TARGET SPECIFIC ORAL ANTICOAGULANTS (TSOACs)

This document is intended as a guideline only and should not replace sound clinical judgment
Please refer to UNMH formulary in Lexicomp for approved use(s) within hospital

PURPOSE:

- This document is intended as a guide to managing oral anticoagulant therapy in hospitalized patients
- It should be coupled with, and not supersede, clinical judgment.
- Evidence-based tools, such as dosing algorithms, should always be used in conjunction with clinical information pertaining to specific patient characteristics and conditions.

BACKGROUND:

- Target specific oral anticoagulants represent a shift in the therapeutic landscape of antithrombosis.
- They are the first oral anticoagulants available since the discovery of warfarin over 60 years ago.
- Due to their specificity, they do not require routine monitoring. They also have an improved pharmacokinetic profile compared to warfarin.

PHARMACOKINETIC COMPARISON TABLE:

	WARFARIN	RIVAROXABAN	APIXABAN	DABIGATRAN ETEXILATE
TARGET	Vitamin K epoxide reductase reducing the functional levels of vitamin K dependent coagulation factors	Factor Xa	Factor Xa	Thrombin
PRODRUG	No	No	No	Yes
BIOAVAILABILITY	>95%	>80%	>50%	~6%
T (MAX)	72-96h	2.5-4h	3h	2h
HALF-LIFE	40h	5-9 h healthy; 9-13 h elderly	8-15 h	14-17 h
MONITORING	INR adjusted	Not needed	Not needed	Not needed
ADMINISTRATION	Once daily	Once or twice daily	Twice daily	Once or twice daily
METABOLISM/ ELIMINATION	CYP 2C9, 3A4, 1A2	CYP3A4; 66% renal, 33% fecal	CYP3A4; 75% fecal, 25% renal	80% renal, 20% fecal
DRUG INTERACTIONS	CYP 2C9, 1A2, and 3A4	Potent CYP 3A4 inhibitor and P-gp inhibitors	Potent CYP 3A4 inhibitor and P-gp inhibitors	P-gp inhibitors

T (max) indicates peak plasma levels; h, hours; P-gp, P-glycoprotein

INITIATION OF TSOAC:

- When considering use of these agents, the pros and cons (in comparison to warfarin) must be weighed, along with patient preferences and values.

PRO(S)	CON(S)
▪ No INR monitoring required ▪ Bridging/induction therapy likely not needed ▪ Short half-life allows easier peri-operative management ▪ Convenient for rural patients or those with other barriers to clinic visits ▪ Fewer drug/diet/disease interactions ▪ Potentially better efficacy & safety for patients with poor INR control on warfarin ▪ Increased patient satisfaction ▪ Less complex patient/family education ▪ Follow up can likely be performed by community providers as well as specialty clinics	▪ No clear advantage over well-controlled warfarin ▪ TSOACs with BID dosing may have negative impact on compliance ▪ Missed doses place a patient at higher risk for adverse event due to short half-life ▪ No specific antidote or monitoring parameter ▪ Higher incidence of GI side effects & discontinuation rate ▪ Possible increased incidence of adverse events (e.g. MI, GI bleed, etc) depending on TSOAC ▪ Lack of monitoring may foster non-compliance ▪ Renal monitoring and dose adjustment required ▪ Higher out-of-pocket costs and copays

- Please refer to the UNMH formulary in Lexicomp for approved uses within the hospital
- **Patients that meet the following criteria may be considered candidates for TSOAC therapy**
  - History of poor INR control on warfarin despite good compliance
  - Considerable barriers to routine monitoring, such as physical or transportation issues
  - Documented warfarin allergy
  - Documented history of non-hemorrhagic adverse effects with warfarin
  - Documented, confirmed warfarin failure such as an ischemic stroke while consistently therapeutic on warfarin
- **Prior to initiation of a TSOAC, the patient should be evaluated for the following:**
  - Appropriate, approved indication at UNMH
  - Adequate insurance coverage or prescription assistance prior to discharge
  - Adequate renal function
  - Compliance history
  - Lack of medication interactions that would preclude use of TSOAC
  - History of any clinical conditions that might preclude use of TSOAC (e.g. history of MI, history of GI bleed, advanced age, low body weight, etc)
  - Ability to comply with prescribed follow-up plan

OUTPATIENT FOLLOW-UP FOR PATIENTS ON TSOAC

- While TSOACs do not require routine monitoring, it is advisable to develop an alternative follow-up plan with either the patient's primary care provider or a specialty outpatient clinic to periodically assess the following:
  - Renal and hepatic function
  - Existence of drug interactions
  - Occurrence of adverse events
  - Development of contraindications
  - Questioning about upcoming procedures
  - Ability to obtain and maintain the medication
  - Barriers to adherence
  - Patient satisfaction with therapy

DABIGATRAN (Pradaxa®)[1]

I. MECHANISM AND INDICATIONS

A. Mechanism: Oral direct thrombin inhibitor (DTI)

B. FDA approved indications: Stroke and systemic embolism prevention in non-valvular atrial fibrillation.

II. DOSING

A. Dosing based on renal function and potential drug-drug interactions

B. Following dosing based on dabigatran prescribing information

RENAL FUNCTION	DOSING
CrCl > 30 mL/min	150 mg PO BID
CrCl 30-50 mL/min on concomitant dronedarone or ketoconazole therapy†	75 mg PO BID
CrCl 15-30 mL/min on concomitant P-gp inhibitor therapy†	Avoid use
CrCl 15-30 mL/min	75 mg PO BID*
CrCl < 15 mL/min	Contraindicated

†See drug-drug interaction explanation below

*Use extreme caution

III. CONVERSION BETWEEN DABIGATRAN AND OTHER ANTICOAGULANTS

	DOSING BASED ON CRCL AND/OR TIMING
DABIGATRAN TO WARFARIN	Note: Dabigatran can contribute to an elevated INR, so the INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days. CrCl > 50 mL/min: Start warfarin 3 days before discontinuing dabigatran CrCl 31-50 mL/min: Start warfarin 2 days before discontinuing dabigatran CrCl 15-30 mL/min: Start warfarin 1 day before discontinuing dabigatran CrCl < 15 mL/min: Not recommended
WARFARIN TO DABIGATRAN	Discontinue warfarin and wait until INR < 2.0, then… CrCl > 30 mL/min: Start dabigatran 150 mg PO BID CrCl 15-30 mL/min: Start dabigatran 75 mg PO BID CrCl < 15 mL/min: Contraindicated
DABIGATRAN TO PARENTERAL ANTICOAGULANT	CrCl ≥ 30 mL/min: Wait 12 hours after last dose of dabigatran before initiating treatment with parenteral anticoagulant CrCl < 30 mL/min: Wait 24 hours after last dose of dabigatran before initiating treatment with parenteral anticoagulant
PARENTERAL ANTICOAGULANTS TO DABIGATRAN	Start dabigatran 0 – 2 hours before the time that the next dose of the parenteral anticoagulant (e.g. LMWH) was to have been administered OR Start dabigatran at the time of discontinuation of a continuously administered parenteral drug (e.g. IV UFH)

IV. DRUG-DRUG INTERACTIONS (DDI) WITH DABIGATRAN

A. Dabigatran exposure may be affected by concomitant use of P-glycoprotein (P-gp) inducers and inhibitors

P-GLYCOPROTEIN EFFECT	INTERACTION	SPECIFIC EXAMPLES	RECOMMENDED ACTION
Inducer of dabigatran metabolism	Reduces exposure to dabigatran	Rifampin	Avoid concomitant use
Inhibitor of dabigatran metabolism	Increases exposure to dabigatran	Ketoconazole, dronedarone	▪ Consider decreasing dose to 75 mg PO BID in patients with CrCl 30-50 mL/min* ▪ Avoid concomitant use of dabigatran and P-gp inhibitors in patients with CrCl 15-30 mL/min

*The use of other P-gp inhibitors (e.g. verapamil, amiodarone, quinidine, clarithromycin) in patients with CrCl 30-50 mL/min does not require a dose adjustment of dabigatran.

RIVAROXABAN (Xarelto®)[2]

I. MECHANISM AND INDICATIONS

A. Mechanism: Oral direct Factor Xa inhibitor

B. FDA-approved indications:
- Stroke and systemic embolism prevention in non-valvular atrial fibrillation
- DVT and PE treatment
- DVT and PE prevention following initial 6 months of treatment for DVT or PE
- DVT prophylaxis following hip or knee replacement surgery

II. DOSING

A. Dosing based on indication and renal function

B. Following dosing based on rivaroxaban prescribing information

INDICATION	RENAL FUNCTION	DOSING
Stroke/systemic embolism prevention in non-valvular atrial fibrillation	CrCl >50 mL/min	20 mg PO once daily with evening meal
	CrCl 15-50 mL/min	15 mg PO once daily with evening meal
	CrCl <15 mL/min	Contraindicated
DVT and PE treatment	CrCl ≥ 30 mL/min	15 mg PO BID with food, for first 21 days, THEN 20 mg PO once daily with food, for remaining treatment
	CrCl <30 mL/min	Contraindicated
DVT and PE prevention following initial 6 months of treatment for DVT or PE	CrCl ≥ 30 mL/min	20 mg PO once daily with food
	CrCl <30 mL/min	Contraindicated
DVT prophylaxis following hip or knee replacement surgery	CrCl ≥ 50 mL/min	Hip replacement: 10 mg PO once daily for 35 days
		Knee replacement: 10 mg PO once daily for 12 days
	CrCl 30-50 mL/min	Use extreme caution
	CrCl <30 mL/min	Contraindicated

III. CONVERSION BETWEEN RIVAROXABAN AND OTHER ANTICOAGULANTS

RIVAROXABAN TO WARFARIN	▪ No clinical trial data available ▪ Rivaroxaban affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin ▪ One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken
WARFARIN TO RIVAROXABAN	▪ Discontinue warfarin and wait until **INR < 3.0**; then start rivaroxaban
RIVAROXABAN TO ANTICOAGULANTS OTHER THAN WARFARIN	▪ Adjust starting time of oral or parenteral rapid-onset anticoagulant based on timing of last rivaroxaban dose ▪ Give first dose at the time the next dose of rivaroxaban would have been taken
ANTICOAGULANTS OTHER THAN WARFARIN TO RIVAROXABAN	▪ Adjust starting time of rivaroxaban based on timing of parenteral or oral anticoagulant other than warfarin ▪ Start rivaroxaban 0 – 2 hours before the time that the next evening dose of the other anticoagulant (e.g. LMWH or non-warfarin oral anticoagulant) was to have been administered, OR ▪ Start rivaroxaban at the time of discontinuation of a continuously administered parenteral drug (e.g. IV UFH)

IV. DRUG-DRUG INTERACTIONS (DDI) WITH RIVAROXABAN

A. DDI involving rivaroxaban include substrates of isoenzymes CYP 3A4/5 and 2J2 and transporters P-glycoprotein (P-gp) and ABCG2.

SUBSTRATE	EFFECT	EXAMPLES	RECOMMENDEDATION
Dual CYP 3A4 and P-gp inhibitors	Increased rivaroxaban exposure and pharmacodynamic effects	Ketoconazole, itraconazole, ritonavir, conivaptan	Avoid concomitant use
Dual CYP 3A4 and P-gp inducers	Decreased rivaroxaban exposure and possibly decreased efficacy	Carbamazepine, phenytoin, rifampin, St. John's Wort	Avoid concomitant use

V. HEPATIC IMPAIRMENT

A. Moderate (Child Pugh class B) to severe (Child Pugh class C) hepatic impairment: avoid use

B. Any hepatic disease associated with coagulopathy: avoid use

APIXABAN (Eliquis®)[3]

I. MECHANISM AND INDICATIONS

A. Mechanism: Oral direct Factor Xa inhibitor

B. FDA approved indication: Stroke and systemic embolism prevention in non-valvular atrial fibrillation.

II. DOSING

CRITERIA	DOSING
Recommended dosing	5 mg PO BID
Patients with any **2** of the following: ▪ Age ≥ 80 years ▪ Body weight ≤ 60 kg ▪ SCr ≥ 1.5 mg/dl	2.5 mg PO BID
Concomitant dual CYP3A4 and P-gp inhibitor therapy*	2.5 mg PO BID

*See drug-drug interaction explanation below; P-gp: P-glycoprotein

III. CONVERSION BETWEEN APIXABAN AND OTHER ANTICOAGULANTS

APIXABAN TO WARFARIN	▪ Apixaban affects INR, so INR measurements during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin ▪ Discontinue apixaban and start both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range
WARFARIN TO APIXABAN	▪ Discontinue warfarin and wait until INR < 2.0; then start apixaban
APIXABAN AND ANTICOAGULANTS OTHER THAN WARFARIN	▪ Discontinue anticoagulant being taken and begin the other anticoagulant at the next scheduled dose

IV. DRUG-DRUG INTERACTIONS (DDI) WITH APIXABAN

A. DDI involving apixaban include substrates of isoenzyme CYP 3A4 and transporter P-glycoprotein (P-gp).

SUBSTRATE	EFFECT	EXAMPLES	RECOMMENDED ACTION
Dual CYP 3A4 and P-gp inhibitors	Increased apixaban exposure	Ketoconazole, itraconazole, ritonavir, clarithromycin	▪ Decrease dose to 2.5 mg PO BID ▪ Patients already taking 2.5 mg PO BID: avoid concomitant use
Dual CYP 3A4 and P-gp inducers	Decreased apixaban exposure	Carbamazepine, phenytoin, rifampin, St. John's Wort	Avoid concomitant use

V. HEPATIC IMPAIRMENT

A. Severe hepatic impairment: avoid use

PERIOPERATIVE MANAGEMENT OF TSOACs[1-5]

Please refer to "UNMH guideline for perioperative management of antithrombotic therapy" on the pharmacy webpage (https://hospitals.health.unm.edu/intranet/pharmacy/index.shtml) for additional guidance

- Assessment of bleeding risk and adequate post-operative hemostasis should be considered prior to anticoagulation re-initiation
- Should not be used concomitantly with warfarin at either prophylactic or treatment doses, as this has not been studied. If overlap therapy is needed, use UFH or enoxaparin

Medication	Cessation	Re-Initiation Post-Op*
DABIGATRAN (Pradaxa®) 150 mg BID	*Low bleeding risk procedure:* ∇♦ – CrCl ≥50 mL/min ($t_{1/2}$ 14-17h) Skip 2 doses – CrCl 30-50 mL/min ($t_{1/2}$ 16-18h): Skip 4 doses	**APPLIES TO ALL TSOACs** ▪ No specific information available ▪ Peak plasma concentrations reached – Dabigatran: 1-2 hours – Rivaroxaban: 2-4 hours – Apixaban 3-4 hours ▪ Recommend re-initiating only if hemostasis is achieved, and – **24-48 hours** after **minor** procedures – **48-72 hours** after **major** procedures ▪ If TSOAC cannot be used post-procedure, consider initiation of parenteral agent ▪ If parenteral agent used as initial bridging therapy (e.g. UFH, LMWH), TSOAC therapy should be resumed – At least **1 hour** after discontinuation of UFH infusion – At least **10 hours** after last dose of LMWH ▪ Recommend consultation with anticoagulation service
	High bleeding risk procedure∇● – CrCl ≥50 mL/min ($t_{1/2}$ 14-17h) Skip 4 doses – CrCl 30-50 mL/min($t_{1/2}$ 16-18h) Skip 6-8 doses	
	More invasive procedures (e.g. major surgery, spinal puncture, placement of a spinal or epidural catheter or port) ▪ Consider longer period of cessation	
RIVAROXABAN (Xarelto®) 20 mg PO daily	*Low bleeding risk procedure:* ∇♦ – CrCl ≥30 mL/min ($t_{1/2}$ 8-9h) Skip 1 dose – CrCl 15-29 mL/min ($t_{1/2}$ 9-10h) Skip 2 doses	
	High bleeding risk procedure∇● – CrCl ≥30 mL/min ($t_{1/2}$ 8-9h) Skip 2 doses – CrCl 15-29 mL/min ($t_{1/2}$ 9-10h) Skip 3 doses	
APIXABAN (Eliquis®) 5 mg PO BID	*Low bleeding risk procedure:* ∇♦ – CrCl ≥50 mL/min ($t_{1/2}$ 7-8h) Skip 2 doses – CrCl 30-49 mL/min ($t_{1/2}$ 17-18h) Skip 4 doses	
	High bleeding risk procedure∇● – CrCl ≥50 mL/min ($t_{1/2}$ 7-8h) Skip 4 doses – CrCl 30-49 mL/min ($t_{1/2}$ 17-18h) Skip 6 doses	

REVERSAL STRATEGIES FOR TSOACs[1-3]

Please refer to "Antithrombotic reversal guidelines" on the pharmacy webpage (https://hospitals.health.unm.edu/intranet/pharmacy/index.shtml) for additional guidance

- There is no reversal agent for dabigatran, rivaroxaban or apixaban
- Management of life-threatening bleed remains empirical
- Measurement of aPTT, TT or ECT may help guide therapy
- Hemodialysis:
  - HD removed 62% of circulating **dabigatran** within 2 hours and 68% within 4 hours
  - Rivaroxaban is NOT removed by hemodialysis
  - Apixaban is NOT expected to be removed by hemodialysis
- Activated charcoal: Administration in < 1-2 hours of ingestion may be helpful in the event of an acute overdose
- Supportive care:
  - Early volume repletion
  - Early RBC repletion
  - Recombinant factor VII or PCC

LABORATORY MEASURMENT AND INTERPRETATION FOR TSOACs[1-4]

- The target specific oral anticoagulants, in general, have predictable pharmacokinetics, pharmacodynamics and metabolism. Therefore, **routine laboratory *monitoring* is NOT recommended**
- Routine laboratory monitoring has not been correlated to clinical outcomes
- Coagulation tests should be interpreted with caution
- Clinical scenarios where TSOAC *measurement* may be desirable or necessary include:
  - Surgery or invasive procedure
  - Hemorrhagic or thrombotic event
  - Suspected drug failure
  - Suspected overdose
  - Assess adherence
  - Presence of major drug-drug interactions
  - Extremes of weight
  - Extremes of age
  - Declining renal function
  - Need for thrombolytics
- **Coagulation test results are mostly helpful as a QUALITATIVE assessment (e.g. determine if anticoagulant effect is present or absent)**
- ***NOTE: standard anti-Factor Xa levels cannot be used to measure the effects of rivaroxaban or apixaban. An assay specific to each drug must be used, and these are not currently available***

LAB TEST	DABIGATRAN	RIVAROXABAN/APIXABAN
PT/INR	Poor sensitivity - DO NOT USE	Normal INR (+ normal aPTT) suggests minimal anticoagulant activity
aPTT	Normal aPTT suggests minimal anticoagulant activity*	Normal aPTT (+ normal INR) suggests minimal anticoagulant activity
TT (thrombin time)	Normal TT excludes presence of significant dabigatran levels**	DO NOT USE
ECT (ecarin clotting time)	Normal ECT excludes presence of significant dabigatran levels***	DO NOT USE
Chromogenic assays	Chromogenic anti-IIa assay not available	Normal anti-Xa assay excludes presence of significant rivaroxaban or apixaban levels†
dPT (dilute PT)	Unknown (promising results) - more sensitive than PT	Unknown (promising results)
Heptest	DO NOT USE	Normal Heptest suggests minimal anticoagulant activity‡
PiCT (prothrombinase induced clotting time)	Unknown (no available evidence)	Normal PiCT suggests minimal anticoagulant activity‡

*Mildly elevated aPTT can be associated with clinically important levels of dabigatran

**Can be affected by other anticoagulants and therefore be oversensitive and inaccurate at high concentrations
***Is not affected by other anticoagulants and sensitive at all concentrations
†Chromogenic anti-Xa assay must be calibrated for rivaroxaban or apixaban to correctly measure levels
ǂPreferred over PT or aPTT in measuring FXa inhibitor activity

CLINICAL MONITORING RECOMMENDATIONS FOR ALL TSOACs[1-3]

- Current renal function (serum creatinine, CrCl)
- Recent liver function panel

References:

1. Pradaxa [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 12/2012.
2. Xarelto [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 11/2012.
3. Eliquis [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company.; 12/2012.
4. Miyares MA, Davis K. Newer oral anticoagulants: A review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health Syst Pharm. 2012(69): e28-e39.
5. Viles-Gonzalez JF, Fuster V, Halperin JL. New anticoagulants for prevention of stroke in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2011(22): 948-55.