VENTURA COUNTY
HEALTH CARE AGENCY

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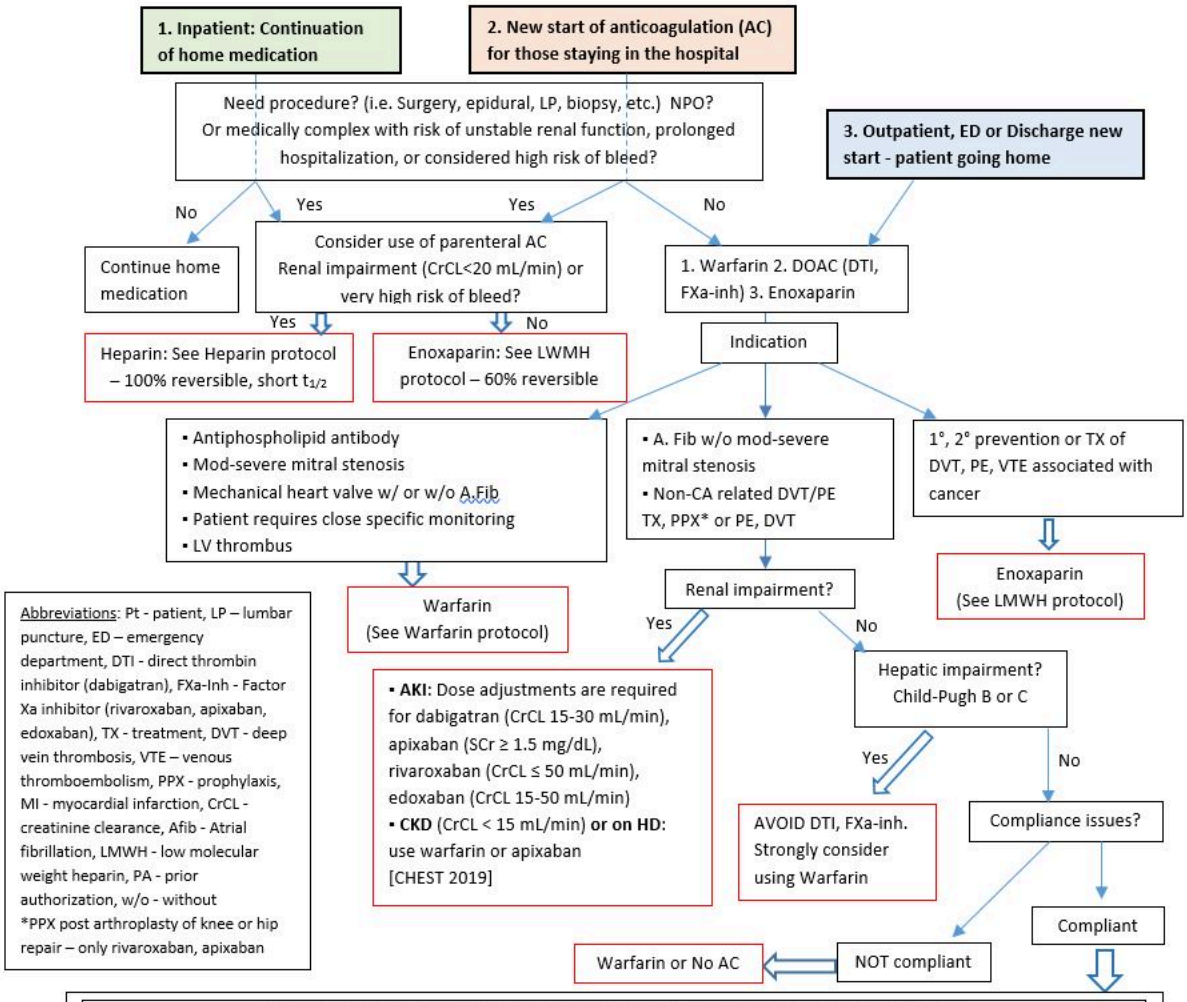
CPG.41 Prescribing of Direct Oral Anticoagulants (DOACs)

The contents of this clinical practice guideline 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.

Decision Tree for Direct Oral Anticoagulants (DOACs) vs. Vitamin K Antagonists vs. Parenteral Anticoagulants



Medication-specific Issues and Attributes that may influence prescribing for DTI, Xa-Inh	
Frequency of Administration	Daily: edoxaban, rivaroxaban; BID: dabigatran, apixaban. (Note: rivaroxaban and apixaban require initial higher +/- more frequent dose)
Require parenteral anticoagulant before transition to DOAC for DVT/ PE treatment	**Before transitioning to dabigatran or edoxaban DVT or PE should be treated with parenteral anticoagulation for initial 5-10 days.**
Existence of antidote	Dabigatran antidote - Idarucizumab; Rivaroxaban and apixaban antidote – andexanet alfa (non-formulary at VCMC/SPH); NO antidote for edoxaban at time of this writing
High creatinine clearance	CrCL > 95 mL/min: AVOID edoxaban
Coronary artery disease	Consider avoiding dabigatran
High bleed risk	Consider apixaban, trend towards less *gastrointestinal* bleeding
Insurance coverage	Gold Coast: all DTI & Xa-Inh covered, MediCal: rivaroxaban only; other insurances: vary
Special populations (pregnant, very high or low weight: See "Guideline for the Prescribing of Direct Oral Anticoagulants (DOACs)"	

Introduction to DOACs

PROS:

- Direct oral anticoagulants (DOACs), both direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) are well tolerated.
- Currently, DOACs does not require routine laboratory monitoring.
- Drug-food interactions are minimal; rivaroxaban and betrixaban 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.

- Dabigatran has an approved antidote, idarucizumab (Praxbind), which is stocked at both Ventura County Medical Center and Santa Paula Hospital. Please refer to *CPG.56 Management of Bleeding Associated with Anticoagulants and Antiplatelet Therapies.*

CONS:

- None of the factor Xa Inhibitors 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. Refer to *CPG.56 Management of Bleeding Associated with Anticoagulants and Antiplatelet Therapies.*
- Non-compliance can lead to higher risk of clots (black box warnings exist regarding higher risk of clot with abrupt stoppage of DOACs). Patients with a demonstrated difficulty adhering to prescribed medication regimens should NOT be offered DOACs over more traditional anticoagulants.
- Dose adjustments are necessary for renal insufficiency.
- Edoxaban is not to be used in patients with CrCL >95 mL/min due to increased risk of ischemic stroke.
- DOACs are to be avoided with hepatic dysfunction and an elevated baseline INR, as such patients were excluded from trials of DOACs because these medications undergo hepatic metabolism.
- Caution should be exercised when prescribing for older patients (age>70).
- 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 DOACs.
- 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. Small trials in patients with cancer have shown 'non-inferiority' vs. enoxaparin, but anticoagulation decisions are to be made on a case-by-case basis in consultation with Hematology/Oncology.
- Warfarin is the agent of choice in patients with renal failure, anti-phospholipid antibody syndrome, valvular atrial fibrillation, prosthetic heart valve with or without of atrial fibrillation, significant non-compliance (see above) or in those whom accurate levels of anticoagulation are needed.
- Betrixaban is only approved for VTE prophylaxis in patients with restricted mobility from acute illness and other risk factors. This medication is not discussed in the American Heart Association/America College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) or the American College of Chest Physician (CHEST) guidelines. For detailed medication information, refer to the manufacturer package insert.
- Brief cost related information:
  - Dabigatran, rivaroxaban and apixaban are on the Ventura County Medical Center/Santa Paula Hospital formulary.
  - Health plans have these agents on Tier II or Tier III – higher copays for patients.
  - Gold Coast formulary: Dabigatran, rivaroxaban, apixaban, and edoxaban only.
  - MediCal formulary: Rivaroxaban only.
  - Available through Patient's Assistance Program – may take up to 2 months for processing.
  - Wholesale costs (cash price):
    - Warfarin 5 mg 30-day supply: $9 (drug cost only)
    - Dabigatran 150mg 30-day supply: $ 250
    - Rivaroxaban 20mg 30-day supply: $323
    - Apixaban: 5mg 30-day supply: $320
    - Edoxaban: 60 mg 30-day supply: $266.34
    - Betrixaban: 80 mg 30-day supply: $540

Specific Scenarios of Prescribing

1. Patients admitted to the hospital with DOACs as home medication and the need for continuation of anticoagulation persists.
    A. Depends on the cause for hospitalization:
        1. Medically complex patients with high risk for undergoing procedures, CT scans with contrast, acute kidney or liver injury, or other complication (e. septic patients): The recommendation is to convert to parenteral anticoagulation as there is a shorter and more reliable half-life with both enoxaparin and heparin.
            i. CrCL ≥ 30 mL/min: Enoxaparin
            ii. CrCL 20-30 mL/min: Dose adjusted enoxaparin or heparin drip
            iii. CrCL < 20 mL/min: Heparin drip
            iv. Any contraindication to enoxaparin or heparin drip (i.e. Heparin induced thrombocytopenia - HIT): Argatroban drip or possible continued use of DOACs only after mandatory consultation with inpatient pharmacy.
        2. Patients with simple medical problems with low risk for undergoing procedures, or acute liver or kidney injury (i.e. patient with simple cellulitis): The recommendation is to continue the patient's home anticoagulant.
    B. Converting DOACs 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):
        1. No significant renal or hepatic disease (i.e. no creatinine clearance less than 30 mL/min, no Child's Class B or C cirrhosis)
        2. Hemodynamically stable
        3. No need for thrombolysis (Alteplase - tissue plasminogen activator (tPA))
        4. No active bleed or risk of bleed, including no inflammatory bowel disease and no history of gastric or duodenal ulcers
        5. Not pregnant
        6. Demonstrated good compliance with medication regimens
        7. Excellent outpatient follow-up already established
        8. No valvular atrial fibrillation
        9. No antiphospholipid antibody syndrome or other hypercoagulable genetic disorders
        10. No mechanical heart valve
    B. Mandatory education about the following aspects of these medications must occur prior to their use:
        1. Must caution patients against abrupt discontinuation of medication.
        2. Due to lack of approved antidote for factor Xa inhibitors, patient should be advised regarding the avoidance of trauma, particularly head trauma (see black box warnings and antidote section on

Attachment A).

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 DOACs.

E. Medications by indication:

1. Non-valvular atrial fibrillation
    i. Possible agents: dabigatran, rivaroxaban, apixaban, edoxaban
2. DVT or PE
    i. Patient should have no evidence of hemodynamic instability, respiratory insufficiency, or other concerning signs or symptoms that would warrant admission/continued hospitalization.
    ii. Possible agents: rivaroxaban, apixaban, dabigatran, or edoxaban
    iii. **Only use dabigatran or edoxaban AFTER initial treatment with a parenteral medication for 5 to 10 days**
3. See Table 3 for further dosing information.

F. For patients who require aspirin therapy, dose is not to exceed 81 mg.

G. Caution use with antiplatelet agents.

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

Admission			
Medication	**DOACs to parenteral anticoagulant**		
Dabigatran	CrCL ≥ 30 mL/min wait 12 hours to start parenteral CrCL < 30 mL/min wait 24 hrs to start parenteral		
Rivaroxaban	Start when next dose is due – from table 2		
Apixaban	Start when next dose is due – from table 2		
Edoxaban	Start when next dose is due		
Discharge			
Medication	**Enoxaparin to DOACs**	**Heparin drip to DOACs**	**Warfarin to DOACs**
Dabigatran	Start 0-2 hours before next scheduled enoxaparin dose	Discontinue drip and start dabigatran at the same time	Start when INR < 2
Rivaroxaban	Start 0-2 hours before next scheduled evening enoxaparin dose	Discontinue drip and start rivaroxaban at the same time	Start when INR <3
Apixaban	Start at the time of next scheduled enoxaparin dose	No information	Start when INR <2
Edoxaban	Start at the time of next scheduled enoxaparin dose	Discontinue drip and start edoxaban 4 hours later	Start when INR <2.5

Table 2. Converting DOACs to warfarin

Medication	DOACs to Warfarin ± parenteral anticoagulation bridge
Dabigatran	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: • CrCL ≥ 30 mL/min: Start parenteral anticoagulant and warfarin together 12 hours after last dose of dabigatran • CrCL <30 mL/min: Start parenteral anticoagulant and warfarin together 24 hours after last dose of dabigatran • NOTE: Dabigatran may contribute to elevated INR. INR in the first 2 days after discontinuance of dabigatran may not be true effect from warfarin.
Rivaroxaban Apixaban Edoxaban	Begin both parenteral anticoagulant and warfarin at the time the next dose of DOAC is due. Discontinue bridging parenteral anticoagulant when INR reaches an acceptable range. See Warfarin protocol on pharmacy resource website http://www.vchca.org/hospitals/pharmacy-resources

Guideline Statements

- 2016 CHEST guideline statement: Antithrombotic therapy for VTE disease [CHEST 2016; 149(2): 315-352]
  - "In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B). Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy."
  - "In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LWMH over VKA therapy (Grade 2B), dabigatran, rivaroxaban, apixaban or edoxaban (Grade 2C for DOACs)."
- 2018 CHEST guideline statement: Antithrombotic therapy for atrial fibrillation. [CHEST 2018; 154(5):1121-1201]
  - "In patients with atrial fibrillation who are eligible for oral anticoagulants, we recommend DOACs over vitamin K antagonist (Strong recommendation, moderate quality evidence). Remarks: Patient and caregiver preferences, cost, formulary considerations, anticipated medication adherence or compliance with INR testing and dose adjustment should be incorporated into clinical decision-making."
- 2019 AHA/ACC/HRS Update on management of patients with Atrial Fibrillation (AF)
  - NEW recommendation with Class of Recommendation (COR) of I and Level of evidence (LOE) of A.
    - Dabigatran, rivaroxaban, apixaban, and edoxaban are recommended over warfarin in DOAC eligible patients with AF (except with moderate to severe mitral stenosis or a mechanical heart valve).
  - For patients with AF who have mechanical heart valves, warfarin is recommended (COR I; LOE B)

References: Blood. 2014; 124(7): 1020-28. Dabigatran, rivaroxaban, apixaban and edoxaban 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. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015; 373:511-520. CHEST

2016; 149(2): 315-352. CHEST 2018; 154(5): 1121-1201. Circulation 2019; 140: e125-e151.

All revision dates: 6/9/2020

Attachments

Attachment A Drug Information for DOACs 05012020.pdf

Approval Signatures

Step Description	Approver	Date
Family Medicine, Medicine, Medical Executive and Oversight Committees	Tracy Chapman: VCMC - Med Staff	6/9/2020
P&T Committee	Jason Arimura: Director-Pharmacy Services	6/8/2020

CPG.41 Clinical Practice Guideline for the Prescribing of Direct Oral Anticoagulants (DOACs)

Attachment A: Drug Information for Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Betrixaban

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Attachment A: Supplement Medication Information				
	Dabigatran (Pradaxa) On VCMC/SP Formulary	**Rivaroxaban (Xarelto)** On VCMC/SP Formulary	**Apixaban (Eliquis)** On VCMC/SP Formulary	**Edoxaban (Savaysa)** Not on VCMC/SP Formulary
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.	Selective inhibitor of factor Xa. Reduces generation of thrombin and thrombus formation by inhibiting *free* factor Xa, prothombinase activity and thrombin-induced platelet aggregation.
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 4. Post-op DVT/PE ppx – Repair of hip	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 6. CV event risk prevention in combo with ASA	1. A. Fib (non-valvular) ppx 2. Ppx post arthroplasty of knee 3. Ppx post hip repair 4. Tx for DVT and PE 5. Secondary PPX for DVT and PE	1. A. Fib (non-valvular) ppx 2. DVT (post parenteral therapy) 3. PE (post parenteral therapy)
Non-FDA approved indications	1. Ppx post arthroplasty of knee	1. Ppx Recent ACS 2. Ppx venous thromboembolism		1. DVT PPX post total arthroplasty of knee
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, SSRI, 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. Use surrounding neuraxial anesthesia or spinal puncture – spinal/epidural hematoma. - **CONTRAINDICATIONS**: Active bleeding, anaphylactic reaction - **Precautions**: Not recommended in prosthetic heart valves. Concurrent use with other anticoagulants, antiplatelets, SSRI. DDI with P-gp, CYP3A4 inducers and inhibitors.	- **BLACK BOX WARNING**: Do NOT use with CrCL> 95 mL/min d/t reduced efficacy. Do not stop abruptly – will increase risk of thrombotic events. Do not remove indwelling epidural catheters sooner than 12 hrs after the last dose and wait 2 hours after catheter removal before administering - **CONTRAINDICATIONS**: Active bleeding, anaphylactic reaction - **Precautions**: Not recommended in prosthetic heart valves. Concurrent use with other anticoagulants, antiplatelets. DDI with P-gp, not recommend for CrCL < 15 mL/min, Hepatic impairment (Class B or C).

Attachment A cont.	**Dabigatran (Pradaxa)**	**Rivaroxaban (Xarelto)**	**Apixaban (Eliquis)**	**Edoxaban (Savaysa)**
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 or dialysis** for stroke/systemic embolism ppx in nonvalvular A. Fib: AVOID - **CrCL <50 + P-gp drug use**: AVOID - **Hepatic impairment**: AVOID	- **A. Fib** (nonvalvular) CrCL <50 or ESRD on HD: 15 mg PO Q PM - **Acute renal failure**: Discontinue - **Post surgical ppx DVT and tx/ppx of DVT/PE**: CrCL <30: Avoid - **DDI** w/ P-gp inh and CYP 3A4 inh: consult RX - **Hepatic impairment** (Child-Pugh B or C) or coagulopathy associated with hepatic disease: AVOID	-**Hepatic Impairment** Class C, severe: Do not use **- Atrial Fibrillation ppx:** 2.5 mg PO bid if meet 2 of the following: SCr ≥1.5 mg/dL, age ≥ 80, or weight ≤ 60 kg -**DVT or PE treatment or ppx**: no dosage adjustment needed for impaired renal function including in hemodialysis - **DDI** with CYP3A4/P-gp inh: consult RX	- Do NOT use for **CrCL > 95 mL/min** in nonvalvular A. Fib - **CrCL 15-50 mL/min**: 30 mg PO daily - **CrCL<15 mL/min**: Do NOT use - **Mod-Severe hepatic impairment** (Child-Pugh B and C): Do NOT use - **Weight ≤ 60 kg**: 30 mg PO daily - **DDI** P-gp inh in DVT or PE: consult RX
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	**Bioavailability**: 62% **Dialyzable**: No **Half-life**: 10-14 hr **Coagulation pathway**: No data
Potential Reversal options	Approved antidote: Idarucizumab (Praxbind) is available at VCMC/SPH. [N Engl J Med 2015; 373:511-520] See CPG.56 "Management of bleeding associated with anticoagulants and antiplatelet therapies"	Andexanet alfa (Andexxa) is not available at either VCMC nor SPH. [N Engl J Med 2016; 375(12)1131-41] See CPG.56 "Management of bleeding associated with anticoagulants and antiplatelet therapies"		No approved antidote. See CPG.56 "Management of bleeding associated with anticoagulants and antiplatelet therapies"
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 DOACs Cons: Inducer of cytochrome P450 3A4 isoenzyme	Higher risk of upper and lower GI bleeding vs warfarin

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, RX – Pharmacist

Notes: *Short list of commonly used P-gp inhibitor/inducers: Amiodarone, azithromycin, captopril, clarithromycin, cyclosporine, dronedarone, ketoconazole, tacrolimus, rifampin, phenobarbital, ritoniavir, 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,