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.
**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 CYP3A4,

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

1. **Inpatient: Continuation of home medication**
   - Need procedure? (i.e. surgery, epidural, LP, biopsy, etc.) NPO?
     - Or medically complex with risk of unstable renal function, prolonged hospitalization, or considered high risk of bleed?
     - Yes → Consider use of parenteral AC
     - No → Continue home medication

2. **New start of anticoagulation (AC) for those staying in the hospital**
   - Renal impairment? (CrCl < 20 mL/min) or very high risk of bleed?
     - Yes → Enoxaparin (See LMWH protocol – 60% reversible)
     - No → Heparin: See Heparin protocol – 100% reversible, short half

3. **Outpatient, ED or Discharge new start - patient going home**
   - 1°, 2° prevention or TX of DVT, PE, VTE associated with cancer
   - Hepatic impairment? Child-Pugh B or C
     - Yes → Compliance issues?
     - No → Warfarin or No AC

**Medication-specific Issues and Attributes that may influence prescribing for DTT, 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 DTT & 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)”
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.g., 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

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

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Enoxaparin to DOACs</th>
<th>Heparin drip to DOACs</th>
<th>Warfarin to DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Start 0-2 hours before next scheduled enoxaparin dose</td>
<td>Discontinue drip and start dabigatran at the same time</td>
<td>Start when INR &lt; 2</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Start 0-2 hours before next scheduled evening enoxaparin dose</td>
<td>Discontinue drip and start rivaroxaban at the same time</td>
<td>Start when INR &lt;3</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Start at the time of next scheduled enoxaparin dose</td>
<td>No information</td>
<td>Start when INR &lt;2</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Start at the time of next scheduled enoxaparin dose</td>
<td>Discontinue drip and start edoxaban 4 hours later</td>
<td>Start when INR &lt;2.5</td>
</tr>
</tbody>
</table>

Table 2. Converting DOACs to warfarin

<table>
<thead>
<tr>
<th>Medication</th>
<th>DOACs to Warfarin ± parenteral anticoagulation bridge</th>
</tr>
</thead>
</table>
| 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 | 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](http://www.vchca.org/hospitals/pharmacy-resources) |
| Apixaban   |                                                       |
| Edoxaban   |                                                       |

Guideline Statements

  ◦ “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)


All revision dates: 6/9/2020

## Attachments

- Attachment A Drug Information for DOACs 05012020.pdf

## Approval Signatures

<table>
<thead>
<tr>
<th>Step Description</th>
<th>Approver</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Medicine, Medicine, Medical Executive and Oversight Committees</td>
<td>Tracy Chapman: VCMC - Med Staff</td>
<td>6/9/2020</td>
</tr>
<tr>
<td>P&amp;T Committee</td>
<td>Jason Arimura: Director-Pharmacy Services</td>
<td>6/8/2020</td>
</tr>
</tbody>
</table>
**Attachment A: Supplement Medication Information**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On VCMC/SP Formulary</td>
<td>On VCMC/SP Formulary</td>
<td>On VCMC/SP Formulary</td>
<td>Not on VCMC/SP Formulary</td>
</tr>
<tr>
<td>Direct thrombin inhibitors and it inhibits both <em>free</em> and <em>clot-bound</em> thrombin as well as thrombin-induced platelet aggregation. Ultimately prevents thrombus development.</td>
<td>Selectively inhibits factor Xa. Does not require cofactor (anti-thrombin III) for activity.</td>
<td>Reversible and selectively inhibits <em>free</em> and <em>clot-bound</em> factor Xa. Does not require cofactor (anti-thrombin III) for activity.</td>
<td>Selective inhibitor of factor Xa. Reduces generation of thrombin and thrombus formation by inhibiting <em>free</em> factor Xa, prothrombinase activity and thrombin-induced platelet aggregation.</td>
<td></td>
</tr>
<tr>
<td>Non-FDA approved indications</td>
<td>1. Ppx post arthroplasty of knee 2. Ppx venous thromboembolism</td>
<td>- 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</td>
<td>- 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.</td>
<td>- BLACK BOX WARNING: Do NOT use with CrCL &gt; 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, SSRI. DDI with P-gp, CYP3A4 inducers and inhibitors.</td>
</tr>
<tr>
<td>Warnings/Precautions</td>
<td>- 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</td>
<td>- 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.</td>
<td>- 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, not recommend for CrCL &lt; 15 mL/min, Hepatic impairment (Class B or C).</td>
<td>- BLACK BOX WARNING: Do NOT use with CrCL &gt; 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 &lt; 15 mL/min, Hepatic impairment (Class B or C).</td>
</tr>
<tr>
<td>Attachment A cont.</td>
<td>Dose adjustment</td>
<td>Pharmacokinetic parameters</td>
<td>Potential Reversal options</td>
<td>Special Considerations</td>
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</tbody>
</table>
| **Dabigatran (Pradaxa)** | - **CrCl <30** or dialysis** for tx or ppx of DVT or PE: No recommendation  
- **CrCl 15-30** for stroke/systemic embolism ppx in nonvalvarul A. Fib): 75 mg PO bid  
- **CrCl < 15 or dialysis** for stroke/systemic embolism ppx in nonvalvarul A. Fib: AVOID  
- **CrCl <50 + P-gp drug use:** AVOID  
- **Hepatic impairment:** AVOID | **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 | **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” | **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 |
| **Rivaroxaban (Xarelto)** | **A. Fib** (nonvalvarul)  
**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 | **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. | Andexanet alfa (Andexxa) is not available at either VCMC nor SPH. [N Engl J Med 2016; 375(12)1131]  
See CPG.56 “Management of bleeding associated with anticoagulants and antiplatelet therapies” | **Higher risk of GI bleeding vs. warfarin**  
Inducer of cytochrome P450 3A4 isoenzyme |
| **Apixaban (Eliquis)** | **-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 | **Bioavailability:** 50%  
**Dialyzable:** No data  
**Half-life:** 7-15 hr  
**Coagulation pathway:** No data | No approved antidote.  
See CPG.56 “Management of bleeding associated with anticoagulants and antiplatelet therapies” | **Pros:**  
Less GI bleeding than other DOACs  
Cons:  
Inducer of cytochrome P450 3A4 isoenzyme |
| **Edoxaban (Savaysa)** | - Do NOT use for **CrCl > 95 mL/min** in nonvalvarul 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 | **Bioavailability:** 62%  
**Dialyzable:** No  
**Half-life:** 10-14 hr  
**Coagulation pathway:** No data | | **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, 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,