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Anticoagulation Toolkit

A Consortium-Developed Quick Reference for Anticoagulation

This toolkit was produced by the **Michigan Anticoagulation Quality Improvement Initiative (MAQI^2)**, a consortium of anticoagulation clinics and experts from across the state of Michigan. Funding for MAQI^2 is provided by **Blue Cross Blue Shield of Michigan and Blue Care Network** through the Collaborative Quality Improvement (CQI) program.

The goal of this toolkit 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 toolkit, please email us to let us know.

Disclaimer: This toolkit is for informational purposes only and does not, itself, constitute medical advice. The toolkit is not a replacement for careful medical judgments by qualified medical personnel. There may be information in the toolkit that does not apply to or may be inappropriate for the medical situation at hand.

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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 $CHADS_2$ in the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines.**[1]

CHA_2DS_2-VASc Scoring Table[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=	

CHA_2DS_2-VASc Risk Stratification			
Score	**Risk**	**ESC Recommendation**[3]	**AHA/ACC/HRS Guidelines**[1]
≥2	High	Anticoagulate	Anticoagulate (Class Ia rec.)
1	Intermediate	Anticoagulate	Consider oral anticoagulant or aspirin (Class IIb rec.)
0	Low	Don't Anticoagulate	No antithrombotic (Class IIa rec.)

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

Useful Links if Anticoagulation is Needed
FDA Approved Anticoagulants
Comparison of warfarin and DOACs
Anticoagulant selection based on pt. characteristics
Identifying patients appropriate for DOACs
Anticoagulant selection decision tree

[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] 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

$CHADS_2$

The $CHADS_2$ score is a validated and widely used tool to predict **stroke risk in non-valvular atrial fibrillation patients**. The higher the score, the greater the stroke risk. **The CHA_2DS_2-VASc (prior page) is now recommended over CHADS2 based on the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines.**[1]

$CHADS_2$ Scoring Table[2]	
Condition	**Points**
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke/TIA or thromboembolism (prior)	2
Total score=	

$CHADS_2$ Risk Stratification		
Score	**Risk**	**ACC/AHA Recommendation**[4]
≥2	High	Anticoagulate
1	Moderate	Anticoagulate or ASA
0	Low	ASA or nothing

$CHADS_2$ Score	Annual Stroke Risk (%)		
	No Warfarin	With Aspirin[3]	With Warfarin[3]
0	1.9	1.5	0.7
1	2.8	2.2	1.0
2	4.0	3.2	1.4
3	5.9	4.7	2.1
4	8.5	6.8	3.0
5	12.5	10.0	4.4
6	18.2	14.6	6.4

Other Links
FDA Approved Anticoagulants
Comparison of warfarin and DOACs
Anticoagulant selection based on pt. characteristics
Identifying patients appropriate for DOACs

In the Active A and Active W Studies, aspirin and clopidogrel, when used in combination, reduce the stroke risk in patients with atrial fibrillation more than aspirin alone but less so than warfarin. In addition, the risk of bleeding with the aspirin/clopidogrel combination was determined to be the same as the risk of bleeding with patients using warfarin alone.

[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] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-2870. doi:10.1001/jama.285.22.2864

[3] 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;146:857-867. doi:10.7326/0003-4819-146-12-200706190-00007

[4] Anderson JL et al. Management of Patients With Atrial Fibrillation. Circulation. 2013; 127: 1916-1926. DOI: 10.1161/CIR.0b013e318290826d

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Bleeding Risk Scores

HAS-BLED Score (warfarin in atrial fibrillation patients)[1]

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	Hemorrhagic 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[2]	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

* major bleed= ICH or bleeding resulting in a hospitalization, a hemoglobin drop > 2 g/dL, or a blood transfusion

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	Focal neurologic deficit of sudden onset lasting >24hr and caused by bleeding.
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 (not including clopidogrel), 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]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

[2]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

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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

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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$_2$DS$_2$-VASc calculator

http://www.sparctool.com/
Combination tool that calculates CHADS$_2$, CHA$_2$DS$_2$-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.

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FDA Approved Oral Anticoagulants

Generic (Trade Name)	FDA approved indication	FDA Recommended dosages
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	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
Apixaban (Eliquis®)[2]	• Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • For the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery • For the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. • **Not recommended in patients with severe hepatic impairment, prosthetic heart valves, or pregnancy**	Nonvalvular Atrial Fibrillation • 5mg BID • 2.5mg BID if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) • 2.5mg BID if coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)(e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) • 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. • In patients with end-stage renal disease (ESRD) maintained on hemodialysis, the recommended dose is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if patient has one of the following patient characteristics (age ≥80 years or body weight ≤60 kg). • **No data available for use in patients with CrCl <15 mL/min**

Generic (Trade Name)	FDA approved indication	FDA Recommended dosages
		<u>Prophylaxis of DVT following hip or knee replacement surgery</u> • 2.5 mg BID with first dose taken 12-24 hours after surgery • Recommended duration of treatment is 35 days for hip replacement and 12 days for knee replacement <u>Treatment of DVT and PE</u> • 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. <u>Reduction in the risk of recurrent DVT and PE following initial therapy</u> • 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE
Dabigatran (Pradaxa®)[3]	• Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation • For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days • To reduce the risk of recurrence of DVT and PE in patients who have been previously treated • **Contraindicated in patients with mechanical prosthetic heart valves** • **Not recommended in patients with bioprosthetic heart valves.** • **Dabigatran has not been studied adequately in pregnant women.**	<u>Nonvalvular Atrial Fibrillation</u> • 150 mg BID for CrCl >30mL/min • 75 mg BID for CrCl 15-30mL/min • If CrCl 30 to 50 mL/min and concomitant use of dronedarone or ketoconazole, consider 75 mg twice daily • Avoid co-administration with P-gp inhibitors if CrCl <30 mL/min • **Contraindicated in patients with CrCl <15 mL/min** <u>Treatment and Reduction in the Risk of Recurrence of DVT and PE:</u> • For patients with CrCl >30 mL/min: 150 mg orally, twice daily after 5-10 days of parenteral anticoagulation • Avoid co-administration with P-gp inhibitors if CrCl <50 mL/min • No dosing recommendations available for patients with CrCl<30 mL/min or on dialysis ***CrCl determined using Cockcroft-Gault formula and actual body weight***

Generic (Trade Name)	FDA approved indication	FDA Recommended dosages
Rivaroxaban (Xarelto®)[4]	• To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation • For treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE • For prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery • **Not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or prosthetic heart valves.** • **Use with caution in pregnant women. Rivaroxban dosing in pregnant women has not been studied.**	Reduction in risk of stroke in nonvalvular atrial fibrillation • 20 mg once daily with the evening meal for patients with CrCl >50 mL/min • 15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min • **Contraindicated in patients with CrCl<15 mL/** Treatment of DVT/PE • 15 mg twice daily with food, for first 21 days. • After 21 days, transition to 20 mg once daily with food, for remaining treatment • **Contraindicated in patients with CrCl<30 mL/min** Reduction in the risk of recurrence of DVT and of PE • 20 mg once daily with food • **Contraindicated in patients with CrCl<30 mL/min** Prophylaxis of DVT following hip or knee replacement surgery • Hip replacement: 10 mg once daily for 35 days • Knee replacement: 10 mg once daily for 12 days • **Contraindicated in patients with CrCl<30 mL/min** ***CrCl determined using Cockcroft-Gault formula and actual body weight***
Edoxaban (Savaysa®)[5]	• To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant	Nonvalvular Atrial Fibrillation • 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min • 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min • **Contraindicated in patients with creatinine clearance (CrCL) > 95**

Generic (Trade Name)	FDA approved indication	FDA Recommended dosages
	• **Contraindicated 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.** • **Use with caution in pregnant women. Edoxaban has not been adequately studied in this population.**	**mL/min (inferior to warfarin for stroke prevention)** Treatment of DVT and PE • 60 mg once daily (following 5-10 days of parenteral anticoagulant) • 30 mg once daily (following 5-10 days of parenteral anticoagulant) for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole) ***CrCl determined using Cockcroft-Gault formula and actual body weight***

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

Other Links
Comparison of warfarin and DOACs
Anticoagulant selection based on pt. characteristics
Identifying patients appropriate for DOACs
Anticoagulant selection decision tree

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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.
- The DOAC clinical trials defined *nonvalvular* differently; and therefore, had different exclusion criteria.[1]
- MAQI[2] recommends only using DOACs in patient populations where good safety and efficacy evidence exists.
- **All trials excluded patients with mechanical valves or moderate to severe (hemodynamically significant) mitral stenosis.**[1]

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	Excluded	Excluded (mod-severe)			
ENGAGE AF-TIMI (edoxaban)	Excluded		Excluded (mod-severe)			

H.S.-hemodynamically significant

[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

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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*
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]
			• AF (non-valvular only)
			• VTE
			  ○ treatment
			  ○ secondary prevention
			  ○ prophylaxis[1]
				• AF (non-valvular only)
				• VTE
				  ○ treatment[2]
				  ○ secondary prevention
					• AF (non-valvular only)
					• VTE
					  ○ treatment[2]

Administration	• Once daily with or without food	• Once or twice daily with largest meal of day[3]	• 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[4]		• 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
Initial parenteral therapy needed for VTE treatment?	Yes	No	No	Yes	Yes
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%[5]	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]After 5-10 days of parental anticoagulant treatment only
[3]Twice daily for first 21 days of VTE treatment. Once daily for other indications.
[4]All are considered effective for stroke reduction in non-valvular AF
[5]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: http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true

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

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Choice of Anticoagulant Based on Patient Characteristics*

Patient Characteristic	Drug Choice	Rationale
Mechanical Heart Valve	warfarin	Dabigatran inferior to warfarin and contraindicated in this group; other DOACs not studied in this patient population
Valvular Disease	warfarin	DOACs not studied extensively in this patient population. See table for valve patients excluded from DOAC trials.
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.
Stable on warfarin[1]	warfarin or DOAC	Warfarin patients should be informed about DOACs so that they can make an informed decision on preferred anticoagulant
CrCl <30 mL/min	warfarin	Very few patients with CrCl<30 were included in the DOAC trials. ESC guidelines[2] recommend against the use of DOACs in this population.
Dyspepsia or upper gastrointestinal symptoms	warfarin, rivaroxaban, apixaban, or edoxaban	Dyspepsia in up to 10% of patients given dabigatran.
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 a further bleed.
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.
Cancer-associated venous thrombosis	LMWH	LMWH is recommended in cancer-associated venous thrombosis.[3] Clinical trials for DOACs included few cancer patients and safety and efficacy comparisons between DOACs and LMWH in this population have not been studied.

*Based on MAQI[2] expert consensus

[1]Warfarin dose has been stable and INRs have mostly been in therapeutic range

[2] 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. doi:10.1093/eurheartj/ehs253

[3] Antithrombotic Therapy for VTE Disease. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians. DOI: 10.1378/chest.11-2301

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Identifying Patients Appropriate for Target-Specific 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]

Criteria	Rationale
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.
Patient understands and accepts that DOACs are not monitored, cannot accurately be measured, and do not have reversal agents.	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
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 antidote or 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

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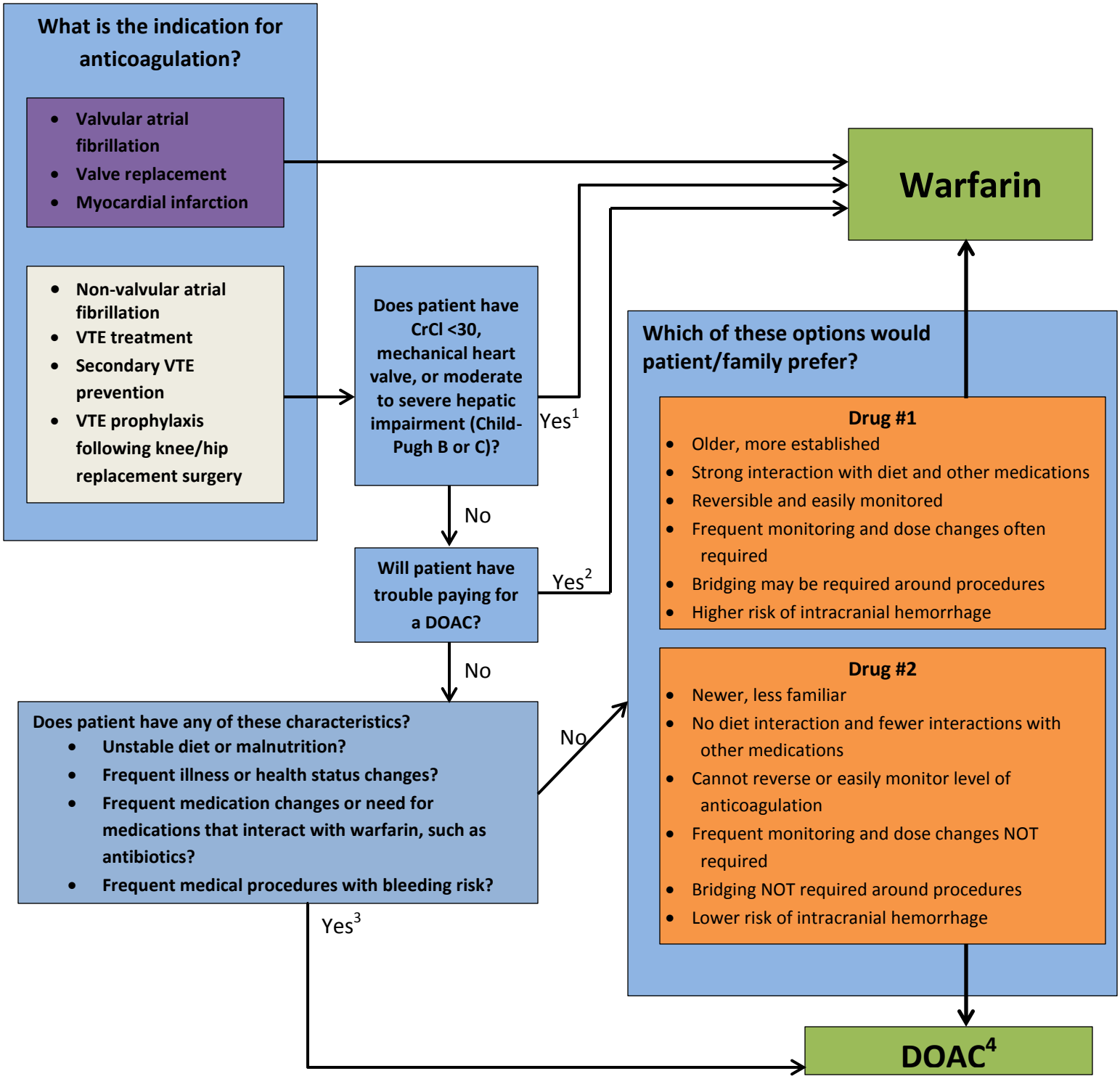
Anticoagulant Selection Decision Tree



1. Very 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 heart valves.
2. DOACs have much higher co-pays compared to warfarin.
3. Warfarin is affected by diet and general health status, has many medication interactions, and may require bridging around certain medical procedures.
4. 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.

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Things to Consider when Starting Patients on 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

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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, then evaluate for risk-benefit of extended therapy (see flowchart below)	1B
PE or DVT of leg in patients with active cancer	2-3	Extended (>3 months) Suggest use of LMWH over warfarin in 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 valve replacement	2.0-3.0	First 3 months following procedure	2B
Post-op VTE prophylaxis[4]**			
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.

**LMWH is recommended over warfarin for post-op VTE prophylaxis (Grade 2C)[4]

[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

[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]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

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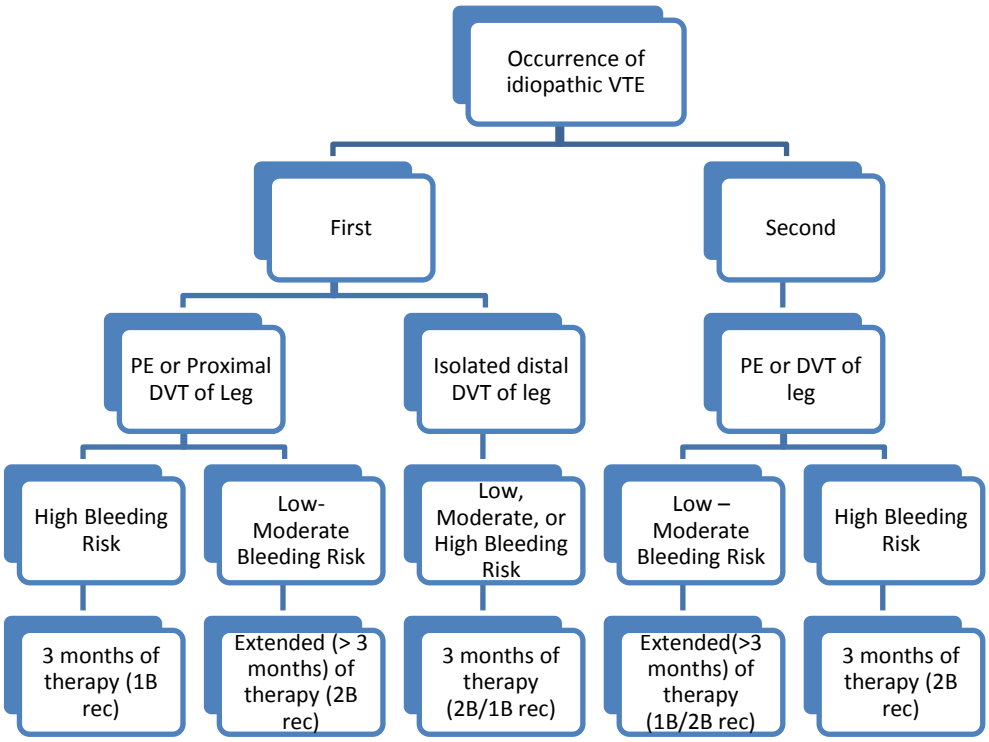
Length of treatment recommendations for idiopathic (unprovoked) VTE[1]



[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

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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

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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

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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

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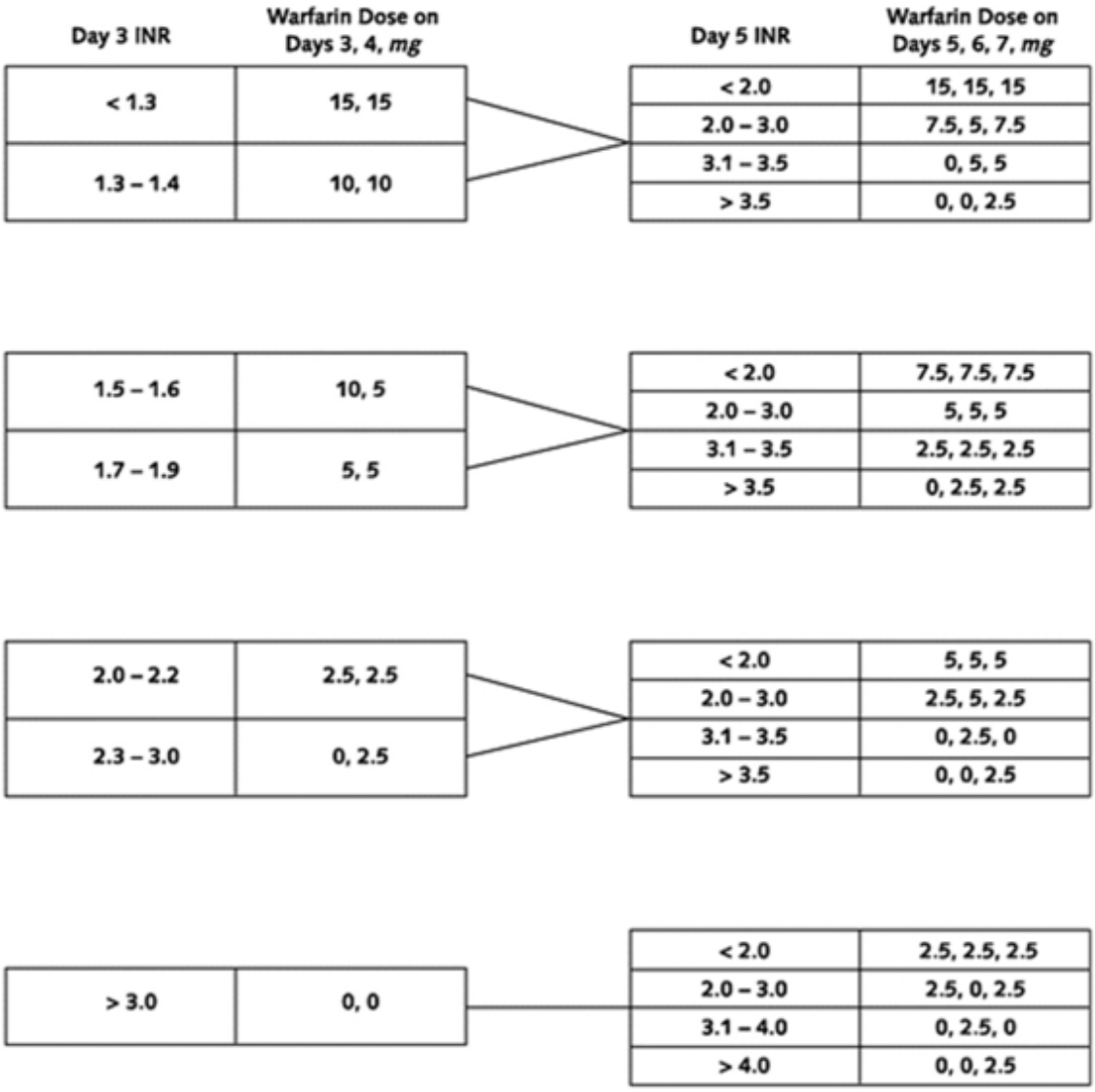
Warfarin Initiation Nomogram (10mg starting dose, INR target range 2-3)[2]

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)

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Conversion from DOACs to Warfarin (Coumadin®)

Generic (Trade Name)	Instructions

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*
	
	• 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.

[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

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Most Clinically Relevant Warfarin-Drug Interactions	
Potentiation of Drug Effect (Increased INR)	**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.

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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 • Clinic contact information
	When to seek immediate medical attention?

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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

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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	>10.003
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

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Warfarin Management around Minor Procedures

Procedure	Recommendation
Minor dental (e.g. tooth extractions, root canals)	• For patients undergoing dental procedures who are not to be considered high risk, anticoagulation with warfarin does NOT need to be discontinued.[1,2] • All patients undergoing elective dental procedures should have an INR performed within 1-3 days before the procedure ○ If a patient's INR is high, delay the procedure in consultation with the managing dentist. • If the planned procedure requires a posterior-superior alveolar block, then anticoagulant therapy must be interrupted since this anesthetic procedure can be complicated by bleeding that cannot be controlled adequately by local measures. • For patients undergoing dental procedures while on warfarin, a prohemostatic agent such as tranexamic can be administered to control bleeding.[1]
Minor dermatologic procedures	Continue warfarin around the time of procedure and optimize local hemostasis instead of other strategies (Grade 2C)[1]
Cataract surgery	Continue warfarin around the time of surgery instead of other procedures (Grade 2C)[1]

[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
[2]Alaali Y, Barnes GD, Froehlich JB, Kaatz S. Management of oral anticoagulation in patients undergoing minor dental procedures. J Mich Dent Assoc. 2012;94:36-41

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Perioperative Bridging Guidelines for Warfarin

	Recommendation	Grade of recommendation
Who should be bridged?	**Based on the BRIDGE trial, the best available evidence to date, the vast majority of AF patients DO NOT benefit from bridging.**[a]	MAQI[2] consensus
	Mechanical heart valve or VTE patients at <u>HIGH</u> risk for thromboembolism.[2]	2C
	Mechanical heart valve or VTE patients with a <u>MEDIUM</u> risk for thromboembolism may need bridging based on assessment of patient factors and type of surgery.[2]	2C
	• See table, *Suggested Risk Stratification for Perioperative Thromboembolis* (below) to identify patients at High or Medium risk. • See table, *Bleeding Risk Stratification for Common Procedures* (below) to identify surgeries/procedures with increased bleeding risk.	
Who does not need to be bridged?	**Based on the best available evidence to date, the vast majority of AF patients DO NOT benefit from bridging.**[b]	MAQI[2] consensus
	Mechanical heart valve or VTE patients at LOW risk for thromboembolism[2]	2C
	• See table below, *Suggested Risk Stratification for Perioperative Thromboembolism* (below) to identify patients at Low risk.	
When to stop warfarin *before* procedure?	Approximately 5 days prior to procedure[2]	1C
When to start LMWH *before* procedure?	Start therapeutic dose when INR falls below therapeutic range[3]	
When to stop LMWH *before* procedure?	Give last dose 24 hours prior to procedure[c,2,3]	
When to restart warfarin *after* the procedure?	Approximately 12-24 h after surgery (evening of or next morning) and when there is adequate hemostasis[2]	2C
When to restart LMWH *after* the procedure?	24 hours after low/moderate bleeding risk surgeries[2] 48-72 hours after high-bleeding risk surgeries[d,2]	
When to stop LMWH *after* the procedure?	When INR is in therapeutic range[3]	

[a] This may include patients at the highest risk of stroke ($CHADS_2$ ≥5), who were underrepresented in the BRIDGE trial and patients with mechanical valve replacement or recent stroke/TIA (within 12 weeks), who were excluded from the BRIDGE trial.[1] A shared decision making process with patients and families is strongly encouraged, especially with limited available data.

[b]The BRIDGE trial clearly showed that in AF patients without a recent (within 12 weeks) stroke/TIA and no mechanical valves, forgoing bridging was found to be non-inferior to bridging in prevention of thromboembolism and decreased the risk of major bleeds. The highest stroke-risk patients ($CHADS_2$ ≥5) were underrepresented in this trial.[1]

[c]May need to be adjusted based on renal function

[d] Restart LMWH 72 hours after endoscopic sphincterotomy[3]

[1]Douketis et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. DOI: 10.1056/NEJMoa1501035

[2]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

[3]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.

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Suggested Risk Stratification for Perioperative Thromboembolism[1]

	Indication for VKA Therapy		
Risk Stratum	**Mechanical Heart Valve**	**Atrial Fibrillation**	**VTE**
High[a]	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 mo) stroke or TIA(transient ischemic attack)	• $CHADS_2$ score of 5 or 6 • Recent (within 3 mo) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 mo) VTE • Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	Bileaflet aortic valve prosthesis and one or more of the of following risk factors: • atrial fibrillation • prior stroke or TIA • hypertension, • diabetes, • congestive heart failure, • age > 75 yo	• $CHADS_2$ score of 3 or 4	• VTE within the past 3-12 mo • Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 mo or palliative)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	• VTE > 12 mo previous and no other risk factors

CHADS2 = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist; TIA = transent ischemic attack ; VTE = **venous thromboembolism**

[a]High-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a CHADS2 score < 5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

[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

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Bleeding Risk Stratification for Common Procedures[1]

Procedure	Low Risk Bleeding (<1.5 %)	High Risk Bleeding (>1.5%, or in vulnerable areas)
Anesthesiology	Endotracheal intubation	Spinal and epidural anesthesia
Cardiac surgery	None	All
Cardiovascular	Diagnostic coronary angiography (controversial)	Pacemaker or defibrillator placement (3.5% on warfarin therapy, 16% with bridging anticoagulation) Coronary intervention Electrophysiology testing and/or ablation
Dental	Tooth extraction Endodontic procedures (root canal)	Reconstructive procedures
Dermatology	Minor skin procedures (excision of basal and squamous cell cancers, nevi, actinic keratoses,	Major procedures (wide excision of melanoma)

Procedure	Low Risk Bleeding (<1.5 %)	High Risk Bleeding (>1.5%, or in vulnerable areas)
Gastroenterology	Passage of endoscope for diagnostic purposes (including balloon enteroscopy) with or without mucosal biopsy Endoscopic retrograde cholangiopancreatography without sphincterotomy Endoscopic ultrasound without fine-needle aspiration Nonthermal (cold) snare removal of small polyps Lumenal self-expanding metal stent placement (controversial)	Large polypectomy (>1 cm) Endoscopic mucosal and submucosal dissection Biliary or pancreatic sphincterotomy Percutaneous endoscopic gastrostomy Endoscopic ultrasound with fine-needle aspiration or needle biopsy Coagulation or ablation of tumors, vascular lesions Percutaneous liver biopsy Variceal band ligation (controversial)
General surgery	Suture of superficial wounds	Major tissue injury Vascular organs (spleen, liver, kidney) Bowel resection Laparoscopy
Gynecologic surgery	Diagnostic colposcopy, hysteroscopy Dilation and curettage, endometrial biopsy Insertion of intrauterine device	Laparoscopic surgery Bilateral tubal ligation Hysterectomy

Procedure	Low Risk Bleeding (<1.5 %)	High Risk Bleeding (>1.5%, or in vulnerable areas)
Interventional radiology	Simple catheter exchange in well-formed, nonvascular tracts (e.g., gastrostomy, nephrostomy, cholecystostomy tubes) Thoracentesis Paracentesis Aspiration of abdominal or pelvic abscesses, placement of small-caliber drains Peripheral catheter placement, nontunneled catheter (peripherally inserted central catheter) placement Inferior vena cava filter placement Temporary dialysis catheter placement	Percutaneous transhepatic cholangiography or nephrostomy Percutaneous drainage of liver abscess or gallbladder Chest tube placement Aggressive manipulation of drains or dilation of tracts Biopsy of organs Hickman and tunneled dialysis catheter placement
Intravascular procedures	Venous access	Arterial puncture Transvenous ablation
Neurology	None	Lumbar puncture Myelography Needle electromyography (controversial)
Neurosurgery	None	Intracranial, spinal surgery

Procedure	Low Risk Bleeding (<1.5 %)	High Risk Bleeding (>1.5%, or in vulnerable areas)
Ophthalmology	Cataract surgery Intraocular injections (Avoid retrobulbar anesthesia - controversial)	Periorbital surgery Vitreoretinal surgery
Orthopedic surgery	Arthrocentesis	Joint replacement Arthroscopy
Otolaryngologic surgery	Diagnostic fiberoptic laryngoscopy or nasopharyngoscopy, sinus endoscopy Fine-needle aspiration Vocal cord injection	Any sinus surgery Biopsy or removal of nasal polyps Thyroidectomy Parotidectomy Septoplasty Turbinate cautery
Plastic surgery	Injection therapy	Reconstruction

Procedure	Low Risk Bleeding (<1.5 %)	High Risk Bleeding (>1.5%, or in vulnerable areas)
Pulmonary	Diagnostic bronchoscopy with or without bronchioalveolar lavage Endobronchial fine-needle aspirate (controversial) Airway stent placement (controversial)	Tumor ablation (laser) Transbronchial biopsy Stricture dilation
Rheumatology	Arthrocentesis	None
Urology	Circumcision Cystoscopy without biopsy	Extracorporeal shock-wave lithotripsy Transurethral prostatectomy Bladder resection Tumor ablation Kidney biopsy
Vascular surgery	None	Carotid endarterectomy Open or endovascular aneurysm repair Vascular bypass grafting

[1]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.

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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

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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 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

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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

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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

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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, 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

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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 interactions that may necessitate DOAC dose adjustment.	See DOAC drug interaction table
Evaluate renal function (Cockcroft-Gault equation to estimate CrCl) prior to DOAC initiation[1] and establish a baseline for CBC and liver function[2]	
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

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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 • Start dabigatran at: ○ 150 mg BID for CrCl >30mL/min* ○ 75 mg BID for CrCl 15-30mL/min* ○ Contraindicated in patients with CrCl <15 mL/min*
Apixaban (Eliquis®)[2]	• Discontinue Warfarin (Coumadin®) and begin Apixaban (Eliquis®)when the INR is below 2.0 • Start apixaban at: ○ 5mg BID ○ 2.5mg BID if patient has two or more of these factors (age≥80, weight ≤60kg, serum creatinine ≥1.5 mg/dL) ○ 2.5mg BID if coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)(e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)
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). • Start rivaroxaban at: ○ Reduction in risk of stroke in nonvalvular atrial fibrillation ▪ 20 mg once daily with the evening meal for patients with CrCl >50 mL/min* ▪ 15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min* ○ Treatment of DVT/PE ▪ 15 mg twice daily with food, for first 21 days. ▪ After 21 days, transition to 20 mg once daily with food, for remaining treatment ○ Reduction in the risk of recurrence of DVT and of PE ▪ 20 mg once daily with food ○ Prophylaxis of DVT following hip or knee replacement surgery ▪ Hip replacement: 10 mg once daily for 35 days ▪ Knee replacement: 10 mg once daily for 12 days
Edoxaban (Savaysa)[4]	Discontinue warfarin and begin edoxaban when the INR is ≤ 2.5.

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

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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

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DOAC Drug Interactions and Dose Adjustments

	Dabigatran[1] creatinine clearance (ml/min)			Rivaroxaban[2] creatinine clearance (ml/min)	
	>50	**30-50**	**15-30**	**>80**	**15-80**
P-gp inducer Rifampin	avoid	Avoid	avoid	avoid	avoid
P-gp inducer and *strong* CYP3A4 inducer					
Carbamazepine				avoid	avoid
Phenytoin				avoid	avoid
St. John's wort				avoid	avoid
P-gp inhibitor and *strong* CYP3A4 inhibitor					
Itraconazole				avoid	avoid
Iopinavir/ritonavir				avoid	avoid
Ritonavir				avoid	avoid
Indinavir/ritonavir				avoid	avoid
Conivaptan				avoid	avoid
Ketoconazole (systemic)	150 mg	75 mg (AF) avoid (DVT)	avoid	avoid	avoid
Clarithromycin	150 mg	150 mg(AF) avoid (DVT)	avoid	avoid	avoid
P-gp inhibitor and *moderate* CYP3A4 inhibitor					
Verapamil	150 mg	150 mg(AF) avoid (DVT)	avoid	caution	avoid
Dronedarone	150 mg	75 mg(AF) avoid (DVT)	avoid	caution	avoid
Diltiazem				caution	avoid
Erythromycin				caution	avoid
P-gp inhibitor and *weak* CYP3A4 inhibitor					
Amiodarone	150 mg	150 mg(AF) avoid (DVT)	avoid		caution
Quinidine	150 mg	150 mg(AF) avoid(DVT)	avoid		caution
Ranolazine					caution
Felodipine					caution

	Apixaban[3] Characteristics: age ≥ 80 yrs, body weight ≤ 60 kg, serum creatinine ≥ 1.5		Edoxaban[4] creatinine clearance (ml/min)
	# of characteristics 0-1	**# of characteristics 2-3**	**No specified CrCl ranges**
P-gp inducer Rifampin	avoid	avoid	Avoid[4]
P-gp inducer and strong CYP3A4 inducer			
Carbamazepine	avoid	avoid	
Phenytoin	avoid	avoid	
St. John's wort	avoid	avoid	
P-gp inhibitor			
azithromycin			30mg (VTE treatment) [4]
P-gp inhibitor and *strong* CYP3A4 inhibitor			
Ketoconazole (systemic)	2.5 mg	avoid	30mg (VTE treatment) [4]
Clarithromycin	2.5 mg	avoid	30mg (VTE treatment) [4]
Itraconazole	2.5 mg	avoid	30mg (VTE treatment) [4]
Iopinavir/ritonavir			
Ritonavir	2.5mg	avoid	
Indinavir/ritonavir			
Conivaptan			
P-gp inhibitor and *moderate* CYP3A4 inhibitor			
Verapamil			Consider dose reduction (AF treatment)[5] 30mg (VTE treatment) [4]
Dronedarone			Consider dose reduction (AF treatment)[5]
Diltiazem			
Erythromycin			30mg (VTE treatment) [4]
P-gp inhibitor and *weak* CYP3A4 inhibitor			
Quinidine			Consider dose reduction (AF treatment)[5] 30mg (VTE treatment) [4]
Amiodarone			
Ranolazine			
Felodipine			

Rivaroxaban, Dabigatran, and Apixaban information adapted from: Kaatz, S, Mahan, C. Stroke Prevention in Patients With Atrial Fibrillation and Renal Dysfunction. Stroke. 2014;45:2497-2505. doi: 10.1161/STROKEAHA.114.005117

[1] Pradaxa® package insert
[2] Xarelto® package insert
[3] Eliquis® package insert
[4] Savaysa® package insert
[5] During the ENGAGE AF-TIMI 48 trial, patients randomized to both the 60mg and 30mg treatment group had doses cut in half if they were taking verapamil, quinidine, or dronedarone. Do not reduce dose to below 15mg.

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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* • *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*

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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

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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

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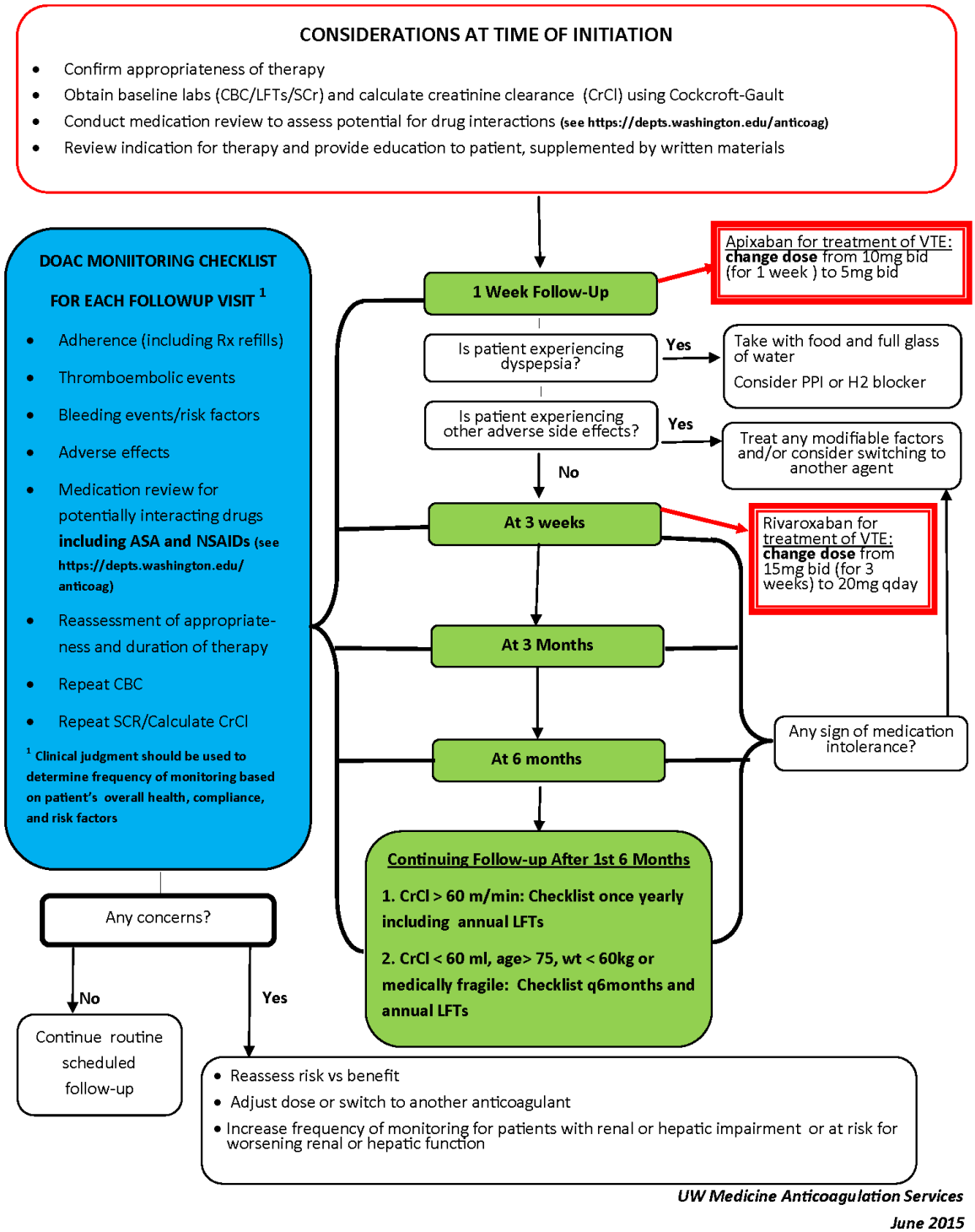
DOAC Management Plan Flowchart

UW Medicine

MANAGEMENT PLAN FOLLOWING INITIATION OF DIRECT ORAL ANTICOAGULANTS (DOACs)

APIXABAN/DABIGATRAN/EDOXABAN/RIVAROXABAN



UW Medicine Anticoagulation Services

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Discontinuation Guide for DOACs prior to Elective Procedures[1]

Renal function (CrCl)	Apixaban		Rivaroxaban		Dabigatran		Edoxaban	
	Low bleeding risk procedure	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**
>50	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure
30-50	Last dose: 3 days before procedure	Last dose:4 days before procedure	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Last dose: 3 days before procedure	Last dose: 4-5 days before procedure	---	---
15-30	---	---	Last dose: 3 days before procedure	Last dose: 4 days before procedure	---	---	---	---

- **Bridging with LMWH is not generally necessary** due to the quick onset/offset of DOACs.
- Discontinuation of DOACs is not necessary for minimal bleeding risk procedures such as minor dermatological procedures, cataract procedures, and dental cleanings/fillings
- High bleeding risk procedures include: any major surgery with extensive tissue injury such as cancer surgeries, major orthopedic surgeries, and reconstructive plastic surgeries; urologic or gastrointestinal surgeries such as bowel resection, nephrectomy, kidney biopsy, and prostate resection; any cardiac, intracranial, or spinal surgery; or any other major operation (procedure duration >45 minutes) or surgery in a highly vascular organ (kidney, liver, spleen, etc.)
- For DOAC management around interventional pain procedures, see table below.

[1] New York State Anticoagulation Coalition and IPRO. Management of Anticoagulation in the Peri-Procedural Period. http://qio.ipro.org/wp-content/uploads/2012/12/MAP2014_5_01.pdf

Resumption of DOACs following Procedures[1]

Apixaban		Rivaroxaban		Dabigatran		Edoxaban	
Low bleeding risk procedure	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**	**Low bleeding risk procedure**	**High bleeding risk procedure**
Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)	Resume on day after procedure (24 hours)	Resume 2-3 days after procedure (48-72 hours)

[1] New York State Anticoagulation Coalition and IPRO. Management of Anticoagulation in the Peri-Procedural Period. http://qio.ipro.org/wp-content/uploads/2012/12/MAP2014_5_01.pdf

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

Drug	Discontinue prior to procedure (5 half-lives)	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 medium 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

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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

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DOAC Reversal Options

	Apixaban	Rivaroxaban	Dabigatran
Oral activated charcoal	Yes (if ingested within 2 hours)	Yes (if ingested within 2 hours)	Yes (if ingested within 2 hours)
Hemodialysis	No	No	Yes
Hemoperfusion with activated charcoal	Possible	Possible	Yes
FFP	No	No	No
Activated factor VIIa	No	No	No
3-factor PCC	Unclear	Unclear	Unclear
4-factor PCC	Possible	Possible	Possible (activated)

Rosenberg D, Ansell. Hosp Pract. 2012 Aug;40(3):50-7. doi: 10.3810/hp.2012.08.989.

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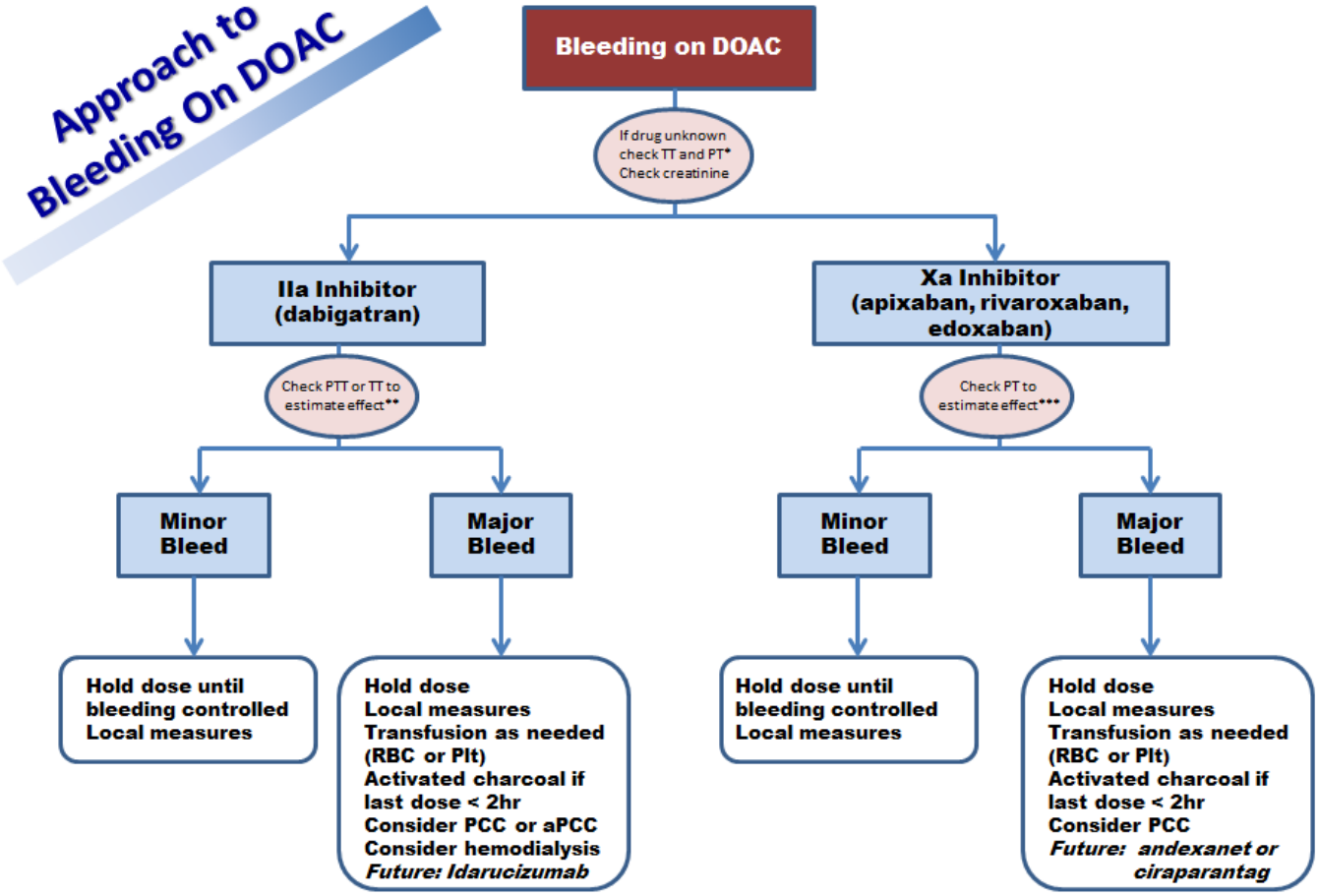
Bleeding Management in DOACs



* Normal TT suggests Xa inhibitor or IIa inhibitor at negligible concentration;
** Normal TT= negligible IIa inhibitor present; normal PTT does not exlcude significant IIa present, but suggests low concentration;
***Only rivaroxaban somewhat responsive to PT and only with some reagents; apixaban not responsive. Chromogenic anti-Xa assay is quantitative, but not readily available.

Presented by Jack Ansell, MD at the 16th Annual Antithrombotic Therapy Symposium, Dearborn, MI 5/22/15. Used with permission.

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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

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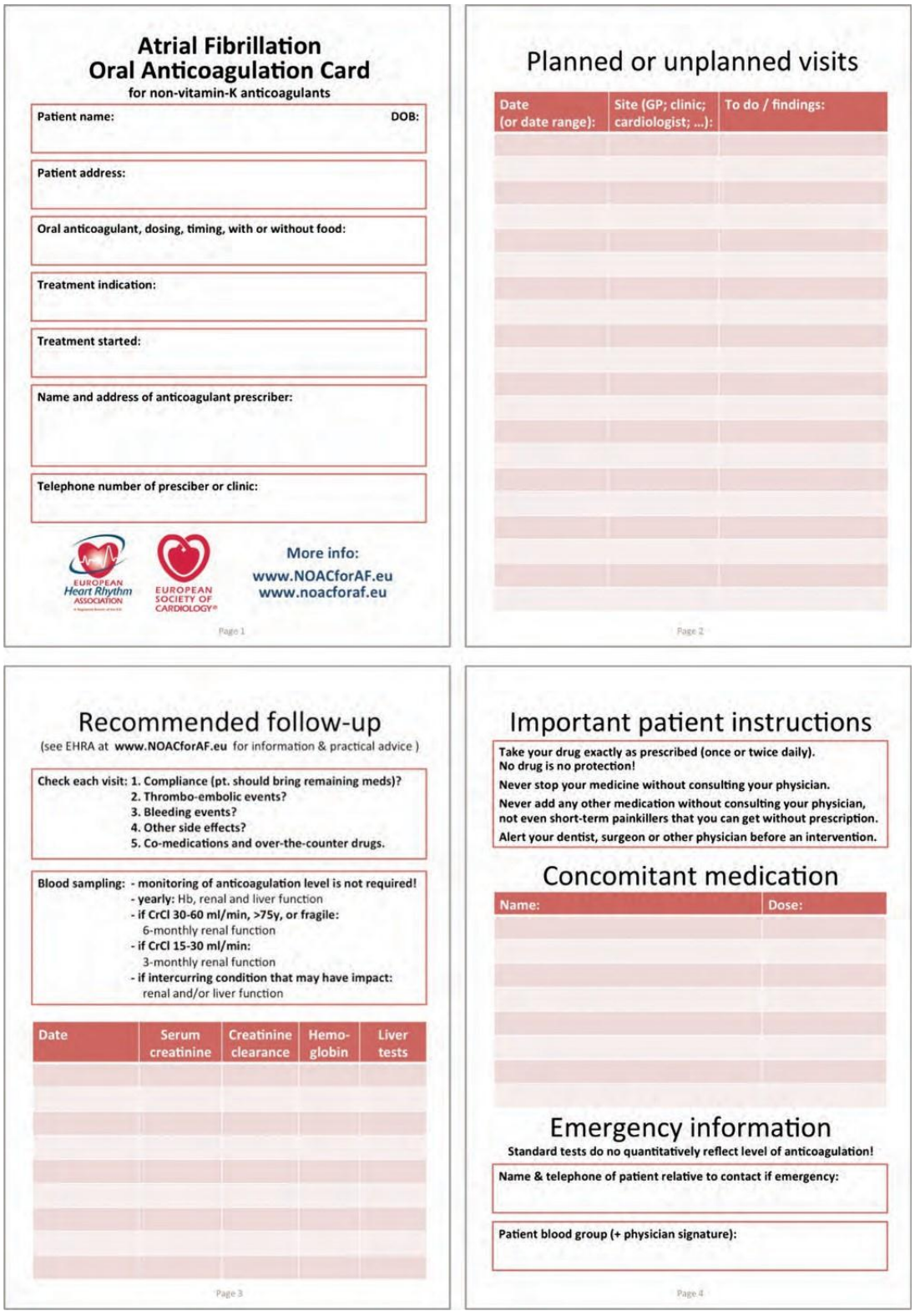
DOAC Patient Card Proposed by the European Heart Rhythm Association



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):

Page 4

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

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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.

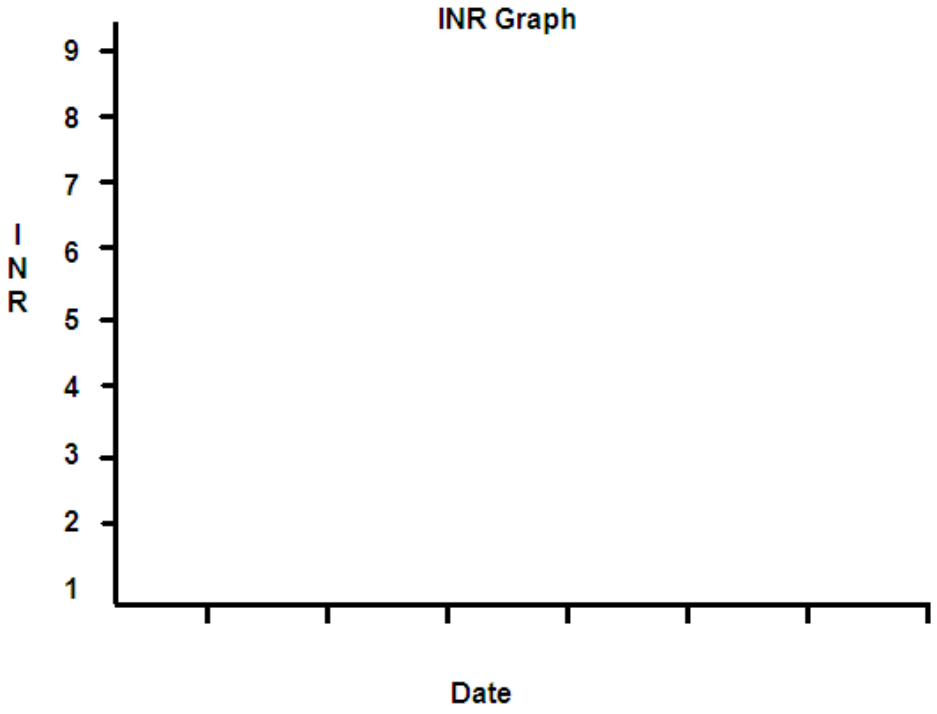
Drill down to root-cause • If possible, keep asking "why" until you feel you have identified the root cause for the AE. • Use cause and effect (fishbone) diagrams, if necessary. Example: 1. Why was her INR high?..She took more than prescribed. 2. Why did she take more than prescribed?....She didn't get 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?				



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Anticoagulation Links

Organization	Link	Description
Anticoagulation Forum	http://acforum.org	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.
Anticoagulation Centers of Excellence	http://excellence.acforum.org/	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.
American College of Chest Physicians-Antithrombotic Guidelines	http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed	A leading source for evidence-based antithrombotic guidelines.
Clot Care	www.clotcare.org	This organization provides information and expert insight on the optimal use of antithrombotic and anticoagulant therapy. Patient and provider resources are available.
Clot Connect	http://www.clotconnect.org/	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.
National Blood Clot Alliance	http://www.stoptheclot.org/	An organization that provides information and resources to providers and patients on the prevention, early diagnosis, and treatment of life-threatening blood clots.
World Thrombosis Day	http://www.worldthrombosisday.org	A website sponsored by International Society on Thrombosis and Haemostasis to increase awareness of VTE.

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Acknowledgements

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Cardiology and Vascular Associates-Commerce, MI Jay Kozlowski, MD	**University of Michigan-Ann Arbor, MI** James Froehlich, MD, MPH Geoffrey Barnes, MD, MSc Eva Kline-Rogers, MS, RN Brian Haymart, MS, RN Tina Alexandris-Souphis, RN, BSN Elizabeth Renner, Pharm.D. Brian Kurtz, Pharm.D.
Henry Ford Hospital-Detroit, MI Gregory Krol, MD Vinay Shah, MD Syed Ahsan, MD	**On behalf of the Michigan Academy of Family Physicians** Robert Jackson, MD Ekram Smith, MD

Toolkit compiled by:
Geoffrey Barnes, MD, MSc
Brian Haymart, MS, RN
Tina Alexandris-Souphis, RN, BSN

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