AP. Cytochrome P450 and drug interactions. Ind J Pharmacol 2001;33:248-59.
- Stading JA, Faulkner MA, Skrabal MZ. Effect of tobacco on INR.[Letter]. Am J HealthSystem Pharm 2007;64:805.

Return to Things to Consider when Starting Patients on Warfarin

Warfarin Patient Education Checklist

Completed	Topic
	What is anticoagulation and how does warfarin work?
	Why does patient need to start taking warfarin?
	How to take warfarin? (time of day, dose, weekly schedule, etc.)
	What is the expected duration of treatment?
	How is warfarin monitored? (INR testing, goal target range for patient, frequency of testing, etc.)
	What are the risks and side-effects of warfarin?
	What are the signs/symptoms of bleeding or clotting to watch for?
	What are the main factors influencing INR? (dietary intake of vitamin K, general health, activity level, alcohol, other medications/supplements, etc.)
	Ways to keep INR in range (consistent vitamin K content in diet, limit alcohol use, adhere to dosing instructions, etc.)
	What to do for missed doses?
	What are the drug-drug interactions to watch for? (including OTC and herbal supplements)
	What are the drug-food interactions to watch for?(Vitamin K rich foods, alcohol, etc.)
	What are some other necessary lifestyle changes? (no contact sports, fall avoidance, pregnancy)
	When and how to notify clinic? • s/sx of bleeding • medication/supplement changes • illness/changes in health status • Surgical procedures requiring warfarin interruption • Clinic contact information
	When to seek immediate medical attention?

Warfarin Education Material Links

Topic	
General warfarin (Coumadin®) information	MAQI Toolkit Medication Guide
Warfarin monitoring	Link
Diet	Link
Drug Interactions	Link
Reducing risk of complication	Link
Other patient resources	Link

Warfarin Maintenance Dosing and INR Recall Algorithms

These algorithms are intended to be used after the patient has gone through the initiation period and a chronic maintenance dose has been established. There may be valid clinical reasons to adjust doses outside these recommendations. Additionally, other algorithms may also be effective.

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%[1]	Increase 10%[1]	No change	Decrease 10%[1]	Hold for one day then decrease 10%[1]	Hold until INR therapeutic and then decrease by 15%*[1]	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

Providers should consider other clinical factors before determining dose changes, including:

- **recent trend in INR values**
- **dietary changes**
- **changes in health status**
- **changes in concomitant medications**
- **alcohol intake**
- **missed doses**
- **other possible explanations for out of range INRs**

In some cases, a dose change may not be necessary if a probable cause for out of range INR is identified

* Additional measures: Attempt to identify reasons for high INR (e.g. drug interactions, change in diet, acute illness), assess for signs/symptoms of bleeding, counsel patient to avoid excessive physical activity and to report signs/symptoms of bleeding, and consider recommending additional servings of foods high in Vitamin K such as green, leafy vegetables.
**Measures in addition to the above: Administer oral vitamin K (2.5-5mg) if patient has no signs of bleeding. If patient has signs or symptoms of bleeding, send patient to ED immediately as more aggressive treatments may be required (i.e. IV vitamin K, fresh-frozen plasma, or prothrombin complex concentrate). Rapid reversal with four-factor prothrombin complex concentrate is suggested over plasma.[2]

INR Recall Algorithm	
# of consecutive in-range INRs	**Repeat INR in**
1	5-10 days
2	2 weeks
3	3 weeks
4	4 weeks

Algorithm may be accelerated for a previously stable patient with a single out-or-range INR.

If the patient has had multiple stable INRs and a consistent weekly warfarin dose for the past 12 week period, it is reasonable to begin waiting up to 12 weeks for the next INR.[2] MAQI[2] recommends reserving the full 12 week recall interval for the most stable patients with low bleeding risk until more extended INR recall data is available. 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 INR.

[1] Adapted from Van Spall HG, Wallentin L, Yusuf S, Eikelboom JW, Nieuwlaat R, Yang S, Kabali C, Reilly PA, Ezekowitz MD, Connolly SJ. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation. 2012 Nov 6;126(19):2309-16. doi: 10.1161/CIRCULATIONAHA.112.101808. Epub 2012 Oct 1.

[2] Holbrook et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi: 10.1378/chest.11-2295

Periprocedural Management of Warfarin

Key points:

- Most patients do not need to have their warfarin interrupted for minimal bleed risk procedures.
- Most warfarin patients do not need to be bridged, unless they are at particularly high thromboembolic risk. There is growing evidence that bridging can increase bleed risk without significantly reducing thromboembolic risk in some patient groups. [1, 2]
- Decisions about periprocedural management should only be made after assessment of patient- and procedure-specific factors and discussions with the patient, management team, and proceduralist.

[1]Siegal et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012 Sep 25;126(13):1630-9. Epub 2012 Aug 21. DOI: 10.1161/CIRCULATIONAHA.112.105221

[2]Douketis et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE Trial). N Engl J Med 2015; 373:823-833. DOI: 10.1056/NEJMoa1501035

Warfarin Interruption and Bridging

Pt bleeding risk factors? • major bleeding or ICH < 3 months ago • platelet abnormality (including aspirin use) • INR above range • Prior bleeding during previous bridging or similar procedure	**Procedure Bleed Risk** **(see bleed risk of common procedures)**	**Low thromboembolic risk** **AF**: CHA_2DS_2-VASc ≤4 and no prior stroke/se **VTE**: VTE >12 months and no other risk factors **MHV**: Bileaflet aortic valve prosthesis without atrial fibrillation and no other stroke risk factors	**Moderate thromboembolic risk** **AF**: CHA_2DS_2-VASc 5-6 or prior stroke/se > 3 months ago **VTE**: VTE within past 3-12 months, non-severe thrombophilia[3], recurrent VTE, active CA (within 6 months) **MHV**: Bileaflet aortic valve prosthesis and one or more risk factors[4]	**High thromboembolic risk[6]** **AF**: CHA_2DS_2-VASc ≥ 7 or prior stroke/se < 3 months ago **VTE**: VTE < 3 months, severe thrombophilia[5] **MHV**: any mitral valve prosthesis, caged-ball or tilting disc aortic valve prosthesis, recent (within 6 months) stroke or TIA
No	Not clinically important or Low	Do not interrupt	Do not interrupt	Do not interrupt
	Inter./ high	-Interrupt -Do not bridge	-Interrupt -Do not bridge (consider bridging if other thrombotic risk factors[7])	-Interrupt -Bridge
	Uncertain	-Likely interrupt[1] -Do not bridge	-Likely interrupt[1] -Do not bridge (consider bridging if other thrombotic risk factors[7])	-Likely interrupt[1] -Bridge
Yes	Not clinically important or Low	-Likely interrupt[1] -Do not bridge	-Likely interrupt[1] -Do not bridge[8]	-Likely interrupt[1] -Likely bridge[2] (unless major bleed or ICH < 3 months ago)
	Inter./high	-Interrupt -Do not bridge	-Interrupt -Do not bridge[8]	-Interrupt -Likely bridge[2] (unless major bleed or ICH < 3 months ago)
	Uncertain	-Interrupt -Do not bridge	-Interrupt -Do not bridge[8]	-Interrupt -Likely bridge[2](unless major bleed or ICH < 3 months ago)

Adapted from: Doherty et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. DOI: 10.1016/j.jacc.2016.11.024 and Douketis et al. Perioperative Management of Antithrombotic Therapy. Chest. 2012;141(2_suppl):e326S-e350S. doi:10.1378/chest.11-2298. Not bridging in low/moderate risk VTE patients is also supported by the 2018 ASH VTE guidelines: DOI: https://doi.org/10.1182/bloodadvances.2018024893

ICH – Intracranial hemorrhage; AF – Atrial Fibrillation; VTE – Venous Thromboembolism; MHV – Mechanical Heart Valve; TE – Thromboembolism

Footnotes: [1] Use clinical judgment, insufficient data, consult proceduralists; [2]Address any reversible patient risk factors such as high INR or aspirin use and consider bleed history before bridging; [3]heterozygous factor V Leiden or prothrombin gene mutation; [4] atrial fibrillation, prior stroke or TIA, HTN, Diabetes, CHF, or age>75; [5] eg. deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities; [6]If TE within past 3 months, consider delaying procedure if possible. [7]eg. prior stroke, TIA, or systemic embolism in AF. [8]According to the 2017 AHA/ACC VHD Guideline Update, bridging can be considered in bileaflet AVR patients with an additional thromboembolic risk factor.

Decisions about interruption and bridging should only be made after assessment of individual patient- and procedure-related factors and discussions with the patient, management team, and proceduralist.

How to Interrupt and Restart Warfarin[1]

1. Check INR 5-7 days prior to procedure
2. Time the discontinuation of warfarin based on INR results according to the following table

INR result (5-7 days before procedure)	Supratherapeutic	Therapeutic	Subtherapeutic
When to start holding warfarin	At least 5 days before	5 days before	3-4 days before

3. Recheck INR 24 hours before procedure to ensure it is at desired level*
4. Warfarin can normally be restarted within the first 24 hours after the procedure at the patient's usual therapeutic dose.

*If INR still above desired level (eg. >1.5), consider low-dose oral vitamin K (1.0-2.5mg) and rechecking INR just prior to procedure.

[1]Doherty et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. DOI: 10.1016/j.jacc.2016.11.024

Consider delaying restart of warfarin if complete hemostasis has not been achieved, if there are patient factors increasing bleed risk, or if there is potential for bleeding in a catastrophic location (eg. Intracranial or intraspinal).[1]

How to Bridge during Warfarin Interruption[1]

Patient/ procedure factors	Bridging agent	When to start bridging agent prior to procedure	When to stop bridging agent prior to procedure	When to restart anticoagulants following procedure**	When to stop bridging agent
CrCl ≥30	LMWH	Start LMWH when INR goes below therapeutic range or after omitting 2-3 doses of warfarin (if INR not checked)	24 hours prior to the procedure.	Warfarin: within 24 hours LMWH: within 24 hours following low risk procedure; after 48-72 hours in high bleed risk procedures	When INR becomes therapeutic
	UFH	Start UFH when INR goes below therapeutic range or after omitting 2-3 doses of warfarin (if INR not checked)	At least 4 hours prior to procedure and if aPTT is in normal range.*	Warfarin: within 24 hours UFH: within 24 hours following low risk procedure; after 48-72 hours in high bleed risk procedures	When INR becomes therapeutic
CrCl <30	UFH (recommended over LMWH***)	Start UFH when INR goes below therapeutic range or after omitting 2-3 doses of warfarin (if INR not checked)	At least 4 hours prior to procedure and if aPTT is in normal range.*	Warfarin: within 24 hours UFH or LMWH: within 24 hours following low risk procedure; after 48-72 hours in high bleed risk procedures	When INR becomes therapeutic
Combination of high patient thrombo-embolic risk AND high procedure bleed risk	Consider individualized strategies to reduce bleed risk: • Using prophylactic/ low-dose parenteral anticoagulant • Initiate warfarin alone after procedure	If decision made to use prophy/low-dose parenteral anticoagulant, start when INR goes below therapeutic range or after omitting 2-3 doses of warfarin (if INR not checked)	If LMWH: 24 hours prior to the procedure. If UFH: At least 4 hours prior to procedure and if aPTT is in normal range.*	Warfarin: within 24 hours LMWH or UFH: within 24 hours following low risk procedure; after 48-72 hours in high bleed risk procedures	When INR becomes therapeutic
Heparin allergy or recent HIT	Follow local protocol	Follow local protocol	Follow local protocol	Follow local protocol	Follow local protocol

[1]Doherty et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. DOI: 10.1016/j.jacc.2016.11.024

*If aPTT is not in normal range, delay procedure and recheck aPTT every 2 hours until in normal range.

** Delay restart of anticoagulation if complete hemostasis has not been achieved, if there are patient factors increasing bleed risk, or if there is potential for bleeding in a catastrophic location (eg. Intracranial, intraspinal)

***Dosing guidance for LMWH is available for pts with a CrCl of 15 to 30mL/min, although caution is advised when using LMWH in this setting

Decisions about bridging should only be made after assessment of individual patient and procedure-related factors and discussions with the patient, management team, and proceduralist.

Example Schedule in Warfarin Patient Bridged with LMWH

Timing	Management
5 days before	Stop warfarin[1]
3 days before	Start LMWH[2]
1 day before	• Administer last dose of LMWH* • Assess INR. If <1.5, proceed with procedure. If 1.5-1-7, consider low dose oral vitamin K (1.0-2.5mg)[2]
Procedure	
12-24 hrs after	Resume warfarin (if adequate hemostasis)[1]
1 day after	Resume LMWH if low bleed risk procedure[1]
2-3 days after	Resume LMWH if high bleed risk procedure[1]
4 days after	Check INR. If >= 2.0 on a single measure, discontinue LMWH[2]

[1]Chest. 2012;141(2_suppl):e326S-e350S. doi:10.1378/chest.11-2298

[2]J Thromb Haemost. 2016 May;14(5):875-85. doi: 10.1111/jth.13305

*Timing of last dose of LMWH should be considered. Last dose of LMWH should be given at least 12 hr (for BID dosing) or 24 hr (for daily dosing) prior to procedure time.

Estimated Bleed Risk for Common Procedures

Minimal/Not clinically important
Minor dental procedures (extraction of 1-2 teeth, periodontal surgery, abscess incision)[2]
Superficial surgeries such as abscess incisions and dermatologic excisions[2]
Cataract or glaucoma procedures[2]
Diagnostic gastrointestinal endoscopy with or without biopsy[4]
Central catheter removal[2]
Low
Pacemaker/defibrillator implantation[1] *
AF ablation (transvenous)[3]
Dilatation and curettage[3]
Cervical biopsy[3]
Prostate biopsy[3]
Angiography/PCI (with transradial access)[3]
Breast or axillary node biopsy (FNA)[3]
Nerve block, peripheral (superficial, compressible)[3]
Intermediate
Arterial revascularization, lower extremity (femoral, popliteal, tibial)[3]
Deep venous reconstruction, lower extremity[3]
Hysterectomy[3]
Left atrial appendage occlusion (WATCHMAN device)
Angiography/PCI (with transfemoral access)[3]
Lower extremity fx ORIF[3]
Complex dental procedures (extractions >3 teeth, dental implants)[3]
Lung biopsy (percutaneous needle)[3]
Chest drain insertion (larger drain)[3]
Nerve block, peripheral (deep and non-compressible)[3]

High
Surgery/procedures in highly vascular organs, such as the kidney, liver, and spleen[1]
Major surgery with extensive tissue injury (eg. cancer surgery, joint arthroplasty, reconstructive surgery)[1]
Bowel resection[1]
Cardiac, intracranial, or spinal surgeries (serious clinical consequences with bleeds)[1]
Urologic surgeries/procedures (kidney biopsy, nephrectomy)[5]
Abdominal vascular surgery, open[3]
Left atrial appendage occlusion (Lariat procedure)
Lumbar puncture[3]
ICD/pacemaker lead extraction[3]
Neuraxial block (spinal, epidural)[3]
Most major surgeries expected to last >45 min[2]
Uncertain
Esophageal biopsy[3]
Pericardiocentesis[3]

[1]2012 ACCP Guidelines. Chest. 2012;141(2_suppl):e326S-e350S. doi:10.1378/chest.11-2298

[2]Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016; 41: 187–205. doi: 10.1007/s11239-015-1319-y

[3]Doherty et al. 2017 ACC Periprocedural Anticoagulation Pathway. DOI: 10.1016/j.jacc.2016.11.024

[4]ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy. http://dx.doi.org/10.1016/j.gie.2015.09.035

[5]Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. N Engl J Med. 2013 May 30;368(22):2113-24. doi: 10.1056/NEJMra1206531.

*Recent evidence from Level 1 randomized, controlled trial suggests that implantation can be done without interruption

Always discuss with proceduralist to determine bleed risk as the complexity of the procedure may vary case to case due to patient factors. For bleed risk information for additional procedures, see references.

Management of Patients Undergoing Elective Cardioversion

	AF for Greater than 48 hours	AF for 48 hour or Less
Starting anticoagulation	Therapeutic anticoagulation (warfarin with target INR 2-3, LMWH at treatment doses, or dabigatran) for at least three weeks prior to the scheduled procedure. (1B recommendation)[1] • Reasonable to use rivaroxaban or apixaban for 3 weeks prior	Suggest starting anticoagulation at presentation (LMWH or unfractionated heparin at full treatment doses) and proceeding to CV rather than delaying CV for 3 weeks of therapeutic anticoagulation or a TEE guided approach. (2C recommendation)[1]
Stopping anticoagulation after successful cardioversion	After at least 4 weeks of therapeutic anticoagulation (1B recommendation)[1]	Suggest therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk. (2C recommendation)[1]

LMWH=low Molecular Weight Heparin
TEE=trans esophageal echo
CV=cardioversion

[1]Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. doi:10.1378/chest.11-2298

Managing Patients on Medications that Interact with Warfarin

	Recommendation
When should my patient have their INR drawn?	If taking a medication known to affect the INR, the patient should have a repeat INR within 3-5 days from the start date of the medication.
What if my patient has a history of warfarin medication interaction or will begin taking a medication known to be "high-risk"?	Patients with a history of warfarin medication interaction, those at significant increase risk of bleeding complications, or who will be taking a medication known to be "high-risk" GIVE a preemptive dose adjustment (i.e. reduce the warfarin on the day that the ACS is notified that the medication has been started). In that scenario, repeat the INR within 3-5 days. **See High-Risk table below for specific suggested preemptive dose adjustments**
What are the most common medications that can significantly <u>increase</u> the INRs?*	Acetaminophen Allopurinol **Amiodarone** Amoxicillin Aspirin Azithromycin **Bactrim** Cimetadine Ciprofloxacin Citalopram Clarithromycin Clopidogrel Cotrimoxazole Diltiazem Entacapone Erythromycin Fenofibrate Fish Oil Fluconazole Fluvastatin Gemcitabine Gemfibrozil Levofloxacin Lovastatin Metronidazole Miconazole (Suppository and Gel) Omeprazole Propafenone Propanolol Simvastatin SSRI's Tamoxifen Tetracycline Tramadol
What are the most common medications that can significantly <u>reduce</u> the INR?*	Barbiturates Bosentan Carbamazepine Cigarette Smoking Chlordiazepoxide Ginseng Griseofulvin Mercaptopurine Multivitamin Supplement Nafcillin Phenobarbital Ribavarin Rifampin Secobarbital St. John's wort Phenytoin

Adapted from University of Michigan Anticoagulation Service Guidelines

*For a more complete list of medications that increase, decrease, or have no effect on INRs, see: Holbrook AM, et al. Systematic Overview of warfarin and its drug and food interactions. Arch Intern Med. 2005 May 23;165(10):1095-106

High-Risk Medications		
Medication	**Generic Name**	**Suggested Dose Change/Recheck***
Pacerone, Cordarone	Amiodarone	Decrease 30%, recheck in 7-10 days from start date
Arixtra	Fondaparinux Sodium	Increase dose by 10-20% and recheck INR every 2-3- days
Bactrim/Septra	Sulratrim,Trimoxazole, Trimethoprim	Decrease 30%, recheck in 7-10 days from start date
Biaxin	Clarithryomycin	Decrease 30%, recheck in 7-10 days from start date
Diflucan	Fluconazole	Decrease 30%, recheck in 7-10 days from start date
Flagyl	Metronidazole	Decrease 30%, recheck in 7-10 days from start date
Rifampin	Rifadin, rimactane, rimycin, rofact	Increase dose by 10-20% and recheck INR every 2-3 days
Tricor	Fenofibrate, antara, triglide, lobibra	Decrease 30%, recheck in 7-10 days from start date
Xeloda	Methotrexate, capecitabine, cytarabine, fludarabine phsphate, fluorouracil, gemcitabine hydrochloride, hydroxyurea, mercaptopurine, pemetrexed	Decrease dose by 20-30% after checking INRs every 2-3 days, then decrease as needed

* These values represent expert opinion and have not been validated by randomized trials

Routine Follow-up Questions for Warfarin Patients

These questions should be asked at each PT/INR follow-up.

Assessment questions:
Is the patient taking warfarin as prescribed? (correct pill strength and schedule)
Does patient have any changes in general health status?
Any changes in diet, especially intake of vitamin K?
Has the patient started or stopped any prescription medications since last PT/INR?
Does the patient have any unusual bruising or bleeding?
Does the patient have any signs of clotting?
Has the patient had any ED visits or hospitalizations since the last PT/INR?
Has patients started or stopped any OTC vitamins, herbal supplements, dietary supplements, or pain relievers?
Does the patient have any procedures scheduled in the near future?
Does the patient have any travel plans that will interfere with monitoring?

Adapted from: Spectrum Health The Medical Group. http://www.spectrum-health.org/physicians/toolkits

Patient self-management of warfarin

Patient self-management (PSM) is a warfarin management strategy in which patients or family members adjusts the warfarin dose based on the INR. Based on evidence that shows decreased thrombotic events and mortality in patients using PSM compared to other management strategies, the 2018 American Society of Hematology Guidelines for VTE now recommend PSM in select patients.[1] However, PSM does require a large investment in training and equipment, and the cost-effectiveness is not clear at this time. Proper patient selection is key.

The AC Forum Centers of Excellence Resource Center (https://acforum-excellence.org/Resource-Center/) has an excellent PSM toolkit for providers and patients. This toolkit covers many important topics from basic information about PSM to specific tools for assessing patient eligibility and warfarin knowledge. The patient toolkit also includes education videos and competency assessments.

PSM toolkit for providers: https://rise.articulate.com/share/UqBL2hCC43e2Fhtw8eseiosvQX-bKP6a#/

PSM toolkit for patients: https://rise.articulate.com/share/kVtvZxSlGB_DEieROFxPg-VdXyxoEDAp#/

[1] American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Advances 2018 2:3257-3291; doi: https://doi.org/10.1182/bloodadvances.2018024893

Minor Bleeding

Minor bleeding, often referred to as nuisance bleeding, is a common problem in patients taking anticoagulants. Some of the most common types of minor bleeding include epistaxis; bleeding gums; prolonged bleeding from small cuts/scrapes; bruising; and small amounts of blood in the urine, stool, or sputum. It is estimated that about 15% of patients will have at least one minor bleeding event per year.[1] Over half of all ED visits for warfarin related bleeding are for minor bleeds.[2]

Recommendations:

- Educate patients that minor bleeding is normal, rarely an emergency, and not usually a reason to stop taking their anticoagulant.
    - Patients can be provided this pamphlet from the National Blood Clot Alliance for reassurance: https://www.stoptheclot.org/wp-content/uploads/2014/02/Nuisance-Bleeding-Flyer.NBCA-copy.pdf

- Patients should notify their provider if they have minor bleeding, or if minor bleeding becomes more frequent or heavy.

- Educate patients on how to prevent bleeding.
    - Do not participate in high-risk sports or activities
    - Always wear protective safety gear such as a bike helmet when biking or gloves when working in the garden or when using sharp tools
    - Use a soft toothbrush and an electric razor instead of blades
    - Use a humidifier and saline nose spray to prevent nasal dryness
    - Take steps to prevent constipation, such as maintaining a high fiber diet, drinking plenty of water, and getting plenty of exercise

- Provide the patient with information on how to manage minor bleeding in the home.
    - Handouts for dealing with epistaxis, minor skin injuries, and minor gastrointestinal and genitourinary bleeding: http://www.anticoagulationtoolkit.org/patients
    - Video on preventing and treating epistaxis in the home: Nosebleeds in Patients on Blood Thinners
    - Patients should keep a couple over the counter products on hand to help stop minor bleeding
        - Oxymetazoline nasal decongestant spray (eg. Afrin, Dristan) is very effective for epistaxis.
        - Hemostatic powders (eg. WoundSeal) are very effective at stopping bleeding from minor skin wounds.

[1]BMJ. 2002 Oct 12; 325(7368): 828–831
[2]Arch Intern Med. 2010 Nov 22;170(21):1926-33. doi: 10.1001/archinternmed.2010.407.

Home Treatment for Dry Nose or Epistaxis

Dry Nose Treatment and Epistaxis Prevention[1]
1. Make sure that patient's room or house is well humidified. [1]
2. Use saline nasal spray 6-10 times/day (2 sprays in each nostril).[1]
3. For additional moisturization[1] • For short term (less than 4-5 days) use a small amount of Vaseline Petroleum Jelly or A & D ointment or saline gel just inside the nose twice a day. • For longer use, obtain an over-the-counter water-based lotion (Eucerin, Neutragena, or equivalent of cosmetic product) two times a day by placing a small amount into the front of the nose and sniffing. • For intense short-term moisturization (such as to treat problematic crusting/frequent bleeding) get a cotton ball greased with petroleum jelly or saline gel and insert into affected nostril at bedtime. Remove in the morning
Epistaxis Treatment
1. Sit or stand upright and lean slightly forward. This will prevent blood from going down the back of your throat.[2]
2. Apply pressure for 5 to 10 minutes.[2]
3. If a nosebleed lasts greater than 10 minutes, spray 2 sprays of Afrin in the nostril that is bleeding and pinch both nostrils tightly for 10 minutes head upright.[1]
4. Do not blow your nose for 12 hours after the bleeding stops. This will allow a strong blood clot to form.[1]
5. Avoid alcohol, hot liquids and hot or spicy foods for two days after the nosebleed. Alcohol and hot liquids in your mouth can dilate blood vessels in your nose and cause the bleeding to start again.[1]
6. If bleeding persists or if there is concern about the amount of bleeding, notify your anticoagulation provider for further instructions. An urgent referral to an ENT physician may be necessary. If unable to reach anticoagulation provider, go to the nearest ER for further evaluation.[1]

[1]University of Michigan Anticoagulation Services' Dry Nose or Epistaxis Protocol

[2] University of Washington Anticoagulation Clinic
http://depts.washington.edu/anticoag/home/sites/default/files/Preventing_Treating_Nosebleeds_1_10.pdf

Refer patients to this video for a demonstration on how to prevent and stop epistaxis: Nosebleeds in Patients on Blood Thinners

Warfarin Reversal Guidelines

In patients with serious bleeding or highly elevated INRs, warfarin reversal may be required. Guidelines from various organizations are below.

CHEST Guidelines[1]:

- For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K. (Grade 2B)

- For patients taking VKAs with INRs >10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered. (Grade 2C)

- For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate (PCC) rather than with plasma. (Grade 2C)
    - Fresh Frozen Plasma (FFP) has the disadvantage of potential allergic reaction or transmission of infection, longer preparation time, and higher volume.

- We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone. (Grade 2C)

ASH Guidelines[2]:

- For patients with life-threatening bleeding during VKA treatment of VTE who have an elevated INR, the ASH guideline panel suggests using 4-factor prothrombin complex concentrates (PCCs) rather than fresh-frozen plasma (FFP) as an addition to cessation of VKA and IV vitamin K (conditional recommendation based on very low certainty in the evidence about effects)

AC Forum Guidance Statement[3]:

- For non-bleeding patients presenting with an elevated INR, we suggest the following:
    - For INRs 4.5-10
        - Withholding warfarin alone or in combination with 1.25–2.5 mg of oral vitamin K
    - For INRs >10
        - 2.5 mg of oral vitamin K
- For warfarin-related major bleeding we suggest rapid reversal of anticoagulation with 5–10 mg intravenous vitamin K and 4-factor non-activated PCC in conjunction with general supportive care and bleeding site interventions.

4F-PCC Dosing

4F-PCC (Kcentra®) is dosed based on units of Factor IX. The dose is determined by the patient's pretreatment INR and body weight.

FDA label dosing:

Pretreatment INR	2–<4	4–6	>6
Dose (units of Factor IX)/kg body weight	25	35	50
Maximum dose*(units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

*Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

4F-PCC is administered via intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 mL/min

Fixed-dose option:

Fixed dose options have been studied and are now supported by the 2017 ACC Guidelines.[4]

- 1000 units for any major bleed
- 1500 units for intracranial bleed

[1]Holbrook, et al. Evidence-Based Management of Anticoagulant Therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. Volume 141, Issue 2, Supplement, Pages e152S–e184S

[2]Witt, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018 Nov 27; 2(22): 3257–3291.

[3]Witt, D.M., Clark, N.P., Kaatz, S. et al. J Thromb Thrombolysis (2016) 41: 187. https://doi.org/10.1007/s11239-015-1319-y

[4]2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. JACC, Volume 70, Issue 24, 19 December 2017, Pages 3042-3067, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2017.09.1085

Resumption of Anticoagulation after Major Bleed

The decision to resume anticoagulation following a major bleeding event should be made based on numerous factors, including the location of bleed, factors contributing to the bleed, comorbid conditions, thromboembolic risk, and patient/family preferences. **Available evidence suggests that, in most cases, resumption of anticoagulation results in better patient outcomes.**[1] The following information can be used to help decide if anticoagulation should be resumed.

Available Guidelines:

- ASH Clinical Practice Guidelines: In VTE patients requiring long-term indefinite anticoagulation (mod-high risk of VTE recurrence) and not at high risk of recurrent bleeding, the ASH guideline panel suggests resumption of oral anticoagulation therapy within 90 days rather than discontinuation of therapy.[1]

Clinical characteristics arguing for or against resuming anticoagulation after major bleed[2]

	Resume	Do not resume
Bleed-related characteristics		
-Known, correctable source	consider very strongly	
-Known, uncorrectable source	consider	
-Unknown source		consider
-Nonlobar ICH location	consider, particularly if strong indication for anticoagulation[3]	
-Lobar ICH location		consider strongly, given relatively high risk of ICH recurrence[3]
Indication for anticoagulation		
-Mechanical heart valve	consider very strongly	
-Idiopathic or recurrent VTE	consider very strongly	
-Provoked VTE, completed 3 mo of therapy		consider very strongly
-VTE + protein C/S or antithrombin deficiency or APLA syndrome	consider strongly	
-AF and prior history of stroke or higher $CHADS_2$ or CHA_2DS_2-VASc score	consider very strongly	
-AF and lower $CHADS_2$ or CHA_2DS_2-VASc score	consider	
-AF with no additional stroke risk factors		consider very strongly
Other characteristics		
-Previously unstable INR control despite adequate adherence		consider
-Renal failure		consider
-Poor prognosis, limited life expectancy		consider

- Other factors when considering anticoagulation resumption: concurrent use of antiplatelets or NSAIDS, INR value at time of bleed, and other comorbid conditions that increase bleed risk (eg. liver disease, hypertension, alcohol abuse)[4]
- Age alone should not be a reason to withhold anticoagulation after a bleeding event.[4]
- Although evidence related to anticoagulation resumption following major bleeding events is based on gastrointestinal or intracranial bleeds in patients taking warfarin, it is reasonable to extrapolate to other types of bleeds and to patients taking DOACs.[2]

When to resume anticoagulation after major bleed

Bleed location	When to resume
Gastrointestinal	Approx. 14 days[2]
Intracranial	Within a month[2]
Other	Once bleeding is resolved and hemostasis is normalized, consider restarting the anticoagulant after weighing risks and benefits of therapy vs. no therapy

Treatment strategies following bleeding in AF patients:

Major bleed:

- In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin.[5]

ICH, specifically:

- In patients with AF and high ischemic stroke risk, we suggest anticoagulation with a DOAC after acute spontaneous ICH (which includes subdural, subarachnoid, and intracerebral hemorrhages) after careful consideration of the risks and benefits (Ungraded consensus-based statement).[5]
- In ICH survivors at high risk of recurrent ICH (eg, those with probable cerebral amyloid angiopathy), we suggest left atrial appendage occlusion (Ungraded consensus-based statement).[5]

[1]Witt, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Advances 2018 2:3257-3291; doi: https://doi.org/10.1182/bloodadvances.2018024893
[2]Witt. What to do after the bleed; resuming anticoagulation after major bleeding. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):620-624.
[3]Hemphill et al. 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. DOI: 10.1161/STR.0000000000000069
[4]Colantino, Alison & Jaffer, Amir & Brotman, Daniel. (2015). Resuming anticoagulation after hemorrhage: A practical approach. Cleveland Clinic journal of medicine. 82. 245-256. 10.3949/ccjm.82a.14047.
[5]Lip, et al. Antithrombotic Therapy for Atrial Fibrillation-CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

DOAC Initiation Checklist

Task	Comments
Establish appropriate dose based on anticoagulant selected, indication and patient factors such as renal function.	See FDA approved anticoagulants for indication and dosing information.
Evaluate for medication or supplement interactions that may necessitate DOAC dose adjustment.	See DOAC drug interaction page
Evaluate renal function (Cockcroft-Gault equation to estimate CrCl) prior to DOAC initiation[1] and establish a baseline for CBC and liver function[2]	Use actual body weight in Cockcroft-Gault equation. Online calculator available at: http://touchcalc.com/calculators/cg
Establish clear expectations for length of treatment based on indication.	
Consider co-administration with a proton-pump inhibitor.[2]	Proton-pump inhibitors do not appear to impact DOAC efficacy based on the clinical trials and may be helpful in reducing dyspepsia (dabigatran) and the risk of gastrointestinal bleeding[3]
If converting from warfarin, see warfarin to DOAC conversion instructions.	
Provide comprehensive patient education.	See DOAC education topic checklist • If rivaroxaban, make sure patient knows to take with the largest meal of the day (typically the evening meal) • If dabigatran, make sure patient knows to take with a full glass of water, to store in the original package, and to not crush.

Establish follow-up plan.	Follow-up plan should include:
	• Who will the patient follow-up with?
	• How often will follow-up occur?
	• When is the next follow-up?
	• What will happen at the follow-ups?
	Follow-ups should check for:
	• compliance
	• thrombo-embolic events
	• bleeding events
	• Medication changes
	  ○ P-gp inhibitors and inducers
	  ○ P-gp/ CYP3A4 inhibitors and inducers
	  ○ antiplatelets
	• need for blood sampling to recheck renal function, hepatic function, and CBC.[2]

[1] January C, Wann L, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014. Doi: 10.1016/j.jacc.2014.03.022

[2]Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013. 15, 625-651. Doi: 10.1093/europace/eut083

[3] Agewall et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J (2013) doi: 10.1093/eurheartj/eht042

ICHECK'D Mnemonic for DOAC initiation

This tool was developed to help providers remember key factors in DOAC selection, dosing, and patient education.

ICHECK'D:

- **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** (medical history)**:** Does the patient have a mechanical heart valve, moderate to severe mitral stenosis, pregnant/nursing, have hepatic impairment (Child-Pugh class B or higher)?
- **E= education** (for patient/care giver)**:** Review risk of bleeding and procedures when dose may need to be held
- **C= compliance:** Missing or skipping doses may increase the risk of a blood clot since DOACs have a short half-life
- **K= kidney function:** Serum creatinine value needed prior to DOAC initiation and while receiving the DOAC in follow up.
    - **NVAF**: when creatinine clearance calculation is needed, Cockcroft-Gault formula using actual body weight should be utilized
    - **VTE**: only dabigatran is dosed using CrCl via Cockcroft-Gault formula (using actual weight)
- **D= dose correct for indication:** Monitor for any changes that may be needed based on above
    - **NVAF:** based on kidney function
    - **Acute VTE**: based on loading dose followed by maintenance dose

ICHECK'D	Apixaban (Eliquis, Bristol-Myers Squibb/Pfizer)	Rivaroxaban (Xarelto, Janssen)	Dabigatran (Pradaxa, Boehringer Ingelheim)	Edoxaban (Savaysa, Daiichi Sankyo)
Indication	**Nonvalvular AF, VTE, VTE prophylaxis (knee and hip)**	**Nonvalvular AF, VTE, VTE prophylaxis (knee and hip)**	**Nonvalvular AF, VTE, VTE prophylaxis (hip only)**	**Nonvalvular AF, VTE**
Concomitant meds	**All patients:** • **If 5 mg or 10 mg twice daily, reduce 50% when given with: clarithromycin, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, voriconazole** • **If 2.5 mg twice daily, avoid giving with: clarithromycin, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, voriconazole** • **Avoid giving with: carbamazepine, phenytoin, rifampin, St. John's wort, enzalutamide, apalutamide**	**All patients:** • **Avoid giving with: clarithromycin, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, voriconazole, carbamazepine, phenytoin, rifampin, St. John's wort, enzalutamide, apalutamide** • **Avoid with CrCl 15 to < 80 mL/min and receiving: diltiazem, dronedarone, erythromycin, verapamil**	**All patients:** • **Avoid giving with carbamazepine, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir** **AF: If CrCl 30-50 mL/min, and concomitant use of P-gp inhibitors* or dronedarone or systemic ketoconazole, reduce dose to 75 mg twice daily. Avoid if CrCl < 30 mL/min with concomitant use of P-gp inhibitors*** **VTE and VTE prophy: Avoid if CrCl < 50 mL/min with concomitant use of P-gp inhibitors*** ***P-gp inhibitors: Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, verapamil**	**All patients:** • **Avoid giving with rifampin, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, desvenlafaxine, duloxetine, venlafaxine, venlafaxine XR, milnacipran, levomilnacipran** **VTE: 30 mg daily if taking **verapamil, quinidine, azithromycin clarithromycin erythromycin, itraconazole (oral), ketoconazole (oral)**
History	**All patients and all indications:** contraindicated if mechanical heart valve, moderate to severe mitral stenosis, hepatic impairment (Child-Pugh class B or higher), pregnant or nursing, triple positive antiphospholipid syndrome			
Education	**All patients (and caregivers) and all indications:** review risk for bleeding, signs and symptoms of bleeding, procedures when dose may need to be held			
Compliance	**All patients (and caregivers) and all indications:** reinforce missing/skipping doses may increase the risk for a blood clot, discuss with caregiver for patients with dementia			
Kidney function	**Nonvalvular AF:** serum creatinine value	**Nonvalvular AF:** CrCl via Cockcroft-Gault formula using actual body weight	**Nonvalvular AF & VTE:** CrCl via Cockcroft-Gault formula using actual body weight	**Nonvalvular AF:** CrCl via Cockcroft-Gault formula using actual body weight
Dose	**Nonvalvular AF:** 5 mg twice daily. Reduce to 2.5 mg twice daily if **at least two** of the following: age ≥ 80 years, body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL **VTE:** 10 mg twice daily x 7 days and then decrease to 5 mg twice daily **Secondary VTE Prevention**: may decrease to 2.5 mg twice daily after at least 6 months of treatment **VTE prophy**: 2.5 mg twice daily for 12 days (knee) or 35 days (hip)	**Nonvalvular AF:** 20 mg daily with evening meal. Reduce to 15 mg daily with evening meal if CrCl 15-50 mL/min or if on dialysis **VTE:** 15 mg twice daily with food x 21 days and then decrease to 20 mg daily with food. After 6 months of treatment may decrease to 10 mg daily. Avoid if CrCl < 30 mL/min **VTE prophy:** 10 mg daily for 12 days (knee) or 35 days (hip). Avoid if CrCl < 30 L/min	**Nonvalvular AF:** 150 mg twice daily. Reduce dose to 75 mg twice daily if CrCl 15-30 mL/min. Avoid if CrCl < 15 mL/min or on dialysis **VTE:** 150 mg twice daily after 5-10 days of parenteral anticoagulant. Avoid if CrCl ≤ 30 mL/min or on dialysis **VTE prophy (hip only):** Initial = 110 mg x 1 then 220 mg daily for 28-35 days. Avoid if sCrCl ≤ 30 mL/min or on dialysis	**Nonvalvular AF:** 60 mg daily if CrCl ≤ 95 mL/min. Reduce dose to 30 mg daily if CrCl is 15-50 mL/min. Avoid if CrCl > 95 mL/min or < 15 mL/min **VTE:** 60 mg daily after 5-10 days of parenteral anticoagulant. Reduce dose to 30 mg daily if CrCl is 15-50 mL/min **or** body weight ≤ 60 kg **or** using any P-gp inhibitors listed above**. Not

		CAD/PAD: 2.5 BID in combination with daily ASA (75-100 mg) **VTE prophy for acutely ill[#]:** 10 mg daily for 31-39 days		recommended if CrCl < 15 mL/min

https://www.healio.com/cardiology/arrhythmia-disorders/news/print/cardiology-today/%7B0d550b79-49ac-4970-be5d-e5872a4c89bf%7D/icheckd-mnemonic-approach-assists-in-caring-for-patients-receiving-direct-oral-anticoagulant

Drug-Drug or Drug-Supplement interactions with DOACs

Although known to have fewer drug-drug interactions than warfarin, DOACs do have some important interactions with common drugs and natural supplements that clinicians and patients should be aware of. Some of these interactions result in clear contraindications while others may require a DOAC dose reduction as noted in package inserts. Some drugs/supplements may directly increase or decrease DOAC metabolism (inducers or inhibitors of CYP3A4 and/or P-gp), while others may increase bleed risk through their own antithrombotic activity.

- **CYP3A4 and/or P-gp Inducers decrease serum DOAC levels→increase thrombotic risk**
- **CYP3A4 and/or P-gp Inhibitors increase serum DOAC levels→increase bleed risk**
- **Consider the additive bleeding risk of drugs or natural supplements that have their own anticoagulant or antiplatelet effects.**

Practical management of DOAC drug-drug interactions

	Apixaban	**Dabigatran**	**Edoxaban**	**Rivaroxaban**
Combined P-gp and strong CYP3A4 inducers	avoid*	avoid*	avoid*	avoid*
P-gp inhibitors		avoid, if possible[2]	avoid, if possible[2]	
Combined P-gp and strong CYP3A4 inhibitors	avoid, or use reduced dose based on package insert if possible[2]			avoid, if possible[2]

*While U.S., Canadian, and European product labeling differ on specific recommendations, the use of P-gp/CYP3A4 inducers concomitantly with DOACs is generally not recommended due to the possibility of interaction resulting in reduced DOAC plasma concentrations.[1]

Examples of drugs with potential DOAC interactions[2]

P-gp/CYP3A4 inducers	Apalutamine Carbamazepine Fosphenytoin	Phenytoin Rifampin St John's Wort	
P-gp inhibitors	Amiodarone Azithromycin Clarithromycin Dronedarone Erythromycin	Fostamatinib Itraconazole Ketoconazole Lapatinib	Neratinib Ritonavir Verapamil HCV antivirals
Combined Pgp/moderate CYP3A4 inhibitors	Diltiazem Verapamil	Dronedarone	Erythormycin
Combined P-gp/strong CYP3A4 inhibitors	Itraconazole Ketoconzole Ombitasvir	Paritaprevir Ritonavir Telaprevir	

- **See package inserts of the various DOACs for information on specific interactions and any necessary dose reductions. Note that not all interactions are known or have been adequately studied. Even though a drug interaction is not listed specifically on package insert, it may be advisable to avoid that drug if other drugs with similar actions are listed.[1]**

- The European Heart Rhythm Association has published a summary table of various drugs and their effect on plasma concentrations of each DOAC.[3] (See tables 3, 4, and 5 at https://doi.org/10.1093/eurheartj/ehy136)

- It is recommended to us more than one source for investigating possible drug-drug interactions (eg Lexi-Comp + Micromedix) and to check sources often for updates.[1]

Examples of natural supplements with potential DOAC interactions*

P-gp Inducers[4]	P-gp Inhibitors[4]	CYP3A4 inducers[5]	CYP3A4 inhibitors[5,6]
Genipin	Apigenin	Echinacea	Bearberry
Licorice root	Berberine	Ginkgo	Bitter orange
Mango	Black pepper extract	Liquorice	Black cohosh
Quercetin	Capsaicin	Rooibos	Cat's claw
Scutellaria	Curcumin	**St. John's wort**	Cranberry
Soy milk	Fisetin		Echinacea
St. John's wort	Ginkgo		Feverfew
Sucralose	Grape juice		Garlic
	Green Tea		Gingko
	Honokiol		Ginseng
	Lemonin		Goldenseal
	Notoginsenoside R1		Grapefruit
	Rutin		Green Tea
	Soybean extract		Milk thistle
			Resveratrol
			Rhodiola
			Saw palmetto
			Silymarin
			Silibinin
			St. John's wort
			Turmeric
			Valerian

Examples of natural supplements with antiplatelet or anticoagulant properties[7,8,*]

Bromelain	Fish Oil	Green Tea	Selenium
Capsaicin	Garlic	L-arginine	Sweet birch bark
Chamomile	Ginger	Licorice	Taurine
Clove	Ginkgo biloba	Lycopene	Vitamin E
Coenzyme Q10	Ginseng	Magnesium	Willow bark
Dong quai	Glucosamine	Passion Flower	Wintergreen leaf
Feverfew	Grape seed extract	Policosanol	

***Note that many of these interactions are theoretical, have not been adequately studied, or may require consuming higher amounts than normally taken.**

- The Natural Medicines website has two helpful resources to identify potential interactions:
    1. Natural medicines database: https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements.aspx
    2. Interaction checker: https://naturalmedicines.therapeuticresearch.com/tools/interaction-checker.aspx

- If there is no clear indication for natural supplements that may affect DOAC serum concentration or that have antithrombotic effects, patients should be encouraged to discontinue them.

[1]Vazquez, S. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. Blood. 2018;132(21):2230-2239. DOI 10.1182/blood-2018-06-848747
[2]adapted from 2019 AC Forum presentation by Sara Vazquez, PharmD. Clinically Relevant Drug Interactions.
[3]Steffel J, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal (2018) 39, 1330–1393. doi:10.1093/eurheartj/ehy136
[4]Di Minno A, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. Blood Reviews. Volume 31, Issue 4, July 2017, Pages 193-203. https://doi.org/10.1016/j.blre.2017.02.001
[5] Williamson E, et al. Herbal Medicine Interactions. https://www.stonybrookmedicine.edu/sites/default/files/herbal_medicines_interactions-1.pdf
[6]Sprouse A, Van Breemen R. Pharmacokinetic Interactions between Drugs and Botanical Dietary Supplements. Drug Metab Dispos. 2016 Feb; 44(2): 162–171. doi: 10.1124/dmd.115.066902
[7] Samuels N. Herbal Remedies and Anticoagulant Therapy. Thromb Haemost. 2005. 93:3-7.
[8]Stanger M, et al. Anticoagulant activity of select dietary supplements. Nutrition Reviews. Vol. 70(2):107–117. doi:10.1111/j.1753-4887.2011.00444.x

Conversion from Warfarin (Coumadin®) to DOACs

Generic (Trade Name)	Instructions
Dabigatran (Pradaxa®)[1]	• Discontinue Warfarin (Coumadin®) and begin dabigatran when INR is below 2.0
Apixaban (Eliquis®)[2]	• Discontinue Warfarin (Coumadin®) and begin Apixaban (Eliquis®)when the INR is below 2.0
Rivaroxaban (Xarelto®)[3]	• Discontinue warfarin (Coumadin®) and begin Rivaroxaban (Xarelto®) when the INR is below 3.0 to avoid periods of inadequate anticoagulation (same instructions for A-fib and VTE).
Edoxaban (Savaysa)[4]	• Discontinue warfarin and begin edoxaban when the INR is ≤ 2.5.

Conversion from Parenteral Anticoagulants to DOACs

Generic (Trade Name)	Low Molecular Weight Heparin (LMWH)	Unfractionated Heparin
Dabigatran (Pradaxa®)[1]	Discontinue LMWH and start Pradaxa® 0-2 hours before the time of the next scheduled administration of LMWH	Stop the infusion and start Pradaxa® at the same time
Apixaban (Eliquis®)[2]	Discontinue LMWH and start Eliquis® at the time of the next scheduled administration of LMWH	Stop the infusion and start Eliquis® at the same time
Rivaroxaban (Xarelto®)[3]	Discontinue LMWH and start Xarelto® 0-2 hours before the time of the next scheduled evening administration of LMWH	Stop the infusion and start Xarelto® at the same time
Edoxaban (Savaysa)[4]	Discontinue LMWH and start Savaysa® at the time of the next scheduled administration of LMWH	Discontinue the infusion and start SAVAYSA® 4 hours later

[1]Pradaxa® package insert
[2] Eliquis® package insert
[3] Xarelto®package insert
[4] Savaysa® package insert

DOAC Patient Education Checklist

Completed	Topic
	What is anticoagulation and how do DOACs work?
	If on warfarin in the past, how are DOACs different from warfarin? *No INR monitoring required, no need for frequent dose adjustments, no Vit. K interactions, much quicker onset/offset of action, likely more expensive*
	Why does patient need to start taking a DOAC?
	What is the expected duration of treatment?
	How to take the DOAC? (dose, frequency, timing, with food?) *Xarelto® must be taken with evening meal (or largest meal of day). Pradaxa® can be taken with or without food but should be taken with a full glass of water. Pradaxa® cannot be crushed. Eliquis® can be taken with or without food. Savaysa® can be taken with our without food.*
	Why is it important not to skip doses? *Very rapid offset-increased risk for clots*
	What to do about missed doses?
	What are the signs/symptoms of bleeding or clotting to watch for? *Be sure to cover signs/symptoms of GI and intracranial bleeds.*
	What medications can increase risk of bleeding? *(ex. ASA, NSAIDs, other anticoagulants such as warfarin and heparin, SSRIs)*
	What are other drug-drug interactions to watch for? *P-gp and CYP3A4 inhibitors and inducers (ex. rifampin, carbamazepine, phenytoin, St. John's wort, dronedarone, ketoconazole, verapamil, amiodarone, clarithromycin, itraconazole, and ritonavir)*
	What kind of lab monitoring will need to be done and how often? *Ex. kidney function, liver function, CBC*
	What to do about taking DOACs around procedures/surgeries?
	How to store DOACs? *Pradaxa® must be kept in its original packaging*
	What are some other necessary lifestyle changes? *avoid contact sports, falls, pregnancy, etc.*
	When and how to notify clinic? • *s/sx of minor bleeding* • *medication changes* • *changes in health status, especially changes in kidney function or pregnancy* • *procedures in which DOAC will be held* • *changes in insurance or financial status that may impact ability to get refills*
	When to seek immediate medical attention? • *s/sx of serious or uncontrolled bleeding*

DOAC Patient Education Materials

Generic (Trade Name)	MAQI Toolkit Link	Drug Company Medication Guides
Dabigatran (Pradaxa®)	Link	Link
Apixaban (Eliquis®)	Link	Link
Rivaroxaban (Xarelto®)	Link	Link
Edoxaban (Savaysa®)	Link	Link

Routine Follow-up Checklist for DOAC Patients

	Interval	Comments
Assess compliance	Each visit	• Instruct patient to bring remaining medication: note and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes; smartphone applications, etc.) Dabigatran must remain in original packaging
Assess for thrombo-embolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • pulmonary circulation
Assess for bleeding	Each visit	• If minor (nuisance) bleeding, are preventive measures possible? (eg. PPI, saline nose spray, etc.). Motivate patient to diligently continue anticoagulation. • If bleeding with impact on quality-of-life or with significant risk, is prevention possible? (consider changing anticoagulant)
Assess for other side effects	Each visit	• Assess for link to DOAC and decide whether to continue, temporarily stop, or change to different anticoagulant
Assess for new co-medications	Each visit	• Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban) or dual P-gp/CYP3A4 inhibitors (if on rivaroxaban or apixaban) • Assess for other medications that may increase risk of bleeding such as anti-platelets **NOTE: DOAC dose adjustments may be required if patient starts taking interacting medications (see drug interaction table).**
Assess labs	Yearly Q 6 months Q 3 months As needed	• Hgb, renal and liver function • Renal function if CrCl 30-60 ml/min* or if on dabigatran and >75 years or fragile • Renal function if CrCl 15-30 ml/min* • If clinically indicated for conditions that may impact renal or hepatic function **NOTE: Declining renal function may require a DOAC dose adjustment (see FDA approved anticoagulants for dosing information).** **Edoxaban is contraindicated for atrial fibrillation in patients with CrCl >95.**

*CrCl determined using Cockcroft-Gault formula and actual body weight

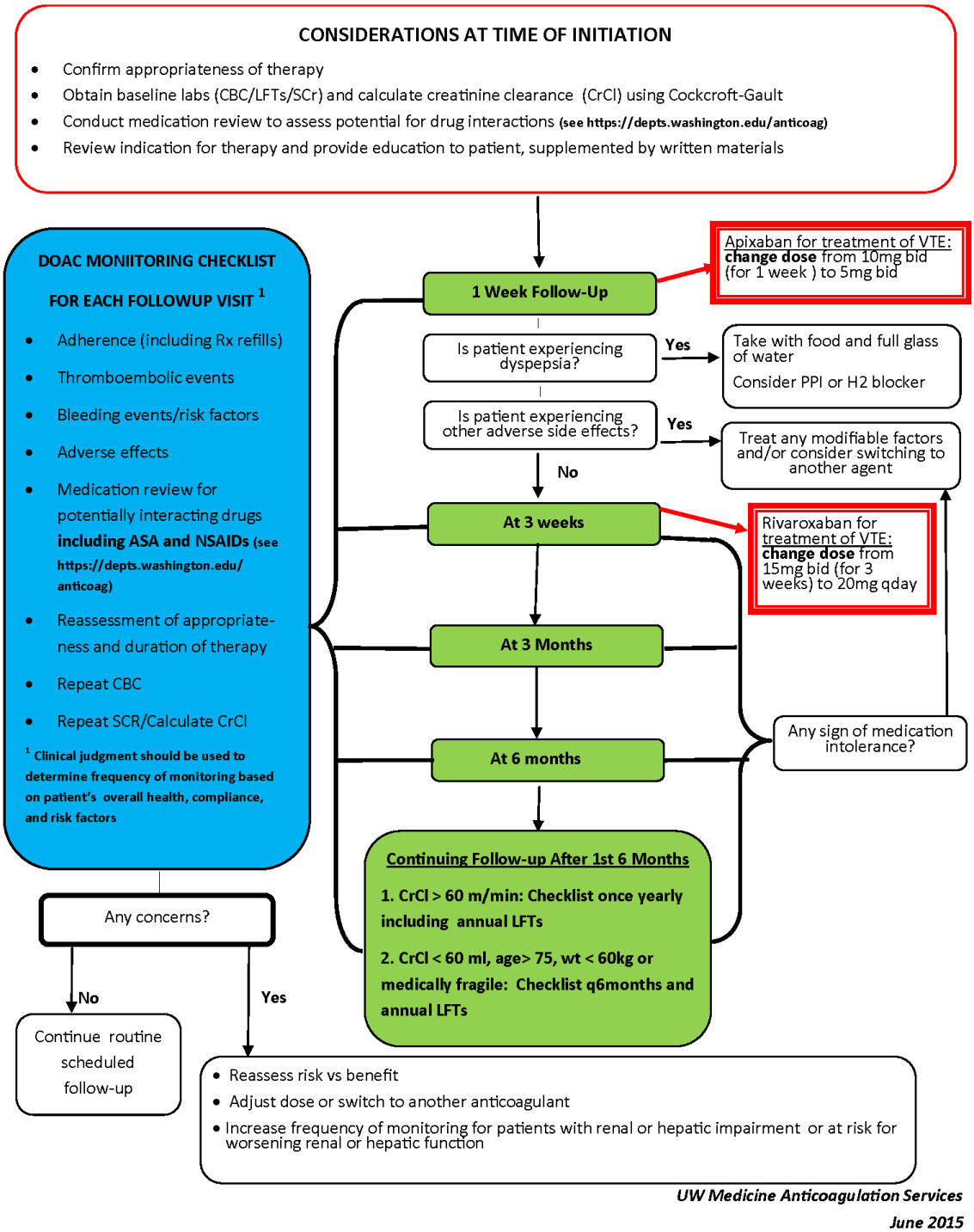
Adapted from: Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013. 15, 625-651. Doi: 10.1093/europace/eut083

DOAC Management Plan Flowchart

UW Medicine

MANAGEMENT PLAN FOLLOWING INITIATION OF DIRECT ORAL ANTICOAGULANTS (DOACs)

APIXABAN/DABIGATRAN/EDOXABAN/RIVAROXABAN



UW Medicine Anticoagulation Services

June 2015

Periprocedural Management of DOACs

Key points:

- Most patients do not need to have their DOAC interrupted for minimal bleed risk procedures.
- Bridging is rarely indicated in patients on a DOAC.
- Decisions on when to stop the DOAC prior to a procedure should be based on CrCl.
- Decisions about periprocedural management should only be made after assessment of patient and procedure-specific factors and discussions with the patient, management team, and proceduralist.

Color code for the following tables:

Do not interrupt	Interrupt but do not bridge

DOAC Interruption and Bridging in AF and VTE

Bleed Risk Evaluation		
Patient bleeding risk factors? Any one of these: • major bleeding or ICH < 3 months ago • platelet abnormality (including aspirin use) • prior bleed during previous bridging	**Procedure bleed risk** **(see next page for bleed risk of common procedures)**	**Whether or not to interrupt**
No	Minimal, No clinically important risk	Do Not interrupt DOAC (time procedure at DOAC trough level)
	Low	-Interrupt DOAC -Do not bridge
	Uncertain, intermediate, or high	-Interrupt DOAC -Do not bridge
Yes	Any bleed risk category	-Interrupt DOAC -Do not bridge

Adapted from:

-Doherty et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. DOI: 10.1016/j.jacc.2016.11.024

-Burnett et al. Guidance for the practical management of direct oral anticoagulants in VTE treatment. J Thromb Thrombolysis. 2016; 41: 206–232.doi: 10.1007/s11239-015-1310-7

-Spyropoulos et al. Periprocedural management of patients receiving a vitamin k antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. J Thromb Haemost. 2016 May;14(5):875-885. doi: 10.1111/jth.1330522016

Decisions about DOAC interruption should only be made after assessing patient- and procedure-specific factors and discussions with patient, management team, and proceduralist.

When to Interrupt and Restart DOAC (PAUSE Trial protocol[1])

DOAC	Procedure Bleed Risk (see next page for examples)	Peri-Procedural DOAC use*									
		Day -5	Day -4	Day -3	Day -2	Day -1	**Day of proc.**	Day +1	Day +2	Day +3	Day +4
Dabigatran (CrCl≥50 mL/min†)	High								**Resume day 2 or 3 (1st dose ≥48 hrs post-procedure)**		
	Low							**1st dose ≥24 hrs post-procedure**			
Dabigatran (CrCl<50 mL/min†)	High								**Resume day 2 or 3 (1st dose ≥48 hrs post-procedure)**		
	Low							**1st dose ≥24 hrs post-procedure**			
Rivaroxaban, apixaban, edoxaban‡	High								**Resume day 2 or 3 (1st dose ≥48 hrs post-procedure)**		
	Low							**1st dose ≥24 hrs post-procedure**			

[1]Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant (PAUSE Trial). JAMA Intern Med. Published online August 5, 2019. doi:10.1001/jamainternmed.2019.2431

Footnotes:

*Decisions about DOAC management should only be made after assessing patient and procedure-specific factors and discussions with patient, management team, and proceduralist. If possible, delay procedure until patient risk factors can be addressed. The PAUSE trial only included atrial fibrillation patients; however, it may be reasonable to extrapolate results to patients with other indications at similar thromboembolic risk. In addition, few patients had interventional pain procedures, so at this time, either the PAUSE protocol or the ASRA guidelines can be used in these patients. Lastly, patients on dabigatran or rivaroxaban with CrCl<30 and apixaban patients with CrCl<25 were excluded from the PAUSE trial.

†CrCl calculated using Cockroft-Gault and actual body weight.

‡Edoxaban was not included in the PAUSE Trial protocol but has a similar half-life as rivaroxaban and apixaban.

Surgery/Procedure Bleeding Risk Classification[1]

Bleed risk	Examples of surgeries/procedures	
High	• **Any surgery requiring neuraxial anesthesia** ○ neuraxial anesthesia/injection ○ epidural anesthesia/injection • **Major intracranial or neuraxial surgery** ○ brain cancer resection ○ laminectomy or neuraxial tumor resection ○ intracranial (subdural, epidural) bleed evacuation • **Major thoracic surgery** ○ lobectomy, pneumonectomy ○ esophagectomy • **Major cardiac surgery** ○ coronary artery bypass ○ valve replacement or repair • **Major vascular surgery** ○ aortic aneurysm repair ○ aortobifemoral bypass, popliteal bypass ○ carotid endarterectomy • **Major orthopedic surgery** ○ hip arthroplasty or hip fracture repair ○ knee arthroplasty or tibial osteotomy ○ shoulder arthroplasty ○ metatarsal osteotomy	• **Major abdominopelvic surgery** ○ hepatobiliary cancer resection ○ pancreatic cancer or pseudocyst resection ○ colorectal and gastric cancer resection ○ diverticular disease resection ○ inflammatory bowel disease resection ○ renal cancer resection ○ bladder cancer resection ○ endometrial cancer resection ○ ovarian cancer resection ○ radical prostatectomy • **Other major cancer or reconstructive surgery** ○ head and neck cancer surgery reconstructive facial, abdominal, limb surgery
Low/ minimal*	• **Gastrointestinal procedures** ○ colonoscopy ○ gastroscopy ○ sigmoidoscopy ○ endoscopic retrograde pancreaticocholangiography ○ capsule endoscopy ○ push enteroscopy ○ Barrett's esophagus ablation • **Cardiac procedures** ○ permanent pacemaker implantation or battery change ○ internal cardiac defibrillator implantation or battery change ○ arterioventricular node ablation ○ coronary artery angiography (radial approach)	• **Dental procedures** ○ tooth extraction (up to two extractions)*[2] ○ periodontal surgery*[2] ○ endodontic (root canal) procedure • **Skin procedures** ○ skin biopsy*[2] ○ superficial surgeries*[2] • **Eye procedures** ○ Cataract or glaucoma surgeries*[2]

[1]Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant (Appendix 1). JAMA Intern Med. Published online August 5, 2019. doi:10.1001/jamainternmed.2019.2431

[2]Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016; 41: 187–205. doi: 10.1007/s11239-015-1319-y

DOAC Discontinuation and Resumption around Interventional Pain Procedures*[1]

Drug	Discontinue prior to procedure	Resume after procedure
Dabigatran (Pradaxa®)	4-5 days 6 days if end-stage renal disease	24 hours
Apixaban (Eliquis®)	3-5 days	24 hours
Rivaroxaban (Xarelto®)	3 days	24 hours

***** These recommendations are for intermediate and high-risk interventional pain procedures. For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide treatment decision. A 2 half-life interval may be considered for low-risk procedures. See table below for risk stratification.

High-Risk Procedures	Intermediate-Risk Procedures**	Low-Risk Procedures**
• SCS trial and implant • Intrathecal catheter and pump implant • Vertebral augmentation (vertebroplasty and kyphoplasty) • Epiduroscopy and epidural decompression	• Interlaminar ESIs (C, T, L, S) • Transforaminal ESIs (C, T, L, S) • Facet MBNB and RFA (C, T, L) • Paravertebral block (C, T, L) • Intradiscal procedures (C, T, L) • Sympathetic blocks (stellate, thoracic, splanchnic, celiac, lumbar, hypogastric) • Peripheral nerve stimulation trial and implant • Pocket revision and IPG/ITP replacement	• Peripheral nerve blocks • Peripheral joints and musculoskeletal injections • Trigger point injections including piriformis injection • Sacroiliac joint injection and sacral lateral branch blocks

C indicates cervical; L, lumbar; MBNB, medial branch nerve block; RFA, radiofrequency ablation; S, sacral; T, thoracic.

**Patients with high risk for bleeding undergoing low- or intermediate-risk procedures should be treated as intermediate or high risk, respectively. Patients with high risk for bleeding may include old age, history of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disease.

[1]Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications: Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Regional Anesthesia & Pain Medicine: May/June 2015 - Volume 40 - Issue 3 - p 182–212. doi: 10.1097/AAP.0000000000000223

Measuring Anticoagulation Effect of DOACs[1]

Test	Availability*	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
PT	Widely available	Not useful	Not useful	Useful for **qualitative** assessment Normal PT probably excludes excess levels[2]	Useful for **qualitative** assessment Normal PT probably excludes excess levels[2]
dPT	Not widely available	Data not available	Data not available		Data not available
mPT	Not widely available	Useful for **qualitative** assessment	Data not available		Data not available
APTT	Widely available	Not useful	Useful for **qualitative** assessment. Normal APTT probably excludes excess drug levels.[2]		Not useful
TT	Widely available, but turnaround time may vary	Not useful	Useful for **qualitative** assessment but may be abnormal even at clinically insignificant concentrations. Normal TT excludes clinically relevant levels.[2]		Not useful
dTT/HEMOCLOT	Not widely available	Not useful	Useful for **quantitative** assessment		Not useful
Anti-FXa assay	Widely available, but turnaround time may vary. Assays must be set up for each Xa drug. Assays for heparin or LMWH cannot be used.	Useful for **quantitative** assessment Normal result excludes clinically relevant levels[2]	No effect	Useful for **quantitative** assessment Normal result excludes clinically relevant levels[2]	Useful for **quantitative** assessment Normal result excludes clinically relevant levels[2]
Anti-FIIa assay	Not widely available	No effect	Useful for **quantitative** assessment		No effect
Ecarin anti-FIIa assay	Not widely available	No effect	Useful for **quantitative** assessment		No effect

APTT, activated partial thromboplastin time; dPT, dilute prothrombin time; dTT, dilute thrombin time; mPT, modified prothrombin time; PT, prothrombin time; TT, thrombin time.

Qualitative=assess if drug is present, Quantitative=assess drug concentration

*Assays or reagents may not be approved for patient care purposes; check with your local laboratories before ordering the test.

[1]Adapted from: Garcia D. Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. J Thromb Haemost. 11: 245–252. DOI: 10.1111/jth.12096

[2]Cuker et al. J Am Coll Cardiol 2014;64:1128. doi:10.1016/j.jacc.2014.05.065

DOAC Bleeding Management (v2 5/17/2019)

Determine Bleed Severity

- Determining bleed severity is a key step in making treatment decisions.
- Bleeds can be classified into major and non-major based on several clinical factors.
- **If one or more of the following factors apply, the bleed should be considered major.**

For additional information , visit www.anticoagulationtoolkit.org

Bleeding in critical site (examples below)		Hemodynamic instability (examples below)		Overt bleeding with either:
•Central nervous system bleeds (intracranial, spinal, intraocular)	•Intra-abdominal	•Elevated heart rate	•SBP <90 mm Hg	•Hemoglobin drop of ≥2 g/dL or
•Pericardial tamponade	•Retroperitoneal	•Decrease in SBP >40 mm Hg	•Orthostatic blood pressure changes	•Administration of ≥2 U of packed RBCs
•Airway, including posterior epistaxis	•Intra-articular	•Mean arterial pressure (intra-arterial)<65 mm Hg	•Urine output <0.5 mL/kg/hr	
•Hemothorax	•Intra-muscular			

Assess for Clinically Relevant Drug Levels

- If last dose taken at least 24 hr ago in patients with normal renal function, drug levels probably not clinically relevant.[1]
- If patient taking dabigatran, a TT can be used to rule out clinically relevant drug levels. Specialized tests can quantify drug levels.
- If apixaban, edoxaban, rivaroxaban, or betrixaban, anti-Xa is the preferred test and can be used to rule out relevant drug levels or quantify levels.
- Don't wait for results before administering reversal agents in life-threatening bleeds[1]

	Specialized Test	Drug Level Interpretation	General Test	Drug Level Interpretation
Dabigatran	dTT, ECT, ECA	Normal: not clinically relevant Results correlate with drug level	TT	Normal: not clinically relevant Prolonged: may/may not be clinically relevant
			aPTT	Normal: likely indicates lower drug level but can't exclude drug presence Prolonged: clinically relevant
Apixaban Betrixaban Edoxaban Rivaroxaban	Anti-Xa	Absent activity: not clinically relevant Results correlate with drug level (if calibrated for specific DOAC)	PT	Normal: does not exclude clinically relevant levels Prolonged: clinically relevant levels

Anti-Xa= anti-factor Xa; aPTT= activated partial thromboplastin time; dTT= dilute thrombin time; ECA= ecarin chromogenic assay; ECT= ecarin clotting time; PT= prothrombin time; TT= thrombin time

Manage Bleeding

All bleeds	Major Bleeds		Minor Bleeds	
	Critical site or life threatening	NOT critical site or life threatening	More serious minor bleeds†	Less serious minor bleeds
•Provide local therapy/ manual compression •Assess for and manage comorbidities contributing to the bleed*	•Stop DOAC •Provide supportive care • Secure airway and large-bore IV access • Aggressive volume resuscitation (NS or LR) • Correct hypothermia and acidosis • Early involvement of other services (eg. surgery) • RBC transfusions to achieve Hgb ≥7 g/dL (≥8 g/dL if pt has CAD) • Platelet transfusion to achieve counts >50 x 10^9/L • Cryoprecipitate transfusion to maintain fibrinogen >100 mg/dL •Stop any antiplatelets •Consider surgical/procedural management •**Administer reversal agent**	•Stop DOAC •Provide supportive care • Secure airway and large-bore IV access • Aggressive volume resuscitation (NS or LR) • Correct hypothermia and acidosis • Early involvement of other services (eg. surgery) • RBC transfusions to achieve Hgb ≥7 g/dL (≥8 g/dL if pt has CAD) • Platelet transfusion to achieve counts >50 x 10^9/L • Cryoprecipitate transfusion to maintain fibrinogen >100 mg/dL •Stop any antiplatelets •Consider surgical/procedural management •**Administer reversal agent if above not effective**	•Stop DOAC •Provide supportive care •Stop any antiplatelets •Consider surgical/procedural management	•Consider continuing DOAC if appropriate indication •Assess risk/ benefits of stopping any antiplatelets •Verify that DOAC dosing is correct and patient taking as directed

*eg. renal dysfunction, liver disease, thrombocytopenia; † Patient requires hospitalization, transfusion, or procedural intervention

DOAC Reversal

Dabigatran	Apixaban, Betrixaban, Edoxaban, Rivaroxaban
•Administer 5 g idarucizumab IV (two separate 2.5 g/50 mL vials) •If bleeding persists and there is laboratory evidence of persistent dabigatran effect after 12-24 hours, a second dose may be reasonable. •If idarucizumab not available, administer aPCC (4F-PCC if aPCC not available) 50 units/kg IV (refer to package insert for max units)[4] •Activated charcoal (50 g) can be considered if ingested within 2-4 hours •Hemodialysis could be considered if drug level is high, especially in patients with poor renal function. •Fresh-frozen plasma is not recommended for DOAC reversal	•Apix/Riva: Admin ANDEXXA per package insert •Betrix/Edox: Admin off-label ANDEXXA* (800 mg at 30 mg/min then 8 mg/min for up to 120 min)[4] •Admin 4F-PCC 50 units/kg IV(if ANDEXXA not avail/used) •If 4F-PCC is not available, consider aPCC 50 units/kg IV (refer to prescribing information for max units) •Consider Activated charcoal (50 g) if ingested <24 hrs •Fresh-frozen plasma is not recommended for DOAC reversal

4F-PCC= four-factor prothrombin complex; aPCC= activated prothrombin complex concentrate; *Off-label ANDEXXA OR 4F-PCC suggested for Betrix/Edox[4]

Restart DOAC

- Most patients benefit from restarting anticoagulation after bleeds, but make sure there is still a valid indication.
  - eg. CHA_2DS_2-VASc is ≥ 1 (in AF), length of treatment hasn't been reached (for VTE treatment or post-op prophylaxis).
- Base plan on the balance between bleeding and thromboembolic risks and discussions with other appropriate practitioners (eg. surgeons), the patient, and caregivers.
- Timing of restart: Delay restart if bleeding occurred in a critical site or if patient has a high risk for re-bleeding. Patients with GI bleed should typically wait at least 7-14 days. Patients with intracranial hemorrhage (and no mechanical valve) should wait at least 4 weeks.[2] In patients with moderate to high risk of recurrent VTE without high risk of recurrent bleeding, ASH suggests resuming anticoagulation within 90 days rather than discontinuation.[3]
- Make sure dose is correct based on age, renal function, weight, and indication and address any reversible risk factors such as interacting medications or unnecessary antiplatelet therapy.

One-Page PDF download is available at: https://anticoagulationtoolkit.org/providers

References:

- Unless otherwise referenced, document adapted from: 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. JACC, Volume 70, Issue 24, 19 December 2017, Pages 3042-3067, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2017.09.1085

[1]Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz J. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016 Mar;14(3):623-7. doi: 10.1111/jth.13227. Epub 2016 Feb 17.

[2]Hemphill, et al. 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke. 2015;46:000-000. DOI: 10.1161/STR.0000000000000069

[3]Witt WM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. DOI 10.1182/ bloodadvances.2018024893

[4]Cuker A, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol.2019;94:697–709. doi.org/10.1002/ajh.25475

DOAC Reversal Options

	Apixaban	Betrixaban	Dabigatran	Edoxaban	Rivaroxaban
Drug-Specific reversal agent	Andexxa®	Off-label Andexxa®*	Praxbind® (idarucizumab)	Off-label Andexxa®*	Andexxa®
Oral activated charcoal[2]	Can be considered‡	Can be considered‡	Yes‡	Can be considered‡	Can be considered‡
Hemodialysis[2]	No	No	Can be considered	No	No
Hemoperfusion with activated charcoal[2]	Unclear	Unclear	Can be considered	Unclear	Unclear
FFP[2]	No	No	No	No	No
Activated factor VIIa[2]	Unclear	Unclear	Unclear	Unclear	Unclear
Activated prothrombin complex concentrate (APCC)	Yes[3]	Yes[2]	Yes[1]	Yes[3]	Yes[3]
3-factor PCC	Unclear	Unclear	Unclear	Unclear	Unclear
4-factor PCC	Yes[1]	Yes[1]	Yes[2]	Yes[1]	Yes[1]

* Suggested off-label dose is an 800 mg bolus given at 30 mg/min followed by a continuous infusion of 8 mg/min for up to 120 min (AC Forum guidance statement[1])

‡If DOAC taken within past 2 hours.

[1] Cuker A, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol.2019;94:697–709. doi.org/10.1002/ajh.25475

[2] Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation Europace (2015) 17, 1467–1507. doi:10.1093/europace/euv309

[3] 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. JACC, Volume 70, Issue 24, 19 December 2017, Pages 3042-3067, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2017.09.1085

Drug Specific DOAC Reversal Agents

	DOAC(s) reversed	Indication(s)	Instructions	Warnings/Precautions
Praxbind® (idarucizumab)[1]	dabigatran	• For emergency surgery/urgent procedures • Life-threatening or uncontrolled bleeding	• Administer 5 g intravenously, provided as two separate 2.5 g/50 mL vials. • If administering through an existing intravenous line, flush with 0.9% Sodium Chloride Injection, USP solution prior to infusion. • No other infusion should be administered in parallel via the same intravenous access. • An additional 5 g dose may be administered after 12 to 24 hours if patient has reoccurrence of clinically relevant bleeding and elevated coagulation parameters (eg. aPTT, ECT)[2]	• Resume anticoagulation as soon as medically appropriate to reduce risk of thromboembolism. Dabigatran can be resumed after 24 hours • Idarucizumab contains 4g of sorbitol. In patients with hereditary fructose intolerance, consider the combined daily metabolic load of sorbitol/fructose from all sources, including idarucizumab and other drugs containing sorbitol to reduce risk of serious adverse reactions.
ANDEXXA® (coagulation factor Xa (recombinant), inactivated-zhzo)[3]	Apixaban, rivaroxaban **Use for reversal of edoxaban or betrixaban would be off-label**	• Life-threatening or uncontrolled bleeding	▪ See table below See package insert for full reconstitution information.[3]	• Thromboembolic events were observed in 18% of trial patients within 30 days of ANDEXXA administration. Monitor patients for s/sx of thromboembolic events and resume anticoagulation therapy as soon as medically appropriate.

[1]http://us.boehringer-ingelheim.com/content/dam/internet/opu/us_EN/documents/Media_Press_Releases/2015/Praxbind.pdf
[2] The safety and effectiveness of repeat treatment with idarucizumab have not been established.
[3]https://www.portola.com/wp-content/uploads/Andexxa-prescribing-information-pdf.pdf

ANDEXXA® Dosing

ANDEXXA® Dosing: Determine if patient requires low dose Andexxa or high dose Andexxa based upon factor Xa inhibitor being reversed, and timing of last dose

Factor Xa Inhibitor	Last dose	Timing of last dose before Andexxa initiation	
		< 8 hours or Unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Andexxa Low Dose	Andexxa Low Dose
	>10 mg / Unknown	Andexxa High Dose	
Apixaban	≤ 5 mg	Andexxa Low Dose	
	>5 mg / Unknown	Andexxa High Dose	

Regimens:		
Dose	**Initial IV Bolus**	**Followed by IV infusion**
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

Conversion from DOACs to other anticoagulants

	Parenteral Anticoagulants	Warfarin
Dabigatran (Pradaxa®)[1]	Discontinue Pradaxa® and start parenteral anticoagulant in 12 hours (CrCl ≥30 mL/min*) or 24 hours (CrCl <30 mL/min*)	• Adjust the starting time of warfarin based on creatinine clearance as follows: ○ For CrCl ≥50 mL/min*, start warfarin 3 days before discontinuing dabigatran. ○ For CrCl 30-50 mL/min*, start warfarin 2 days before discontinuing dabigatran. ○ For CrCl 15-30 mL/min*, start warfarin 1 day before discontinuing dabigatran. ○ For CrCl <15 mL/min*, no recommendations can be made. • Because dabigatran can increase INR, the INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days
Apixaban (Eliquis®)[2]	Discontinue Eliquis® and start parenteral anticoagulant at the next scheduled dose of Eliquis®	• Apixaban affects INR, so initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue apixaban and begin warfarin with a concomitant parenteral anticoagulant when the next dose of apixaban would have been due, discontinuing the parenteral anticoagulant when INR reaches goal range.
Rivaroxaban (Xarelto®)[3]	Discontinue Xarelto® and start parenteral anticoagulant at the next scheduled dose of Xarelto®	• No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. • Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. • One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.
Edoxaban (Savaysa)[4]	Discontinue Savaysa® and start parenteral anticoagulant at the next scheduled dose of Savaysa ®	• For patients on 60 mg of edoxaban, reduce dose to 30 mg and begin warfarin concomitantly. • For patients on 30 mg of edoxaban, reduce dose to 15 mg and begin warfarin concomitantly. • During transition, INR should be done at least weekly just prior to daily dose of edoxaban (to minimize influence on INR). • Discontinue edoxaban once a stable INR ≥ 2.0 is achieved.

*CrCl determined using Cockcroft-Gault formula and actual body weight

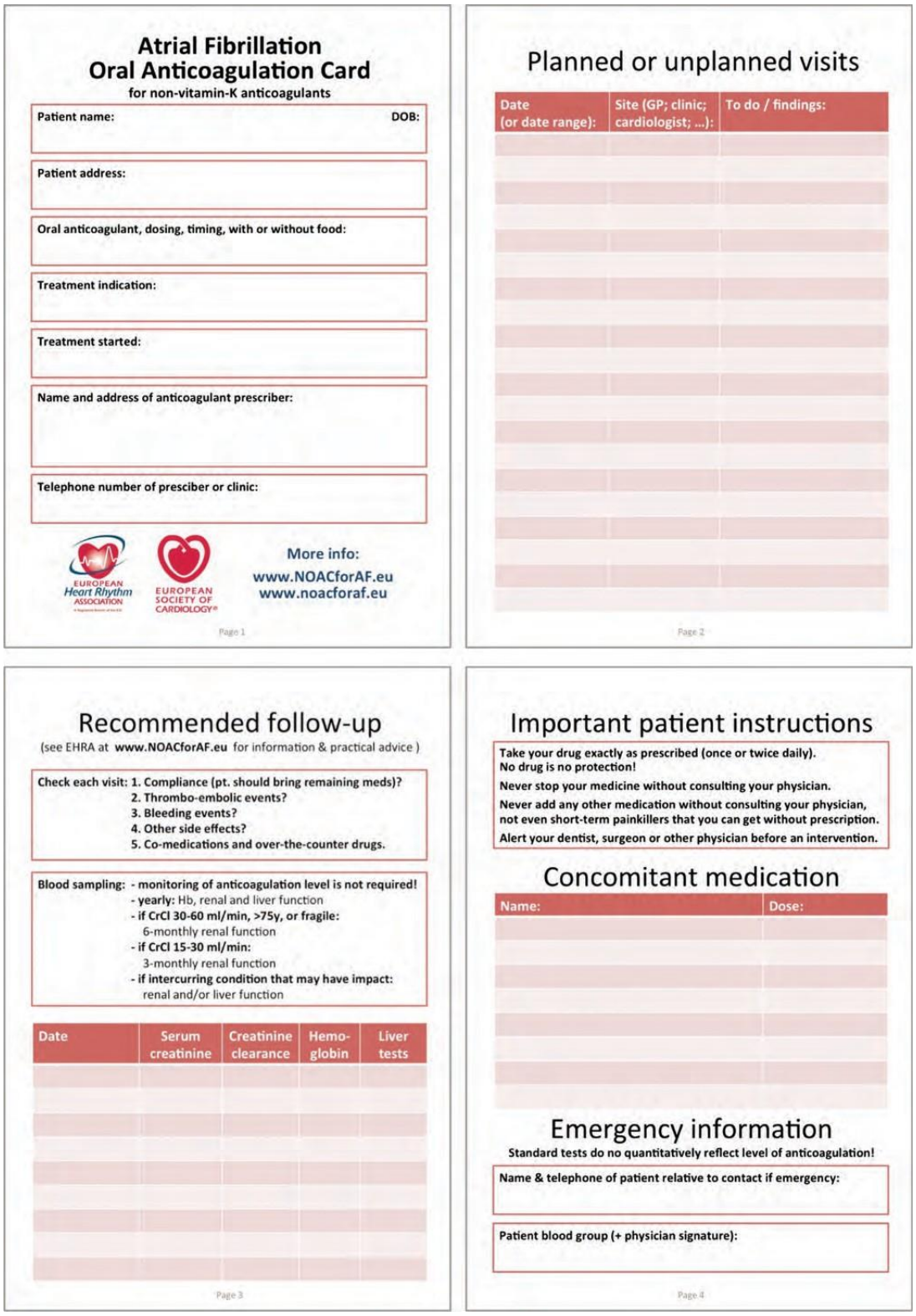
[1] Pradaxa® package insert

[2] Eliquis® package insert

[3] Xarelto®package insert

[4] Savaysa® package insert

DOAC Patient Card Proposed by the European Heart Rhythm Association



Atrial Fibrillation Oral Anticoagulation Card

for non-vitamin-K anticoagulants

Patient name: DOB:

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication:

Treatment started:

Name and address of anticoagulant prescriber:

Telephone number of presciber or clinic:

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

More info:
www.NOACforAF.eu
www.noacforaf.eu

Page 1

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; ...):	To do / findings:

Page 2

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit: 1. Compliance (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling: - monitoring of anticoagulation level is not required!
- **yearly:** Hb, renal and liver function
- **if CrCl 30-60 ml/min, >75y, or fragile:**
  6-monthly renal function
- **if CrCl 15-30 ml/min:**
  3-monthly renal function
- **if intercurring condition that may have impact:**
  renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Page 3

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do no quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact if emergency:

Patient blood group (+ physician signature):

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To print patient cards, go to: http://www.escardio.org/communities/EHRA/publications/novel-oral-anticoagulants-for-atrial-fibrillation/Documents/English-EHRA-DOAC-card-A7.pdf

Warfarin Adverse Event Analysis Form

This form can be used to help identify root causes of adverse events and develop action plans to prevent similar events. Using this form ensures that information is collected and analyzed in a systematic way, making it more likely that a root cause is identified and proper prevention strategies put in place.

Patient Information

Pt. Name: **Age:**	**Warfarin start date:** / / Target range: -
Indication: ☐A-fib/A-flutter ☐DVT ☐PE ☐CM/CHF ☐Valve Replacement/Repair ☐MI/LV Thrombus ☐Hypercoagulable condition ☐Other:	**If indication was DVT or PE, type:** ☐Provoked ☐Unprovoked ☐Recurrent
Planned length of treatment: ☐1 month ☐indefinitely ☐3 months ☐other_____ ☐6 months ☐unknown ☐1 year	**Anticoagulation history:** ☐Prior bleeds ☐Prior thrombotic event ☐Hx of non-adherence with warfarin schedule ☐Hx of non-adherence with INR draws

Adverse Event Information

Date of AE:	**INR at time of AE:**	**Date of INR:** / /
Possible reason(s) for out of range INR:		

Type of AE	Location	Severity
☐Bleed	☐Intracranial ☐GI ☐GU ☐Other:_____	☐Minor ☐Major ☐Life-threatening ☐Fatal
☐Clot	☐CVA ☐DVT ☐Pulmonary Embolism ☐Peripheral Embolism ☐Other:_____	

Patient Factors	
Concurrent medications	☐Aspirin (81mg) ☐Aspirin (325mg) ☐Clopidogrel ☐Prasugrel ☐Ticagrelor ☐Other anti-platelet:_____ ☐LMWH ☐Fondaparinux ☐Other notable medications:_____
HAS-BLED co-morbidities (if bleeding event)	☐HTN(1) ☐Abnormal renal function(1) ☐Abnormal liver function(1) ☐Age≥65*(1) ☐H/o Stroke(1) ☐H/o bleeding (1) ☐Labile INRs (TTR < 60%)(1)* ☐Concomitant antiplatelet or NSAID use(1) ☐Concomitant alcohol use(1) HAS-BLED score:_____ (A score of 3 or more indicates increased one year bleed risk on anticoagulation sufficient to justify caution or more regular review) * If TTR is unavailable, check labile INRs if patient's INRs were generally unstable prior to event.

CHA2DS2-VASc co-morbidities (if embolic stroke event in A-fib patient)	☐CHF(1) ☐HTN(1) ☐Age ≥75(2) ☐Age 65-74(1) ☐H/o Stroke/TIA(2) ☐H/o vascular disease (MI, PAD, aortic plaque)(1) ☐Diabetes Mellitus(1) ☐Female (1) CHA2DS2-VASc score:_____
Clotting risk factors (DVT/PE)	☐Prior DVT/PE ☐hypercoagulable state ☐Cancer ☐ Obesity ☐ CHF ☐Surgery within past 6 weeks ☐ Lower extremity injury/casting past 6 weeks ☐Childbirth within past 6 weeks ☐ Oral contraceptive use ☐ Smoking ☐ Age>60 ☐ Prolonged bedrest or periods of sitting ☐other clotting risk factor(s):_____
Other possible contributing patient factors	☐Cognitive disorder ☐Unstable living conditions ☐H/O non-compliance with dosage ☐H/O non-compliance with blood draws ☐Other:_____

Other pertinent information found during chart review

Information from last few anticoagulation related interactions with patient prior to AE
Date of interaction: _____/_____/_____ Weekly warfarin dose: _____ INR:_____ Date : ____/_____/_____ Management for INR: ☐No weekly dose change ☐Weekly dose change to:_____ ☐One-time dose increase: _____ ☐One-time dose decrease:_____ ☐Dietary Vit. K recommendation:_____ Next scheduled INR: ___/___/_____ Other information from interaction:
Date of interaction: _____/_____/_____ Weekly warfarin dose: _____ INR:_____ Date : ____/_____/_____ Management for INR: ☐No weekly dose change ☐Weekly dose change to:_____ ☐One-time dose increase: _____ ☐One-time dose decrease:_____ ☐Dietary Vit. K recommendation:_____ Next scheduled INR: ___/___/_____ Other information from interaction:

Date of interaction: _____/_____/_____ Weekly warfarin dose: _____ INR:_____ Date : ____/_____/_____
Management for INR: ☐No weekly dose change
☐Weekly dose change to:_____
☐One-time dose increase: _____
☐One-time dose decrease:_____
☐Dietary Vit. K recommendation:_____
Next scheduled INR: ___/___/_____
Other information from interaction:

Root Cause Analysis

When doing the root cause analysis, focus on finding process/system/environmental vulnerabilities that, if "fixed" would have prevented the event. If a human error is involved, try to identify any system, process, or environmental factors that contributed to the error.

Start by identifying the High Level cause for the event:

☐ High INR
☐ Low INR
☐ Co-morbid conditions
☐ unknown
☐ Other:_____

Then, use the categories below to brainstorm the most likely factor(s) that contributed to the event.

Category	Description/Examples	Contributing factors
Patient-Specific factors	Pre-existing or co-morbid medical conditions, concurrent medications, physical limitations, language and communication barriers, cultural issues, or social support	_____ _____ _____
Policies/Procedures/ Protocol issues	Are they complete, updated, and accurate? Did they cover this situation adequately? Were they used properly in this situation?	_____ _____ _____
Human resource issues	Is staffing adequate? Is staff properly trained? Does staff have proper supervision?	_____ _____ _____
Communication issues	Was there a communication issue between staff, the patient, or providers that contributed?	_____ _____ _____

Information management issue	Was necessary information available, accurate, and complete?	_____ _____ _____
Information Technology/ Equipment	Was there a technical or equipment issue that contributed?	_____ _____ _____
Other contributing factors	_____ _____ _____ _____ _____	

From the list of contributing factors, pick the most likely contributing factor(s) that <u>can be controlled and addressed</u> and try to drill down to the root cause. Perform a "5 Whys" to help drill down to the root cause. A root cause is a factor that, if removed, would have prevented the event from happening.

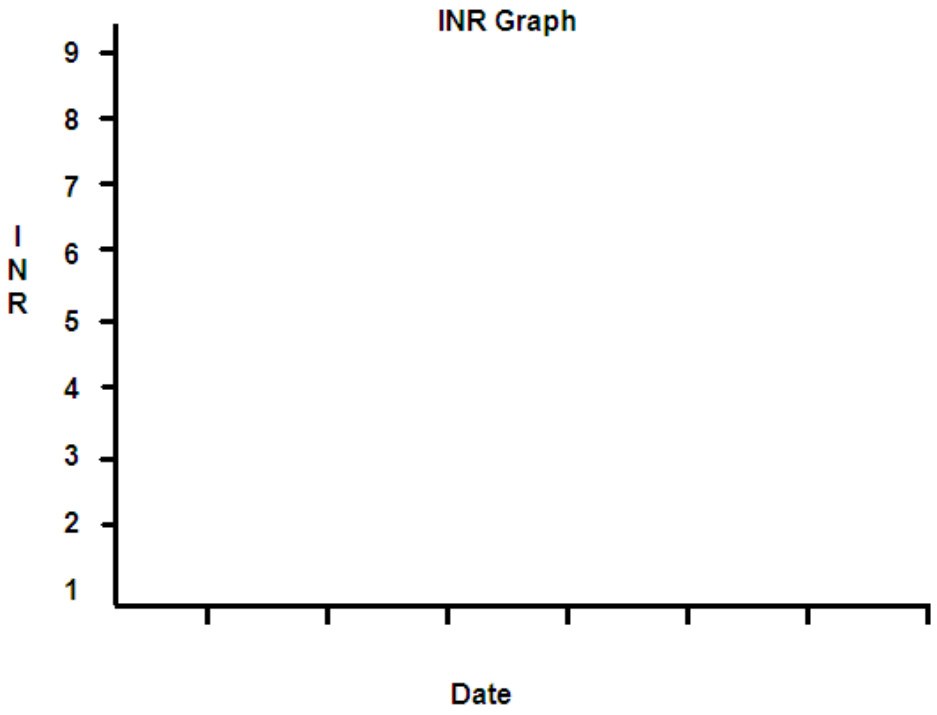
Drill down to root-cause • If possible, keep asking "why" until you feel you have identified the root cause for the AE. • Use cause and effect (fishbone) diagrams, if necessary. Example: 1. Why was her INR high?..She took more than prescribed. 2. Why did she take more than prescribed?....She didn't get the message to decrease dose. 3. Why didn't she get the message to decrease dose?....ACS was leaving a message on the wrong number. 4. Why was the ACS leaving a message at the wrong number?....New staff member was looking at the wrong number in the record system. 5. Why was the staff member looking at the wrong number?....**She wasn't trained properly on the new system (root cause).**	1. Why _____? Answer:_____ 2. Why _____? Answer:_____ 3. Why _____? Answer:_____ 4. Why _____? Answer:_____ 5. Why _____? Answer:_____ **Root cause(s): _____** **_____**
Root cause category (for tracking purposes, if needed)	☐Patient-Specific factors ☐Policies/Procedures/Protocols ☐Human Resource ☐Communication ☐Information Management ☐Information technology/equipment ☐Other _____

Action Plan

Is this an isolated incident or is this part of a larger trend?	☐Isolated incident ☐Part of a larger trend
What action(s) will be taken to address this root cause to prevent it from happening again?	☐No action clearly needed at this time. Will continue to monitor for trends indicating a need for system/process change. ☐Process/Workflow improvement: _____ _____ ☐Structure/Staffing change:_____ _____ ☐Protocol change:_____ _____ ☐Communication change:_____ _____ ☐Staff education:_____ _____ ☐Other change:_____ _____
Follow-up on plan	Date:_____/_____/_____ Status: _____ _____ _____ _____ _____ Date:_____/_____/_____ Status: _____ _____ _____ _____ _____ Date:_____/_____/_____ Status: _____ _____ _____ _____ _____

Timeline and INR Graph (if needed)

Date				
INR				
What happened?				



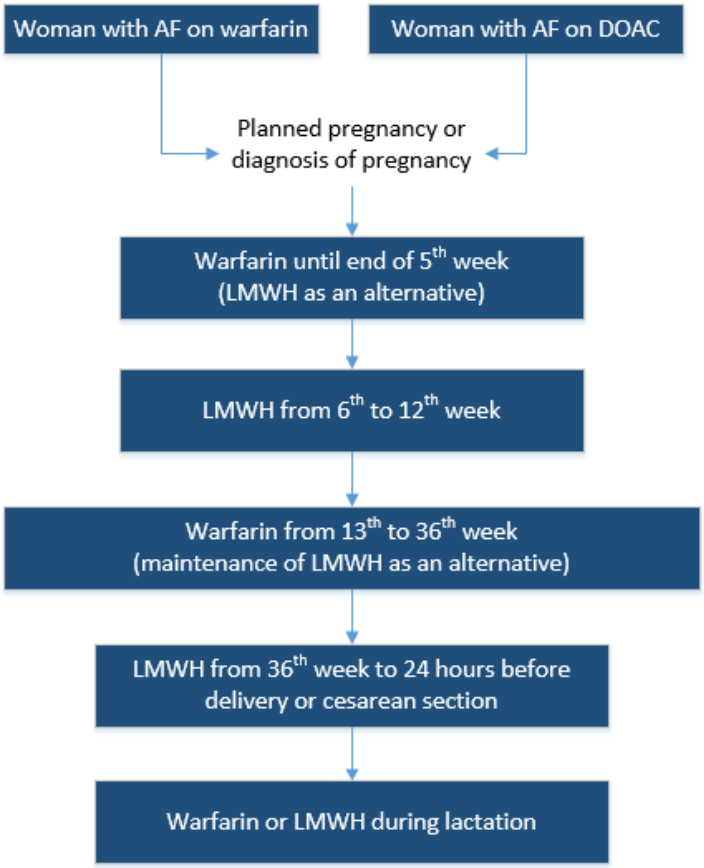
Anticoagulation in Special Populations

Atrial Fibrillation in pregnancy and breastfeeding[1]

- There is general consensus that in order to minimize the risk of warfarin embryopathy, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation because of the high risk of fetal defects, especially if the dose of warfarin is higher than 5 mg per day.

- For women receiving oral anticoagulant (OAC) for prevention of stroke/TE in AF who become pregnant, CHEST guidelines suggest discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL), especially in patients with a warfarin dose required of > 5 mg/day (or phenprocoumon > 3 mg/day or acenocoumarol > 2 mg/day) (Ungraded consensus-based statement).

- If patient was switched back to OAC after 12 weeks, OAC should then be replaced by adjusted-dose LMWH (target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL) in the 36th week of gestation (Ungraded consensus-based statement).



- For women on treatment with long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, CHEST guidelines suggest performing frequent pregnancy tests and

use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Ungraded consensus-based statement).

- For pregnant women, CHEST guidelines suggest avoiding the use of DOACs (Ungraded consensus-based statement).

- For lactating women using warfarin, acenocoumarol, or UFH who wish to breast-feed, CHEST guidelines suggest continuing the use of warfarin, acenocoumarol, LMWH, or UFH (Ungraded consensus-based statement)

- For breast-feeding women, CHEST guidelines suggest alternative anticoagulants rather than DOACs (Ungraded consensus-based statement).

[1]Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

VTE in pregnancy and breastfeeding

Question	Recommendation[1]
Treatment of acute VTE and superficial vein thrombosis in pregnancy	
Do you anticoagulate in acute VTE?	Antithrombotic therapy is **recommended**.
Which anticoagulant should be used?	Low-molecular-weight heparin (LMWH) is recommended over unfractionated heparin (UFH) or any oral anticoagulant.
Do you use once-per-day or twice-per-day LMWH dosing in acute VTE?	Either dosing regimen is acceptable. (note: These guidelines do not specify if pre-pregnancy weight or weight at time of diagnosis of VTE should be used for dosing)
Do you anticoagulate in acute superficial vein thrombosis?	Anticoagulation with LMWH is **suggested**. (note: The guideline committee did not reach agreement on LMWH dosing, but there was consensus that patients should be treated for the remainder of the pregnancy and 6 weeks post-partum.)
Do patients receiving therapeutic LMWH need routine monitoring of anti-FXa levels to guide dosing?	Routine monitoring of anti-FXa levels to guide dosing is **not suggested**.
Do patients with low-risk acute VTE require a hospital admission?	Initial outpatient therapy over hospital admission is suggested • Vital sign abnormalities, severe pain requiring analgesia, extensive VTE, advanced gestational age, maternal comorbidities that limit tolerance of recurrent VTE or are associated with increased risk of bleeding, contraindications to LMWH, and lack of adequate support at home are all indicators for initial hospitalization.
Should delivery be scheduled or spontaneous?	• If receiving therapeutic-dose LMWH for management of VTE, scheduled delivery with prior discontinuation of anticoagulant therapy is suggested. • If receiving prophylactic-dose LMWH, spontaneous delivery is suggested.
What anticoagulant should be used during breastfeeding?	UFH, LMWH, warfarin , fondaparinux, or danaparoid are recommended. • The agents with greatest experience in this patient population and the best evidence for safety are warfarin, acenocoumarol, and LMWH. • Direct Oral Anticoagulants (DOACs) are not recommended.

Question	Recommendation[1]
VTE Prevention in pregnancy	
Should anticoagulant prophylaxis be used in women undergoing assisted reproduction?	Prophylactic antithrombotic therapy to prevent VTE is **not suggested** (except in severe ovarian hyperstimulation syndrome). • Prophylaxis is suggested in patients that develop severe ovarian hyperstimulation syndrome.
Should antepartum anticoagulant prophylaxis be used for pregnant patients with prior VTE?	• For women who have a history of VTE that was unprovoked or was associated with a hormonal risk factor, antepartum anticoagulant prophylaxis is **recommended**. • For women who have a history of prior VTE associated with a non-hormonal temporary provoking risk factor and no other risk factors, antepartum anticoagulant prophylaxis is **not suggested**.
Should postpartum anticoagulant prophylaxis be used for women with prior VTE?	Postpartum anticoagulant prophylaxis is **recommended**.
Should antepartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?	• For women who are heterozygous for the factor V Leiden or prothrombin mutation and in those who have protein C or protein S deficiency, regardless of family history of VTE, antepartum antithrombotic prophylaxis is **not suggested**. • For women who have no family history of VTE but have antithrombin deficiency or are homozygous for the prothrombin gene mutation, antepartum antithrombotic prophylaxis is **not suggested.** • For women with antithrombin deficiency who have a family history of VTE and in those who are homozygous for the factor V Leiden mutation or who have combined thrombophilias, regardless of family history of VTE, antepartum antithrombotic prophylaxis **is suggested.**
Should postpartum anticoagulant prophylaxis be used for pregnant women with thrombophilia to prevent a first venous thromboembolic event?	• For women without a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation or who have antithrombin, protein C, or protein S deficiency, antithrombotic prophylaxis is **not suggested**. • For women with a family history of VTE who are heterozygous for the factor V Leiden mutation or prothrombin mutation,

Question	Recommendation[1]
	postpartum antithrombotic prophylaxis is **not suggested**. • For women with a family history of VTE who have antithrombin deficiency, postpartum antithrombotic prophylaxis is **recommended**. • For women with a family history of VTE who have protein C or protein S deficiency, postpartum antithrombotic prophylaxis **is suggested**. • For women with combined thrombophilias or who are homozygous for the factor V Leiden mutation or prothrombin gene mutation, regardless of family history, postpartum antithrombotic prophylaxis **is suggested**.
Should anticoagulant prophylaxis be used for pregnant women with clinical risk factors for VTE (Other than known thrombophilia or history of VTE)?	For women with no or 1 clinical risk factor (excluding a known thrombophilia or history of VTE), antepartum or postpartum prophylaxis is **not suggested**. • Examples of clinical risk factors include: increased body mass index, immobilization, medical comorbidities, and placental-mediated pregnancy complications
Should intermediate-dose LMWH prophylaxis or standard-dose LMWH prophylaxis be used for preventing first or recurrent VTE in pregnant women?	• Standard-dose LMWH prophylaxis during the antepartum period is suggested. • Either standard- or intermediate-dose LMWH prophylaxis during the postpartum period is suggested. [note: For the purposes of this guideline, the committee defined intermediate dose as any dose greater than the standard prophylactic dose (40 mg once per day) but less than the therapeutic dose(1.5mg/kg/day or 1mg/kg/bid).]

More information about the American Society of Hematology guidelines for VTE in pregnancy, including the full guidelines, a mobile app, and teaching slides are available at:
https://www.hematology.org/Clinicians/Guidelines-Quality/VTE/9167.aspx

[1]Bates S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Advances 2018 2:3317-3359; doi: https://doi.org/10.1182/bloodadvances.2018024802

Anticoagulant-Antiplatelet Combination Therapy

Many patients with an indication for anticoagulation may also have an indication for single or dual antiplatelet therapy. The table below covers some possible indications for combination therapy and the latest research and guidelines for these situations.

Indication for combination therapy	Information
Primary CVD prevention	The use of aspirin for primary prevention of atherosclerotic cardiovascular disease (ASCVD) should no-longer be routine based on the 2019 AHA/ACC guidelines for primary prevention of cardiovascular disease.[1] According to the new 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 prevention of CV events in stable CAD or PAD without another indication for anticoagulation	The COMPASS trial showed that patients taking rivaroxaban (2.5mg BID) + aspirin had a reduction in cardiovascular events but higher major bleeding.[2] • The increase in bleeding events were mostly GI bleeding. There was no increase in intracranial or fatal bleeding. • The greatest benefit of this combination therapy is expected in the highest risk patients (eg. polyvascular disease, HF, diabetes, and CKD). The FDA has approved the 2.5mg BID dose of rivaroxaban for this indication.

Secondary CV event prevention in AF patients with recent ACS/PCI	Triple therapy (anticoagulant + dual antiplatelet) may only be needed for the highest risk patients following recent ACS or PCI.
	• Several studies now suggest that dual therapy (anticoagulant + clopidogrel) may best balance ischemic and bleeding event risk for most patients.
	  ○ Warfarin + clopidogrel (WOEST trial)
	  ○ Rivaroxaban + clopidogrel (PIONEER AF-PCI)
	  ○ Dabigatran + clopidogrel (RE-DUAL PCI)
	  ○ Apixaban + clopidogrel (AUGUSTUS)
	
	The 2019 AHA/ACC Atrial Fibrillation guidelines state that dual treatment with clopidogrel and dose adjusted warfarin, rivaroxaban (15 mg daily), or dabigatran (150mg daily) is a reasonable decision over triple therapy to reduce the risk of bleeding.[3] Data supporting the use of apixaban in this scenario was published after the 2019 AHA/ACC guideline.

Indication for combination therapy	Information
Secondary CV event prevention in AF patients with stable CAD and <u>no ACS/PCI within 12 months</u>	In AF patients with stable CAD, there is little evidence that adding antiplatelet therapy to patients already taking anticoagulants reduces stroke/systemic embolism, death, or MI. However, the risk of major bleeding and ICH is substantially increased.[4,5] CHEST and European Society of Cardiology guidelines for AF recommend oral anticoagulation monotherapy in AF patients with stable CAD and no PCI/ACS in the previous 12 months[4,6]

[1] 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Journal of the American College of Cardiology (2019). https://doi.org/10.1016/j.jacc.2019.03.010

[2]Eikelboom J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017; 377:1319-1330. DOI: 10.1056/NEJMoa1709118

[3]2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2019;139:e000–e000. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665

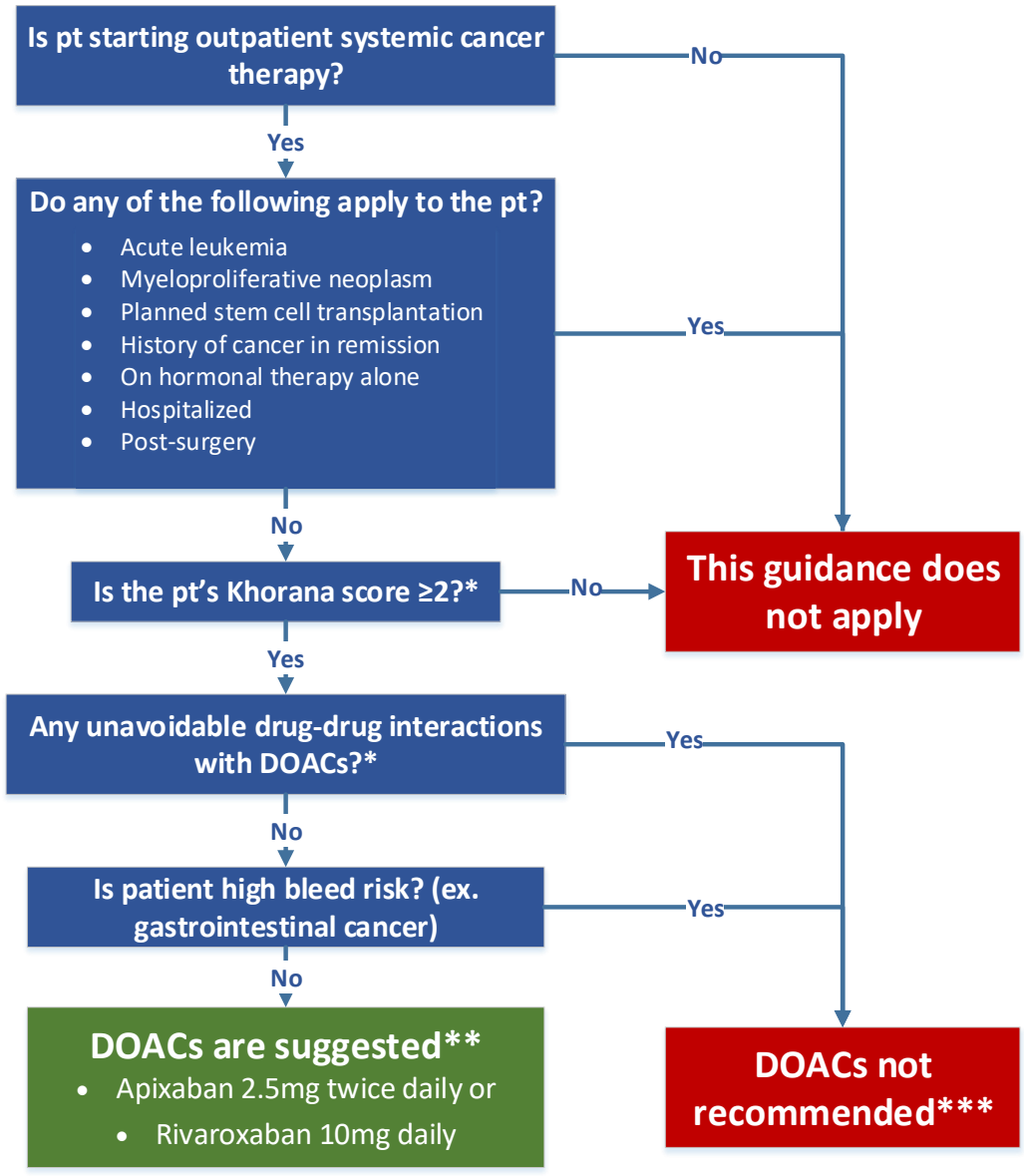
[4]Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

[5]Yasuda S, et al. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. N Engl J Med 2019; 381:1103-1113. DOI: 10.1056/NEJMoa1904143

[6]2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7; 37(38):2893-2962.

VTE Prevention in Ambulatory Cancer Patients

Patients with active cancer have an increased risk of VTE. Two recent trials (AVERT[1] and CASSINI[2]) have shown that DOACs can reduce VTE risk in ambulatory cancer patients initiating chemotherapy. The following flowchart is based on a guidance statement from the International Society on Thrombosis and Haemostasis.[3]



*See the following page for the Khorana score calculation. Consult with a pharmacist or hematologist to evaluate for potential DOAC drug-drug interactions.

** Apixaban or rivaroxaban recommended since they were used in the AVERT and CASSINI trials. Treatment up to 6 months after initiation of chemotherapy is suggested. Regular monitoring of platelet counts and bleeding risk complications is recommended.[3]

*** In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOACs (such as in patients with concern of drug interaction or high risk of gastrointestinal bleeding), prophylactic doses of LWMH is suggested.[3]

To evaluate VTE risk in cancer patients receiving outpatient chemotherapy, the Khorana Score can be utilized.[4]

Khorana Score

Patient Characteristic	Risk Score
Cancer location: stomach or pancreas (very high risk)	2
Cancer location: lung, lymphoma, gynecologic, bladder, testicular (high risk)	1
Pre-chemotherapy platelet count ≥ 350 $X10^9/L$	1
Hemoglobin < 10 g per deciliter or use of red blood cell growth factors	1
Pre-chemotherapy leukocyte count > 11 x $10^9/L$	1
Body Mass Index ≥ 35 kg/m^2	1

VTE Risk	Total Score
Low	0
Intermediate	1-2
High	≥3

[1]Carrier M, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer (AVERT trial). N Engl J Med 2019; 380:711-719. DOI: 10.1056/NEJMoa1814468
[2]Khorana A, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med 2019; 380:720-728. DOI: 10.1056/NEJMoa1814630
[3]Wang T, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. J Thromb Haemost. 2019;17:1772–1778.
[4]Khorana A, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood (2008) 111 (10): 4902-4907. doi.org/10.1182/blood-2007-10-116327

Anticoagulation Links

Organization/Document	Description	Link
Anticoagulation Forum	The largest peer organization of anticoagulant service providers in North America. Members include international anticoagulation experts that provide education and guidance for applying the latest research into practice.	http://acforum.org
Anticoagulation Centers of Excellence	Part of the Anticoagulation Forum, this program offers providers guidelines, tools, and other information in order to achieve the highest possible level of care and improve outcomes.	http://excellence.acforum.org/
AC Forum Clinical Guidance	Guidance provided by panels of clinical experts across several topics, including management of VTE and reversal of Direct Oral Anticoagulants.	https://acforum.org/web/education-guidance.php
AC Forum Core Elements of Anticoagulation Stewardship Programs	Key steps in developing a coordinated, system-level program that health systems can implement to improve anticoagulation-related outcomes and reduce adverse events.	https://acforum.org/web/education-stewardship.php
American College of Chest Physicians-Antithrombotic Guidelines	A leading source for evidence-based antithrombotic guidelines.	http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed
American College of Physicians Atrial Fibrillation patient resources	• Excellent resources for providers to give to patients with AF. Hard copies of the pamphlet and DVD copies of the videos can be ordered for free from this link	• Afib-What you and your family should know (pamphlet) • Afib-What you and your family should know (video) • Stroke and Stroke Risk (video) • Afib Medications (video) • Afib Self Management (video)
Society of Vascular Medicine	• Society of Vascular Medicine (http://www.vascularmed.org/) is a professional organization that was founded in 1989 to foster a broad mission. The goals of the Society are to improve the integration of vascular biological advances into medical practice, and to maintain high standards of clinical vascular medicine.	• Online shared decision making tool for anticoagulant choice in AF: http://www.mybloodclots.org/ • Online toolkit to help providers develop an outpatient DVT diagnosis and treatment pathway: www.mydeepveinthrombosis.com/

American Society of Hematology (ASH)-Clinical Practice Guidelines	Since 2014, ASH has developed clinical practice guidelines for venous thromboembolism. Over 200 evidence-based recommendations are available across various topics.	https://www.hematology.org/vte/
Clot Care	This organization provides information and expert insight on the optimal use of antithrombotic and anticoagulant therapy. Patient and provider resources are available.	www.clotcare.org
Clot Connect	A project from the University of North Carolina at Chapel Hill's Hemophilia and Thrombosis Center which connects providers and patients to clinically relevant education resources on deep vein thrombosis, pulmonary embolism, thrombophilia and anticoagulation.	http://www.clotconnect.org/
National Blood Clot Alliance	An organization that provides information and resources to providers and patients on the prevention, early diagnosis, and treatment of life-threatening blood clots.	http://www.stoptheclot.org/
World Thrombosis Day	A website sponsored by International Society on Thrombosis and Haemostasis to increase awareness of VTE.	http://www.worldthrombosisday.org

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