

Guideline for the Prescribing of Novel Oral Anticoagulants (NOACs): Dabigatran (Pradaxa®), Rivaroxaban (Xarelto®), Apixaban (Eliquis®)

The contents of this CPG are to be used as a guide. Healthcare professionals should use sound clinical judgment and individualize patient care. This CPG is not meant to be a replacement for training, experience, CME, or studying the latest literature and drug information.

Introduction to NOACs

PROS:

- Novel anticoagulants (NOACs) (both direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban)) are well tolerated.
- None of the novel anticoagulants require routine laboratory monitoring
- Drug-food interactions are minimal; only rivaroxaban should be taken with food to help absorption
- Drug-drug interactions are less than for warfarin (however, dabigatran interacts with P-glycoprotein and rivaroxaban/apixaban are inducers of cytochrome P450 3A4)

CONS:

- None of the NOACs -- neither dabigatran, rivaroxaban, nor apixaban -- have proven effective, well studied antidotes at the time of this writing. In the event of trauma while on these agents, the risk of critical bleeding (i.e. CNS bleeding, bleeding that cannot be stopped) is high. See VCMC Clinical Practice Guideline on reversal of these agents, "Management of Bleeding Associated with Target-Specific Oral Anticoagulants."
- Non-compliance can lead to higher risk of clots (black box warnings exist regarding higher risk of clot with abrupt stoppage of NOACs). Patients with a demonstrated difficulty adhering to prescribed medication regimens should NOT be offered novel anticoagulants over more traditional anticoagulants
- Dose adjustments are necessary for renal insufficiency
- NOACs are to be avoided with hepatic dysfunction and an elevated baseline INR, as such patients were excluded from trials of novel anticoagulants because novel anticoagulants undergo hepatic metabolism.
- Caution should be exercised when prescribing for older patients (age>70). Contraindicated (with rare exceptions for exceptionally good health and follow-up; clinical judgment is imperative) for age >75.
- Extra caution should be used in patients with increased risk of bleeding, including but not limited to those with inflammatory bowel disease or history of gastric or duodenal ulcers.
- Extensive DVT or massive PE should be treated with parenteral anticoagulants and not NOACs
- Utility of treatment in special populations (patients with active cancer, morbid obesity or very low body weight; pregnant women, nursing mothers, patients with serious thrombophilic defects, or those requiring concomitant antiplatelet therapy) is yet to be established.
- Brief cost related information
 - These three drugs are "restricted" status at VCMC/SP hospitals.
 - Health plans have these agents on Tier II or Tier III – higher copays for patients.
 - Gold Coast and Medi-Cal require Prior Authorization or a Therapeutic Authorization Request.
 - Available through Patient's Assistance Program – may take up to 2 months for processing.
 - Out of pocket costs (cash price):
 - Warfarin 5 mg 30 day supply: \$9 (drug cost only)
 - Dabigatran 150mg 30 day supply: \$ 333.08
 - Rivaroxaban 20mg 30 day supply: \$301.54
 - Apixaban 5mg 30 day supply: \$155

Specific Scenarios of Prescribing

1. Patients admitted to the hospital with NOACs as home medication and the need for continuation of anticoagulation persists.
 - a. Depends on the cause for hospitalization:
 - i. Medically complex patients with high risk for receiving procedures, CT scans with contrast, acute kidney or liver injury, or other complication (i.e. septic patients): The recommendation is to convert to parenteral anticoagulation.
 1. CrCL \geq 30 mL/min: Enoxaparin
 2. CrCL 15-30 mL/min: Dose adjusted enoxaparin or heparin drip
 3. CrCL < 15 mL/min: Heparin drip
 4. Any contraindication to enoxaparin or heparin drip (i.e. HIT): Argatroban drip or possible continued use of NOACs only after mandatory consultation with inpatient pharmacy.
 - ii. Patients with simple medical problems with low risk for receiving procedures, CT scans with contrast, or acute liver or kidney injury (i.e. patient with simple cellulitis): The recommendation is to continue the patient's home anticoagulant
 - b. Converting NOACs to parenteral anticoagulation: Use Table 1.
2. Inpatient, ED, or clinic patients with new indication for anticoagulation for either non-valvular atrial fibrillation or DVT/PE on discharge.
 - a. Candidates for these therapies must meet ALL of the following criteria (clinical judgment is imperative):
 - i. 75 years of age or younger
 - ii. No significant renal or hepatic disease (i.e. no creatinine clearance less than 30, no Child's Class B or C cirrhosis)
 - iii. Hemodynamically stable
 - iv. No need for thrombolysis (tPA)
 - v. No active bleed or risk of bleed, including no inflammatory bowel disease and no history of gastric or duodenal ulcers
 - vi. No medical or social need for admission
 - vii. No IV pain medicine needed
 - viii. No O2 requirement
 - ix. Not pregnant
 - x. No history of Heparin Induced Thrombocytopenia (HIT)
 - xi. Demonstrated good compliance with medication regimens
 - xii. Excellent outpatient follow-up already established
 - xiii. No antiphospholipid antibody syndrome
 - b. Mandatory education about the following aspects of these medications must occur prior to their use:
 - i. Must caution patients against abrupt discontinuation of medication.
 - ii. Due to lack of approved antidote, patient should be advised regarding the avoidance of trauma, particularly head trauma (see black box warnings and antidote section on Table 3).
 - c. Highly recommended that the patient's family obtain the medications from the outpatient pharmacy and bring them to the hospital prior to discharge, to confirm no gap in anticoagulation due to inability to obtain/ afford the medications

- d. Use Table 1 “Discharge” section to transition into NOACs.
- e. Medications by indication:
 - i. Non-valvular atrial fibrillation
 - 1. Possible agents: dabigatran, rivaroxaban, apixaban
 - 2. See Table 3 for further dosing information.
 - ii. DVT or PE
 - 1. Patient should have no evidence of hemodynamic instability, respiratory insufficiency, or other concerning signs or symptoms that would warrant admission/continued hospitalization.
 - 2. Possible agents: rlvaxaban, apixaban (may use dabigatran after initial treatment with a parenteral agent x 5 days)
 - iii. See Table 3 for further dosing information.
- f. For patients who require aspirin therapy, dose is not to exceed 81 mg
- g. Other antiplatelet agents are to be avoided

Table 1. Converting from/to parenteral anticoagulation and from warfarin to NOACs

Medication	Admission	Discharge		
	NOACs → parenteral anticoagulant	Enoxaparin → NOACs	Heparin drip → NOACs	Warfarin → NOACs
Dabigatran	CrCL ≥ 30 mL/min wait 12 hours to start parenteral CrCL < 30 mL/min wait 24 hrs to start parenteral	Start 0-2 hours before next scheduled enoxaparin dose	Discontinue drip and start dabigatran at the same time	Start when INR < 2
Rivaroxaban	Start when next dose is due – from table 2/ micromedex	Start 0-2 hours before next scheduled <u>evening</u> enoxaparin dose	Discontinue drip and start rivaroxaban at the same time	Start when INR <3
Apixaban	Start when next dose is due – from table 2	Start at the time of next scheduled enoxaparin dose	No information	Start when INR <2

Table 2. Converting NOACs to warfarin

Medication	NOACs → Warfarin ± parenteral anticoagulation bridge
Dabigatran	<p>Manufacturer recommends that dabigatran may be converted directly to oral warfarin based on creatinine clearance without a bridging parenteral anticoagulant. This is such a high risk scenario that our recommendation is to NOT follow the manufacturer recommendation and instead do the following:</p> <p>CrCL ≥ 30 mL/min: Start parenteral anticoagulant and warfarin together 24 hours after last dose of dabigatran</p> <p>CrCL <30 mL/min: Start parenteral anticoagulant and warfarin together 48 hours after last dose of dabigatran</p> <p>NOTE: Dabigatran may contribute to elevated INR. INR in the first 2 days after DC of dabigatran may not be true effect from warfarin.</p>
Rivaroxaban Apixaban	<p>Begin both parenteral anticoagulant and warfarin at the time the next dose of NOAC is due. Discontinue bridging parenteral anticoagulant when INR reaches an acceptable range. See Warfarin protocol on pharmacy resource website</p> <p>http://www.vchca.org/hospitals/pharmacy-resources</p>

Table 3.	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Mechanism of Action	Direct thrombin inhibitors and it inhibits both free and clot-bound thrombin as well as thrombin-induced platelet aggregation. Ultimately prevents thrombus development.	Selectively inhibits factor Xa. Does not require cofactor (anti-thrombin III) for activity.	Reversible and selectively inhibits free and clot-bound factor Xa. Does not require cofactor (anti-thrombin III) for activity.
FDA Approved indications	1. A. Fib (non-valvular) prophylaxis (ppx) 2. DVT tx (post parenteral therapy) and ppx 3. PE tx (post parenteral therapy) and ppx	1. A.Fib (non-valvular) ppx 2. DVT tx and 2°ppx 3. PE tx and 2°ppx 4. Ppx post arthroplasty of knee 5. Ppx post hip repair	1. A.Fib (non-valvular) ppx 2. Ppx post arthroplasty of knee 3. Ppx post hip repair 4. Tx for DVT and PE 5. PPX for DVT and PE following initial therapy
Non-FDA approved indications	1. Ppx post arthroplasty of knee 2. Ppx post hip repair	1. Ppx Recent ACS 2. Ppx venous thromboembolism	1. PPX Venous thromboembolism
AHA statement	“useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent A.Fib and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCL <15) or Advance liver disease (impaired baseline clotting function” (LOE 1B, superiority to warfarin)	No statement regarding use in non-valvular A.Fib. It is expected to make a recommendation that it is useful alternative to warfarin with LOE 2B due to non-inferiority (and not superiority).	Same as Rivaroxaban
Warnings/Precautions	- BLACK BOX WARNING: Do not stop abruptly – will increase risk of thrombotic events. - CONTRAINDICATIONS: Active pathological bleeding, mechanical prosthetic heart valve , anaphylactic reaction. - Precautions: DDI with P-gp* inducers/inhibitors, Renal impairments, elderly	- BLACK BOX WARNING: Do not stop abruptly – will increase risk of thrombotic events. - CONTRAINDICATIONS: Active bleeding, anaphylactic reaction - Precautions: use with HIV PI, other anticoagulants, antiplatelets, DDI with P-gp and strong CYP3A4 [†] inducers, elderly, renal, hepatic impairment.	- BLACK BOX WARNING: Do not stop abruptly – will increase risk of thrombotic events. - CONTRAINDICATIONS: Active bleeding, anaphylactic reaction - Precautions: Not recommended in prosthetic heart valves. Concurrent use with other anticoagulants, antiplatelets. DDI with P-gp, CYP3A4 inducers and inhibitors.
Dosing for FDA approved indication	1. A.Fib ppx: 150mg PO bid 2. DVT tx and ppx: 150mg PO bid 3. PE tx and ppx: 150 mg PO bid	1. A.Fib (nonvalvular) ppx: 20 mg PO Q PM 2. DVT tx and 2°ppx: 15 mg PO bid x 21 days then 20mg PO daily w/Food 3. PE tx and 2°ppx: 15 mg PO bid x 21 days then 20mg PO daily w/Food 4. Ppx post arthroplasty of knee: 10 mg PO daily x 12 days. Start at least 6-10 hrs post-surgery 5. Ppx post hip repair: 10 mg PO daily x 35 days. Start at least 6-10 hrs post-surgery	1. A.Fib (nonvalvular) ppx: 5 mg PO bid 2. Ppx post arthroplasty of knee: 2.5 mg PO bid x 12 days. Start 12-24 hrs after surgery. 3. Ppx post hip repair: 2.5 mg PO bid x 35 days. Start 12-24 hrs after surgery. 4. Tx for DVT and PE: 10 mg PO bid x 7 days then 5 mg PO bid 5. PPX for DVT and PE following initial therapy: 2.5 mg PO bid
Dose adjustment	- CrCL <30** or dialysis for tx or ppx of DVT or PE: No recommendation - CrCL 15-30 for stroke/systemic embolism ppx in nonvalvular A.Fib): 75 mg PO bid - CrCL < 15 for stroke/systemic embolism ppx in nonvalvular A.Fib: AVOID - CrCL <50 + P-gp drug use: consult pharmacist - Hepatic impairment: AVOID	- A.Fib (nonvalvular) CrCL 30-50: 15 mg PO Q PM CrCL <30: Avoid - Post surgical ppx DVT and tx/ppx of DVT/PE CrCL <30: Avoid - Acute renal failure: Discontinue - DDI with P-gp inh and CYP 3A4 inh: consult pharmacist - Hepatic impairment (Child-Pugh B or C) or coagulopathy associated with hepatic disease: AVOID	- Hemodialysis: AVOID - Hepatic impairment, severe: Do not use ≥ 80 y.o - ≤ 60 kg AND or Scr ≥ 1.5 mg/dL } → 2.5 mg bid - DDI with CYP3A4/P-gp inh: consult pharmacist

Table 3 continued	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Pharmacokinetic parameters	Bioavailability: 3-7% Dialyzable: Yes, about 50% at 4 hours Half-life: 12-17 hr; longer (up to 34 hr) in renal impairment. Coagulation pathway: prolongs aPTT, ecarin clotting time, PT	Bioavailability: 66-100%; increased bioavailability for 20mg when given with food. Dialyzable: No Half-life: 5-12 hr; longer (up to 19 hr) in elderly Coagulation pathway: Prolongs PT and aPTT. No data on use of INR value.	Bioavailability: 50% Dialyzable: No data Half-life: 7-15 hr Coagulation pathway: No data
Potential Reversal options	No approved antidote. See “Management of Bleeding Associated with Target-Specific Oral Anticoagulants Flowsheet” [No antidote currently being studied as of 2014]	No approved antidote. Possibly reversibility with Kcentra (4-Factor PCC) See “Management of Bleeding Associated with Target-Specific Oral Anticoagulants Flowsheet” [Antidote currently in phase II clinical trial as of 2014]	No approved antidote. Possibly reversibility with Kcentra (4-Factor PCC) See “Management of Bleeding Associated with Target-Specific Oral Anticoagulants Flowsheet” [Antidote currently in phase II clinical trial as of 2014]
Special Considerations	Up to a 10% incidence of dyspepsia Higher risk of GI bleeding vs. warfarin Small increased risk of MI seen in trials vs. warfarin Interacts with P-glycoprotein	Higher risk of GI bleeding vs. warfarin Inducer of cytochrome P450 3A4 isoenzyme	Pros: Less GI bleeding than other NOACs Cons: Inducer of cytochrome P450 3A4 isoenzyme
Definitions: A. Fib – Atrial fibrillation, DVT – Deep vein thrombosis, PE – Pulmonary embolism, TX – treatment, PPX – prophylaxis, BBW – black box warning, CI – Contraindication, DDI – drug drug interaction, P-gp- P-glycoprotein, CYP – cytochrome P450 enzyme			
Notes: *Short list of commonly used P-gp inhibitor/inducers: Amiodarone, azithromycin, captopril, clarithromycin, cyclosporine, dronedarone, ketoconazole, tacrolimus, rifampin, phenobarbital, ritonavir, verapamil, etc. **CrCL measured in ml/min †Short list of commonly used CYP3A4 inhibitor/inducers: Clarithromycin, itraconazole, fluconazole, grapefruit juice, diltiazem, voriconazole, CBZ, phenytoin, rifampin, St. John’s wart,			

References: Blood. 2014; 124(7): 1020-28. Dabigatran, rivaroxaban and apixaban package inserts, 2014. American Heart Association Guideline on Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation, 2012. Curr Cardiol Rep. 2014; 16: 463. Gastroenterology. 2013; 143: 105-112. Thrombosis. 2013: Article ID 640723.

Note: The plan is to revisit this policy every 6-12 months as new data becomes available and refinements to the policy are warranted.

Approval: FM 9/14, P&T 10/14, ER 10/14, Med 10/14, MEC 11/14