TEAM-A
The Evolution of Anticoagulation Management Atrial Fibrillation

MEDICATIONS FOR REDUCING THE RISK OF STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

The purpose of this medication chart is to provide information about the medications that can be used to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation. Please consult clinical practice guidelines, assess the patient's risk for stroke or systemic embolism and risk of bleeding, and utilize clinical judgment when selecting a medication.

	ANTICOAGULANTS				
NAME	**WARFARIN (COUMADIN®, JANTOVEN®)**	**DABIGATRAN (PRADAXA®)**	**RIVAROXABAN (XARELTO®)**	**APIXABAN (ELIQUIS®)**	**EDOXABAN (SAVAYSA™)**
CLASS	• Vitamin K antagonist	• Direct thrombin inhibitor	• Direct factor Xa inhibitor	• Direct factor Xa inhibitor	• Direct factor Xa inhibitor
MECHANISM OF ACTION	• Inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X), which inhibits clots from forming • Also inhibits the synthesis of anticoagulant proteins C and S[3]	• Selectively and reversibly blocks thrombin (IIa), which inhibits the conversion of fibrinogen to fibrin, thus preventing clots from forming[8] • Must be converted by esterases to active metabolite	• Selectively and reversibly blocks the active site of factor Xa, which inhibits the coagulation cascade and, thus, prevents clots from forming[9]	• Selectively and reversibly blocks the active site of factor Xa, which inhibits the coagulation cascade and, thus, prevents clots from forming[11]	• Selectively and reversibly blocks the active site of factor Xa, which inhibits the coagulation cascade and, thus, prevents clots from forming[14]

CONTRAINDICATIONS	• Black Box Warning[3]
	  • Bleeding risk
	• Other CI[3]
	  • Pregnancy
	  • Hemorrhagic tendencies or blood dyscrasias
	  • Recent or contemplated surgery of the CNS or eye, or traumatic surgery resulting in large open surfaces
	  • Bleeding tendencies
	  • Active ulceration or overt bleeding of GI, GU, or respiratory tract
	  • CNS hemorrhage
	  • Cerebral aneurysms
	  • Dissecting aorta
	  • Pericarditis, pericardial effusions
	  • Bacterial endocarditis
	  • Threatened abortion, eclampsia, and preeclampsia
	  • Unsupervised patients with conditions associated with potential high level of noncompliance
	  • Spinal puncture or other procedures with potential for uncontrollable bleeding
	  • Hypersensitivity to warfarin
	  • Major regional or lumbar block anesthesia
	  • Malignant hypertension
		• Black Box Warning
		  • Increased risk of stroke when discontinuing without other anticoagulation
		• Active pathological bleeding[8]
		• Hypersensitivity reaction to dabigatran
			• Black Box Warning[9]
			  • Increased risk of stroke when discontinuing without other anticoagulation
			  • Spinal/epidural hematoma
			• Other CI[9]
			  • Active pathological bleeding
			  • Hypersensitivity reaction to rivaroxaban
				• Black Box Warning[11]
				  • Increased risk of stroke when discontinuing without other anticoagulation
				  • Spinal/epidural hematoma
				• Other CI[11]
				  • Active pathological bleeding
				  • Hypersensitivity reaction to apixaban
					• Black Box Warning[14]
					  • Reduced efficacy in nonvalvular atrial fibrillation patients with CrCL >95 mL/min
					  • Premature discontinuation of edoxaban increases the risk of ischemic events
					  • Spinal/epidural hematoma
					• Other CI[14]
					  • Active pathological bleeding
					  • Not recommended for patients with mechanical heart valves or moderate-to-severe mitral stenosis

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DOSING (oral, unless otherwise indicated)	• Individualized dosing
	• Titrate warfarin to target INR of 2.5 (range of 2.0-3.0)[3]
	• Patients with valvular AF may have a different INR goal
		• Only indicated in patients with nonvalvular atrial fibrillation[8]
		• CrCl > 30 mL/min: 150 mg BID
		• CrCl 15-30 mL/min: 75 mg BID
		• CrCl < 15 mL/min or ESRD requiring dialysis: avoid use
		  • No dosing recommendations provided from manufacturer as these patients were not studied in the RE-LY trial
		• Discontinue in patients who have acute renal failure
			• Only indicated in patients with nonvalvular atrial fibrillation[9]
			• CrCl > 50 mL/min: 20 mg daily with the evening meal
			• CrCl 15-50 mL/min: 15 mg daily with the evening meal
			• CrCl < 15 mL/min or ESRD requiring dialysis: avoid use
			• Avoid in patients with moderate and severe hepatic impairment
			• Discontinue in patients who have acute renal failure
				• Only indicated in patients with nonvalvular atrial fibrillation[11]
				• 5 mg BID
				• 2.5 mg BID in patients with ≥ 2 of the following:
				  • Age ≥ 80 years old
				  • Weight ≤ 60 kg
				  • SCr ≥ 1.5 mg/dL
				• Avoid in patients with severe hepatic impairment; no dosing recommendations provided for moderate hepatic impairment
				• 5 mg BID in patients with ESRD maintained on hemodialysis (based on pharmacokinetic and pharmacodynamic data)
				• Note: AHA/ASA recommends avoiding use with CrCl < 25 mL/min[12]
					• Only indicated in patients with nonvalvular atrial fibrillation[14]
					• CrCL 51-95 mL/min: 60 mg daily
					• CrCL 15-50 mL/min: 30 mg daily
					• CrCL >95 mL/min: do not use
					• Not recommended in patients with moderate or severe hepatic impairment; no dose reduction is necessary in patients with mild hepatic impairment

MONITORING– EFFICACY	• PT/INR[3]
	  • Hospitalized patients: daily until the INR stable, then 2-3 times weekly, then less often depending on INR[4]
	  • Outpatients: every few days until INR stable, then extend follow-up intervals to every 1 to 4 weeks depending on INR[3,4]; for patients with consistently stable INRs, longer follow-up may be considered[5]
		• No routine assessment of anticoagulant effect[8]
		  • Most (but not all) PTT assays will be prolonged in the presence of clinically relevant dabigatran concentrations; a normal thrombin time excludes the presence of dabigatran; a modified thrombin time provides best quantitative estimate of dabigatran effect
			• No routine assessment of anticoagulant effect[10]
			  • Most (but not all) PT assays will be prolonged in the presence of clinically relevant rivaroxaban concentrations; the absence of anti-Xa activity (regardless of assay calibration) excludes the presence of rivaroxaban; an anti-Xa activity calibrated for rivaroxaban provides the best quantitative estimate of rivaroxaban effect
				• No routine assessment of anticoagulant effect[11]
				  • PT or PTT may or may not be prolonged in the presence of clinically relevant apixaban concentrations; the absence of anti-Xa activity (regardless of assay calibration) excludes the presence of apixaban; an anti-Xa activity calibrated for apixaban provides the best quantitative estimate of apixaban effect
					• No routine assessment of anticoagulant effect necessary
					  • Many (but not all) PT assays will be prolonged in the presence of clinically relevant edoxaban concentrations; the absence of anti-Xa activity (regardless of assay calibration) excludes the presence of edoxaban; an anti-Xa activity calibrated for edoxaban provides the best quantitative estimate of edoxaban effect.

MONITORING– SAFETY	• CBC, PT/INR[6]	• Renal function (SCr)[8]
		  • Assess prior to starting dabigatran
		  • Then assess as clinically indicated
		• CBC[a]
			• Renal function (SCr)[9]
			  • Assess prior to starting[a]
			  • Then assess as clinically indicated[a]
			• Hepatic function[10]
			• CBC[10]
				• Renal function (SCr)[11,12]
				  • Assess prior to starting
				  • Then assess as clinically indicated
				• Hepatic function
				• CBC[12]
					• Renal function (SCr)[14]
					  • Assess prior to starting
					• Hepatic function[14]

REVERSAL	• Vitamin K • Urgent reversal: prothrombin complex concentrate or fresh frozen plasma[3]	• No specific antidote[8] • Can be dialyzed	• No specific antidote[9] • Not dialyzable due to high protein binding • Activated charcoal may be considered in overdose situations	• No specific antidote[11] • Not dialyzable due to high protein binding • Activated charcoal may be considered in overdose situations	• No specific antidote[14] • Hemodialysis does not significantly contribute to clearance[14]
ADVERSE EFFECTS	Major[3,6,7] • Hemorrhage Other • Skin necrosis or gangrene • Systemic atheroemboli and cholesterol microemboli; "purple toes syndrome"	• Bleeding • Gastrointestinal effects (dyspepsia and gastritis-like symptoms)[8]	• Bleeding[9]	• Bleeding[11]	• Bleeding[14] • Anemia[14]
ADVANTAGES	• Long experience with medication; well-known risk-benefit profile • Demonstrated effectiveness • Once daily dosing • Long half-life • Reversible • Safer in renal failure compared to the other oral anticoagulants • Inexpensive drug cost	• No routine monitoring of anticoagulant efficacy • Short half-life; fast on and fast off (benefit when starting)	• No routine monitoring of anticoagulant efficacy • Once daily dosing • Short half-life; fast on and fast off (benefit when starting)	• No routine monitoring of anticoagulant efficacy • Short half-life; fast on and fast off (benefit when starting)	• No routine monitoring of anticoagulant efficacy • Once daily dosing • Short half-life; fast on and fast off (benefit when starting) • Not metabolized by CYP3A4

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DISADVANTAGES	• Many drug interactions (but manageable if PT/INR monitored and warfarin dose adjusted appropriately) • Dietary interactions due to vitamin K content in food; patients need to maintain consistency with their vitamin K intake • Frequent lab monitoring • Narrow therapeutic window • Slow onset and offset • Possible need for bridging when patient has surgery/procedure	• No ability to monitor safety and efficacy • Drug interactions with P-gp inducers and inhibitors, especially inhibitors with reduced renal function • GI side effects • Twice daily dosing • Capsule cannot be opened • Storage: once bottle opened, drug must be used within 4 months; must be stored in original bottle (no pill boxes) • Short half-life; fast on and fast off (problem for missed doses) • Cost	• No ability to monitor safety and efficacy • Drug interactions with combined P-gp and CYP450 3A4 inhibitors/inducers • Cost • Short half-life; fast on and fast off (problem for missed doses)	• No ability to monitor safety and efficacy • Drug interactions with strong CYP3A4 and P-gp inhibitors/inducers • Cost • Twice daily dosing • Dosing is a bit more complicated for some patients than with other agents • Short half-life; fast on and fast off (problem for missed doses)	• No ability to monitor safety and efficacy • Drug interaction with P-gp inducers • Cost • Dosing based on SCr assessment • Short half-life; fast on and fast off (problem for missed doses)
RELATIVE COST OF THE DRUG	$	$$$	$$$	$$$	$$$
PATIENT ASSISTANCE		• Pradaxa Savings Card • Pradaxa house call program (patient support)	• Xarelto Savings Card • Xarelto CarePath (patient support)	• Eliquis 360 Support (patient support and savings)	• Savaysa Savings Card
FDA POSTMARKET DRUG SAFETY INFORMATION		http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm248694.htm			
FDA MEDICATION GUIDE	http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088578.pdf	http://www.fda.gov/downloads/Drugs/DrugSafety/UCM231720.pdf	http://www.fda.gov/downloads/Drugs/DrugSafety/UCM280333.pdf	http://www.fda.gov/downloads/Drugs/DrugSafety/UCM333961.pdf	Not available yet

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Notes:
a. No citation/recommended by developers of this resource.
b. There is no FDA-approved dosing for atrial fibrillation. CHEST 2012 guidelines recommend use with aspirin if chosen for CVA prophylaxis against cerebrovascular accidents in patients with nonvalvular atrial fibrillation.
c. At the time of publication, the ecarin clotting test (ECT) was not available in most laboratories.

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