Target Specific Oral Anticoagulants

		Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Drug Classification		Selective thrombin inhibitor	Selective direct Xa inhibitor	Selective direct Xa inhibitor
FDA Approved Indications		- Nonvalvular AF - Treatment of VTE & PE - Reduce risk of recurrent VTE & PE	- Nonvalvular AF - Treatment of VTE & PE - Reduce risk of recurrent VTE or PE - VTE prophylaxis (hip & knee)	- Nonvalvular AF - Treatment of VTE & PE - Reduce risk of recurrent VTE or PE - VTE prophylaxis (hip & knee) - FDA approved for nonvalvular AF patients on hemodialysis
Relative risk reduction compared to warfarin	Trial: AF: VTE/PE:	RE-LY (150 and 110 mg) RE-COVER	ROCKET-AF (20 and 15 mg) EINSTEIN	ARISTOTLE (5 and 2.5 mg) AMPLIFY and AMPLIFY-EXT
	Stroke & embolism	35% ($CHADS_2$ 2.1), 150 mg superior, 110 mg noninferior	21% ($CHADS_2$ 3.47), noninferior to warfarin	21% ($CHADS_2$ 2.1), superior to warfarin
	ICH	74% (both doses)	41%	49%
	GIB	48% increase (150 mg) but post-market suggests similar	38% increase	No increase
Half-life		12-17 hrs 14-17 hrs (elderly)	5-9 hrs 9-12 hrs (elderly)	8-15 hrs
Time to max effect		2 hrs	2-4 hrs	3 hrs
Elimination		80% renal 20% biliary	66% renal 33% biliary	25% renal 75% biliary
Dosage		*AF*: • 150 mg BID • If CrCl 15-30 use 75 mg bid *VTE treatment & Recurrent VTE:* CrCl > 30: 150 mg BID after 5-10 days of parenteral AC CrCL < 30: dosing recs not provided	*AF:* • 20 mg DAILY with pm meal • If CrCl 15-50 use 15 mg daily *VTE prophylaxis:* 10 mg DAILY for 35 days after hip surgery & 12 days after knee surgery *VTE treatment:* 15 mg BID for 21 days, then 20 mg DAILY *Recurrent VTE:* 20 mg daily	*AF*: • 5 mg BID • Reduce from 5 mg to 2.5 mg BID for pts with 2 of 3 "high-risk" criteria: age ≥ 80, wt ≤ 60 kg, creat ≥ 1.5 • Can be given to pts on HD *VTE prophylaxis:* 2.5 mg BID for 35 days after hip surgery & 12 days after knee surgery *VTE treatment:* 10 mg BID for 7 days, followed by 5 mg BID *Recurrent VTE:* 2.5 mg BID
Dosing considerations and Contraindications		- Do not use if CrCl < 15 mL/min - Avoid in pregnancy, breastfeeding or in severe liver disease		
Monitoring		No lab testing available. All NOACs affect the INR. Measuring INRs during co-administration may not be useful for determining an appropriate dose of warfarin.		
Peri-procedure use (see U-Connect for UW guidelines)	Pre-op	- CrCl ≥ 50: d/c 1-2 days prior to standard risk procedure; d/c 3-5 days prior to high bleeding risk surgery - CrCl < 50: d/c 3-5 days prior to standard risk procedure; d/c > 5 days prior to high risk surgery	- Discontinue 24 hrs prior to surgery - CrCl ≤ 30: d/c 48 hrs prior to standard risk procedure; d/c 72 hrs before high risk surgery	- Discontinue 48 hrs prior to elective moderate to high risk surgery for bleeding - Discontinue 24 hrs prior to elective low risk surgery for bleeding - Bridging usually not needed
	Post-op	- For low bleed risk surgery restart 12-24 hrs post-op if ok with surgeon (for all 3 NOACs) - For high bleed risk surgery restart 48-72 hrs post-op if ok with surgeon (for all 3 NOACs)		
Switching from NOAC to warfarin		- If CrCl ≥ 50: start warfarin 3 days prior to stopping dabigatran - If CrCl 31-50: start warfarin 2 days prior to stopping dabigatran - If CrCl 15-30: start warfarin 1 day prior to stopping dabigatran	Initiate warfarin & a parenteral anticoagulant 24 hrs after stopping rivaroxaban	If continuous anticoagulation is necessary, stop apixaban & begin both a parenteral anticoagulant & warfarin when next dose is due; stop parenteral anticoagulant when INR at goal

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Switching from NOAC to IV UFH or enoxaparin	- If CrCl >30, start UFH or enoxaparin 12 hrs after last dose - If CrCl <30, consider starting UFH or enoxaparin 24 hrs after last dose	- If CrCl >30, start UFH or enoxaparin 12 hrs after last dose - If CrCl <30, consider starting UFH or enoxaparin 24 hrs after last dose	Start UFH or enoxaparin 12 hrs after the last apixaban dose
Switching from warfarin to NOAC	Allow INR to drop to < 2.0 before initiating	Allow INR to drop to < 3.0 before initiating	Allow INR to drop to < 2.0 before initiating
Switching from parenteral AC to NOAC	• Start NOAC 2 hrs before the time to next subcutaneous anticoagulant dose • Start NOAC at the time of IV heparin discontinuation		
Recommendations for bleeding besides blood products (see UW guidelines on U-Connect)	- For all NOACs hemostasis expected within 12-24 hrs after last dose - No antidote currently available - Dabigatran is only NOAC that can be moderately reversed by hemodialysis - Oral activated charcoal given within 2 hrs may decrease plasma concentrations		
Missed Dose	- Take missed dose ASAP, but if next dose is < 6 hrs away, skip the missed dose - Do not take 2 doses at the same time	- If taking 15 mg BID: Take ASAP to ensure 30 mg daily - For daily dose: Take missed dose immediately	-Take missed dose ASAP on same day - The dose should not be doubled to make up for a missed dose
Drug Interactions	- P-gp inhibitors may ↑ serum concentration (i.e. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil) - P-gp inducers may ↓ serum concentration (i.e. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin)	- P-gp & strong CYP3A4 inhibitors may ↑ serum concentration (i.e. amiodarone, cyclosporine, ketoconazole, quinidine, verapamil, azole antifungals, nicardipine, ritonavir) - P-gp & strong CYP3A4 inducers may ↓ serum concentration (i.e. carbamazepine, dexamethasone, phenytoin, prazosin, rifampin, nafcillin)	Same as Rivaroxaban
Use for electrical cardioversion	Demonstrated to be effective anticoagulant in the setting of cardioversion with guidelines similar to warfarin		
Nonbleeding Side Effects	Dyspepsia (5-10%)	None	
Advantages	- Fixed dose - No bridging - No INR monitoring required - No food restrictions & fewer drug interactions		
Disadvantages	- Cost - Lack of antidote & difficult to manage bleeding - Difficult to determine compliance - Missed dose may place pt at increased risk of thromboembolic event - Renal monitoring and dose adjustment required		
Lab Frequency follow-up	Yearly: Hgb, renal and liver function 6 monthly: Renal function if CrCl 30-60 ml/min, or if on dabigatran and > 75 years or fragile 3 monthly: If co-morbidity or condition that may impact renal or hepatic function		
Pricing	All 3 NOACs are covered by major insurers in Madison area. GHC required a prior authorization. May consider checking with pt's insurance company before prescribing to see what their copayment will be.		

References:

- European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation (2013) 15, 625-651.
- Chest Supplement, Antithrombotic Therapy and Prevention of Thrombosis, 9th edition, ACCP.
- RE-LY trial: NEJM 2009; 361:1139
- ROCKET-AF trial: NEJM 2011: 365:883.
- ARISTOTLE trial: NEJM 2011: 365:981.
- Package inserts from Pradaxa, Xarelto, & Eliquis

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