UNIVERSITY HOSPITAL AT DOWNSTATE/DOWNSTATE HEALTH SCIENCES UNIVERSITY
POLICY AND PROCEDURE

	No. PTSAF-19B
Subject: Direct Oral Anticoagulant Guideline	**Page: 1 of 11**
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Committee Approval: Medication Safety Committee Pharmacy and Therapeutics Committee Executive Performance Improvement Council (EPIC)	**TJC Standards:** **MM.01.01.03:** The organization safely manages high-alert and hazardous medications. **NPSG.03.05.01:** Reduce the likelihood of patient harm associated with the use of anticoagulant therapy. **Issued by: Regulatory Affairs**

I. PURPOSE

Direct oral anticoagulants (DOACs) are considered high-risk medications by the Institute for Safe Medication Practices and the University Hospital at Downstate/Downstate Health Sciences University. They possess the potential for serious patient harm if used in error. This guideline provides recommendations for clinicians on how to dose, monitor, and reverse DOAC therapy.

II. POLICY

Treatment with DOACs will follow the standardized prescribing, administration, and monitoring guidelines as outlined in this document. Patient-specific deviations shall be discussed on a case-by-case basis, and treatment will be individualized as needed by responsible providers with appropriate education and monitoring.

III. DEFINITION(s)

1. Anticoagulation: Pharmacologic therapy that will alter a patient's coagulation cascade, which will ultimately impair a patient's ability to form fibrin clots. A therapeutically anticoagulated patient will also be at a higher risk of experiencing a hemorrhage.

2. Reversal of Anticoagulation: The process of administering a pharmacologic reversal agent or blood product to effectively restore an anticoagulated patient's coagulation cascade.

IV. RESPONSIBILITIES

Pharmacy

V. PROCEDURES/GUIDELINES

A. DIRECT ORAL ANTICOAGULANTS

1. Direct Oral Anticoagulant Prescribing
    a. The DOACs available at Downstate Health Sciences University include:
        i. Direct factor Xa inhibitors: apixaban (Eliquis®) and rivaroxaban (Xarelto®)
        ii. Direct thrombin inhibitor: dabigatran (Pradaxa®)

    b. Prior to prescribing a DOAC, providers should order CBC, aPTT, PT/INR, BMP, and liver function tests if not already available.

    c. Initial DOAC dosing will depend on agent, indication, and patient-specific factors (e.g., renal and hepatic function, age, weight, and concomitant medications). See **Tables 1-3**.

    d. To determine how to convert/transition to and from DOAC agents, see **Table 4**.

    e. Contraindications to DOAC therapy include active bleeding, hypersensitivity to medication, and mechanical heart valves or significant rheumatic heart disease (e.g., mitral stenosis).

    f. DOAC therapy may be inappropriate for patients with inadequate renal or hepatic function, extreme weight gain, known thrombophilia, valvular heart disease, mechanical heart valves, gastrointestinal absorption issues, a history of non-compliance with medication therapy, or major drug interactions. If you have any questions, contact the pharmacy and/or Hematology.

Table 1. Apixaban Indications and Dosing

Indication	Normal Dosage	Renal Insufficiency	Hepatic Impairment
Non-valvular atrial fibrillation	5 mg twice daily **unless the** patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily	CrCl 15 to 29 mL/min: 2.5 mg twice daily Intermittent Hemodialysis: No dose adjustment is necessary unless either ≥80 years old or body weight ≤60 kg, then reduce the dose to 2.5 mg twice daily	Avoid in patients with severe hepatic impairment (Child-Pugh class C)
Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) treatment	10 mg twice daily for 7 days as an *initial load*, followed by 5 mg twice daily	No dosage adjustment is recommended	
VTE prophylaxis following total hip arthroplasty (THA) or total knee arthroplasty (TKA)	2.5 mg twice daily beginning 12 to 24 hours postoperatively	No dosage adjustment is recommended	

DOSAGE ADJUSTMENT OF APIXABAN WITH CONCOMITANT MEDICATIONS

- Strong dual CYP3A4 and P-glycoprotein inhibitors (e.g., ketoconazole, itraconazole, ritonavir):
  - Recommended apixaban dose 5 mg twice daily: Reduce apixaban dose by 50%
  - Recommended apixaban dose of 2.5 mg twice daily: Avoid concomitant use
- Strong dual CYP3A4 and P-glycoprotein inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort): Avoid concomitant use

Table 2. Rivaroxaban Indications and Dosing

Indication	Normal Dosage	Renal insufficiency	Hepatic Impairment
Non-valvular atrial fibrillation	20 mg once daily with the evening meal	• CrCl 15 to 50 mL/min: 15 mg once daily with the evening meal • CrCl <15 mL/min: Avoid use; apixaban or warfarin is preferred	Avoid in patients with moderate to severe hepatic impairment (Child-Pugh class B or C)
Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) treatment	15 mg twice daily with food for 21 days as an *initial load*, followed by 20 mg once daily with food	• CrCl <30mL/min: Avoid use	
VTE prophylaxis in acutely ill medical patients	10 mg once daily, without regard to meals	• CrCl <30mL/min: Avoid use	
VTE prophylaxis following total hip arthroplasty (THA) or total knee arthroplasty (TKA)	10 mg once daily, without regard to meals (initiated 6-10 hours after surgery once hemostasis is confirmed)	• CrCl 30 to 50 mL/minute: No dosage adjustment is necessary. Use with caution and monitor for signs or symptoms of bleeding. Discontinue in patients who develop acute renal failure. • CrCl <30mL/min: Avoid use	
Stable Coronary Artery Disease or Peripheral Artery Disease (prevention of major CV events)	2.5 mg twice daily (given with daily low-dose aspirin)	• CrCl <15mL/min: No adjustments provided. Patients excluded from clinical trials.	

DOSAGE ADJUSTMENT OF RIVAROXABAN WITH CONCOMITANT MEDICATIONS

- CYP3A4/P-glycoprotein inhibitors (e.g., ketoconazole, ritonavir, erythromycin, fluconazole, clarithromycin, amiodarone): Avoid concomitant use
- CYP3A4/P-glycoprotein inducers (e.g., rifampin, carbamazepine, phenytoin, and St. John's wort): Avoid concomitant use

Table 3. Dabigatran Indications and Dosing

Indication	Normal Dosage	Renal Insufficiency	Hepatic Impairment
Non-valvular atrial fibrillation	150 mg twice daily	• CrCl 15-30 mL/min: 75 mg twice daily (safety and efficacy of this dose have not been established) • CrCl <15 mL/min or hemodialysis: Not recommended	Avoid in patients with moderate to severe hepatic impairment (Child-Pugh class B or C)
Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) treatment	150 mg twice daily (manufacturer recommends at least 5 days of initial therapy with a parenteral anticoagulant before transitioning to dabigatran)	• CrCl >30 mL/min: No dosage adjustment unless the patient has CrCl <50 mL/min and is receiving concomitant P-gp inhibitors, then avoid co-administration • CrCl ≤30 mL/min: No dosage adjustments provided (has not been studied)	
VTE prophylaxis following Total hip arthroplasty (THA)	110 mg given 1 to 4 hours after completion of surgery or after hemostasis is achieved, followed by 220 mg daily for 10 to 14 days	• CrCl >30 mL/min: No dosage adjustment unless the patient has CrCl <50 mL/min and is receiving concomitant P-gp inhibitors, then avoid co-administration • CrCl ≤30 mL/min or hemodialysis: not recommended	

DOSAGE ADJUSTMENT OF DABIGATRAN WITH CONCOMITANT MEDICATIONS

DVT and PE (treatment) or VTE prophylaxis in THA:

- Any P-glycoprotein inducer (e.g., rifampin): Avoid concurrent use
- Any P-glycoprotein inhibitor (e.g., amiodarone, clarithromycin, dronedarone, ketoconazole [oral], quinidine, verapamil, and others) with CrCl <50 mL/min: Avoid concurrent use

Nonvalvular atrial fibrillation:

- Any P-glycoprotein inducer (e.g., rifampin): Avoid concurrent use
- Dronedarone or ketoconazole (oral) with CrCl 30-50 mL/min: Reduce dose to 75 mg twice daily
- Any P-glycoprotein inhibitor with CrCl <30 mL/min: Avoid concurrent use

Table 4. Transitioning Between Anticoagulants

From	To	Action
Apixaban (Eliquis®)	Warfarin	• Start warfarin now and consider adding a parenteral bridging agent when the next apixaban dose would have been due • Start INR monitoring 2 days after stopping apixaban* • Stop parenteral bridging agent when INR is at goal
	Other DOAC or LMWH/UFH	• Start new agent when the next apixaban dose would have been due
Dabigatran (Pradaxa®)	Warfarin	• CrCl >50 mL/min: start warfarin 3 days before stopping dabigatran • CrCl 30-50 mL/min: start warfarin 2 days before stopping dabigatran • CrCl 15-29 mL/min: start warfarin 1 day before stopping dabigatran • CrCl <15 mL/min: contact Hematology and/or Pharmacy • Start INR monitoring 2 days after stopping dabigatran*
	Other DOAC	• Start a new agent when the next dabigatran dose would have been due
	LMWH/UFH	• CrCl ≥30 mL/min: start 12 hours after the last dose of dabigatran • CrCl <30 mL/min: start 24 hours after the last dose of dabigatran
Rivaroxaban (Xarelto®)	Warfarin	• Start warfarin now and consider adding a parenteral bridging agent when the next rivaroxaban dose would have been due • Start INR monitoring 2 days after stopping rivaroxaban* • Stop parenteral bridging agent once INR is at goal
	Other DOAC or LMWH/UFH	• Start new agent when the next rivaroxaban dose would have been due
Warfarin	Apixaban, Dabigatran	• Start apixaban or dabigatran when INR <2
	Rivaroxaban	• Start rivaroxaban when INR <3 *or* when INR ≤2.5 in patients with higher bleeding risk
LMWH (enoxaparin)	DOAC†	• Start DOAC when the next dose of enoxaparin would have been due
UFH Infusion	DOAC†	• Start DOAC at the same time the heparin infusion is stopped

Note: *INR values drawn sooner may be falsely elevated by DOAC agents.

Note: †If already received ≥48 hours of therapeutic LMWH or UFH for treatment of DVT/PE, consider discussing with Hematology and/or Pharmacy regarding the optimal duration of the *initial load* for apixaban and rivaroxaban. Take into consideration clot burden, thrombotic risk, and bleeding risk of the patient.

2. Direct Oral Anticoagulant Administration and Monitoring
    a. Prior to prescribing and order verification, providers and pharmacists will verify laboratory values to ensure there are no current contraindications to DOAC therapy.

    b. Providers should perform periodic monitoring of CBC, renal, and liver function tests.

    c. Because therapeutic ranges are not yet established for DOACs, no routine monitoring is required unless clinically indicated. Contact Hematology for any questions.

Table 5. Administration of Direct Oral Anticoagulants

DOAC	Administration
Apixaban	• Administer without regard to meals. • Tablets may be crushed and swallowed *or* administered enterally.
Dabigatran	• Do **NOT** break, chew, or open capsules. **MUST be swallowed whole.**
Rivaroxaban	• Doses >10 mg should be taken with a meal. • Tablets may be crushed. • May be administered via G-tube, but should **NOT** be administered via J-tube.

B. **REVERSAL OF DIRECT ORAL ANTICOAGULANT**

1. In the setting of a major or life-threatening bleed, discontinue DOAC immediately.

2. All clinicians should review coagulation results and contraindications prior to ordering, verifying, and administering reversal agents.

Table 6. Management of Major or Life-Threatening Bleed

DOAC	Recommended Action	Monitoring
Direct Thrombin Inhibitor (dabigatran)	• Administer idarucizumab 5 g IV (split into two 2.5 g doses within 15 minutes of each other) * • If idarucizumab is not available, administer 4F-PCC (Kcentra®) 50 units/kg IV† • Consider activated charcoal for known recent ingestion (within 2-4 hours) • Hemodialysis can be considered • Contact Blood Bank for approval	• aPTT may be used for qualitative assessment but may not be sensitive or specific to the degree of anticoagulation with dabigatran
Factor Xa Inhibitors (apixaban, rivaroxaban)	• 4F-PCC (KCentra®) 50 units/kg IV • Consider activated charcoal for known recent ingestion (within 2-4 hours) • Do NOT administer vitamin K	• For rivaroxaban: PT may be useful for qualitative assessment but may not be specific to the degree of anticoagulation • For apixaban: PT and aPTT may be measured but are insensitive to the degree of anticoagulation • An anti-Xa assay calibrated for LMWH or UFH can rule out clinically relevant drug concentrations but is not useful for quantification

Note: *An additional 5-gram dose may be considered with the reappearance of clinically relevant bleeding

Note: †The optimal dosing of KCentra® in this population is not well-established. The European Heart Rhythm Association and NCS/SCCM recommend KCentra® at a dose of 50 units/kg (maximum 5,000 units).

3. 4-factor prothrombin complex concentrate [4F-PCC] (Kcentra®) may be used off-label. Consultation with the NYC Poison Center is recommended when using 4F-PCC for DOAC reversal.:
    a. KCentra® is given as an IV infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 mL/min (~210 units/min)

    b. Monitor for adverse reactions: hypotension, infusion reactions, and thrombotic events, including stroke, pulmonary embolism, and deep vein thrombosis, which may occur days or weeks after reversal of anticoagulation

    c. KCentra® is stocked in the Blood Bank and is procured in Pharmacy. Blood Bank approval is required prior to prescribing. Refer to (BLB-1) “Procedures for Ordering Blood Products”.

4. Idarucizumab (Praxbind®) is an immediate and specific reversal agent for the direct thrombin inhibitor dabigatran.
    a. Administer 5 g dose, split into two 2.5 g IV bolus doses:
        i. Administer 1st dose over 5-10 mins, followed by the 2nd dose within 15 mins.

    b. Monitor for ongoing bleeding and may administer a repeat 5 g dose if needed.

    c. Monitor for adverse reactions: hypersensitivity, new thrombotic event after reversal.

VI. ATTACHMENTS

None

VII. REFERENCES

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DATE REVIEWED	REVISION REQUIRED (CLICK BOX)		RESPONSIBLE STAFF NAME AND TITLE
	YES	NO	
12/2019	☒	☐	Pharmacy & Therapeutics Committee, Medical Executive Committee
09/2021	☒	☐	Pharmacy & Therapeutics Committee, Medical Executive Committee
03/2022	☒	☐	Medication Safety Committee, Pharmacy & Therapeutics Committee
07/12/2024	☐	☒	Medication Safety Committee, Pharmacy & Therapeutics Committee
1/2026	☒	☐	Manisa Tanprayoon, PharmD
	☐	☐	