HOUSTON Methodist LEADING MEDICINE

RECOMMENDATIONS FOR TRANSITION FROM ORAL FACTOR Xa INHIBITORS (APIXABAN/RIVAROXABAN) TO PARENTERAL ANTICOAGULATION

Disclaimer: This guidance document is intended as a suggested approach, not a protocol, for transitioning patients taking an oral Factor Xa Inhibitor (FXaI) to parenteral anticoagulation using anti-Xa apixaban or rivaroxaban concentrations. These recommendations do not replace clinical judgment and/or individual, patient-specific assessment of bleeding and thrombotic risks. See pages 2-3 for detailed guidance and supplemental information.

Risk Factors for Apixaban/Rivaroxaban Accumulation and/or Delayed Clearance in Hospitalized Patients†

- Advanced age (≥75 years)
- Antiplatelet therapy
- Cirrhosis (moderate/severe)
- ICU admission
- Kidney disease (acute or chronic +/- renal replacement therapy
- Mechanical circulatory support devices

Recent Use of Oral Factor Xa Inhibitors
(Apixaban or Rivaroxaban)

Assessment for Patient-Specific Risk Factors associated with Oral FXaI Accumulation†

Risk Factors Absent:
Utilize Standard Package Insert Transition

Initiate appropriate parenteral anticoagulant (LMWH, UFH, or DTI)

Risk Factors Present:
Consider Concentration-Guided Transition Strategy: Check Oral FXaI-specific Anti Xa Concentration

Pathway A

anti-Xa apixaban ≤100 ng/mL
anti-Xa rivaroxaban ≤100 ng/mL

Initiate appropriate parenteral anticoagulant (LMWH, UFH, or DTI)

Pathway B

anti-Xa apixaban 101-200 ng/mL
anti-Xa rivaroxaban 101-200 ng/mL

Interdisciplinary, patient-specific assessment of bleeding/thrombotic risk and anticoagulant indication

Bleeding Risk > Thrombotic Risk

Consider HOLDING parenteral anticoagulant initiation. Repeat FXaI anti-Xa concentration in 6-12 hours

Repeat concentration <100:
Move to Pathway A

Thrombotic Risk > Bleeding Risk

Initiate appropriate parenteral anticoagulant (LMWH, UFH, or DTI) with caution

Pathway C‡

anti-Xa apixaban >200 ng/mL
anti-Xa rivaroxaban >200 ng/mL

Consider HOLDING parenteral anticoagulant initiation. Repeat FXaI anti-Xa concentration in 12-24 hours

Repeat concentration <100:
Move to Pathway A

Repeat concentration 100-200:
Move to Pathway B

‡There are unique, specific clinical scenarios (i.e., ST-segment elevation myocardial infarction, active pulmonary embolism with/without hemodynamic collapse) where initiation of parenteral anticoagulation therapy may be warranted despite an anti-Xa apixaban/rivaroxaban concentration ≥200 ng/mL. In these situations, initiation of parenteral anticoagulation with close monitoring for bleeding may be appropriate following collaborative interdisciplinary discussion amongst the treatment team.

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RECOMMENDATIONS FOR CONCENTRATION-GUIDED TRANSITION FROM ORAL FACTOR Xa INHIBITORS (APIXABAN/RIVAROXABAN) TO PARENTERAL ANTICOAGULATION

Disclaimer: This guidance document and its recommendations are intended as a suggested approach, not a protocol, for transitioning patients taking an oral Factor Xa Inhibitor to parenteral anticoagulation. These recommendations do not replace clinical judgment and/or individual, patient-specific assessment of bleeding and thrombotic risks. These recommendations do not address every possible clinical scenario that may arise when transitioning patients from an oral FXaI to parenteral anticoagulation.

1. **Determining History of Oral Factor Xa Inhibitor Use & Assessment of Risk Factors associated with Bleeding**
    a. All patients with **confirmed, inpatient/prior to admission use** of apixaban or rivaroxaban (i.e., within 72 hours) should undergo comprehensive assessment for presence of risk factors associated with oral FXaI accumulation and/or major bleeding
        i. Patients with risk factors for oral FXaI accumulation: consider ordering an anti-Xa apixaban or rivaroxaban concentration at the time of the next scheduled FXaI dose, or ASAP if the last dose was administered >12 hours ago (apixaban) or >24 hours ago (rivaroxaban)
        ii. Patients without risk factors for oral FXaI accumulation: utilize the Standard Package Insert Recommendations for transitioning to parenteral anticoagulation
    b. All patients with **unconfirmed or unknown timing** of last apixaban or rivaroxaban dose should have baseline coagulation labs (i.e., PTT, PT/INR, anti-Xa unfractionated) ordered on admission, and undergo comprehensive assessment for presence of risk factors associated with oral FXaI accumulation and/or major bleeding
        i. In this scenario, the anti-Xa unfractionated test serves as a screening tool to assess for recent oral FXaI use. In patients with recent oral FXaI use, the anti-Xa unfractionated test can be elevated due to assay interference, indicating qualitative presence or either apixaban, rivaroxaban, or another anticoagulant in the serum
            - Patients with risk factors for oral FXaI accumulation AND anti-Xa unfractionated result above the lower limit of detection: consider ordering an anti-Xa apixaban or rivaroxaban concentration ASAP
            - Patients without risk factors for oral FXaI accumulation OR undetectable anti-Xa unfractionated result: initiate the appropriate parenteral anticoagulant

Table 1: Risk Factors for Oral FXaI Accumulation/Delayed Clearance in Hospitalized Patients			
Acute Kidney Injury	Advanced Age (≥75)	Cirrhosis (Moderate/Severe)	Concurrent Antiplatelet Therapy
Continuous Renal Replacement Therapy	Critical Illness/ICU Admission	End-Stage Renal Disease	Mechanical Circulatory Support Devices

2. **Initiation of Parenteral Anticoagulation using Anti-Xa Apixaban or Rivaroxaban Concentrations**
    a. General Notes:
        i. Parenteral anticoagulation should be initiated no earlier than the time of the next scheduled dose of FXaI (i.e., 12 hours following the last dose of apixaban and 24 hours following the last dose of rivaroxaban), regardless of the anti-Xa apixaban or rivaroxaban concentration, as per package insert guidance
        ii. Exception: oral FXaI treatment failure, for example, new pulmonary embolism confirmed on objective imaging studies where parenteral anticoagulation may need to be initiated without delay and without respect to timing of last oral FXaI dose to prevent morbidity/mortality
    b. **Pathway A**: anti-Xa Apixaban or Rivaroxaban Concentration ≤100 ng/mL
        i. If the initial anti-Xa apixaban or rivaroxaban concentration is ≤100 ng/mL, initiate the appropriate parenteral anticoagulant without delay
    c. **Pathway B**: anti-Xa Apixaban or Rivaroxaban Concentration 101-200 ng/mL
        i. Transition decisions in Pathway B require interdisciplinary assessment of patient-specific risk factors for bleeding/thrombotic risks, as well as the indication for parenteral anticoagulation. All decisions to delay transition to parenteral anticoagulation ***must be communicated*** and agreed upon with the responsible physician
            - Patients whose **risk for bleeding outweighs the risk for thrombosis, and/or patients who are receiving anticoagulation for indications other than active thromboembolism** (i.e., atrial fibrillation, history of VTE >3-12 months without active clots), consider HOLDING transition to parenteral anticoagulation. Check a repeat anti-Xa apixaban or rivaroxaban concentration in 6–12-hour intervals
                - Once repeat anti-Xa apixaban or rivaroxaban concentration is ≤100 ng/mL, move to Pathway A and initiate appropriate parenteral anticoagulant
            - Patients whose **risk for thrombosis outweighs the risk for bleeding, and/or patients who are receiving anticoagulation for active thromboembolism**, consider initiation of appropriate parenteral anticoagulant with close monitor for signs/symptoms of bleeding

Table 2: Patient-Specific Factors associated with Increased Bleeding Risk		
Advanced Age (≥75)	Anemia	Cirrhotic Liver Disease
Dialysis-Dependent Kidney Disease	Excessive Alcohol Intake (≥8 drinks/week)	History of Major Bleeding
Hypertension (SBP >160 mmHg)	Impaired Kidney Function	Malignancy
Medications Predisposing to Bleeding Conditions	Previous Stroke	Prior Bleeding Event from Bridging*
Quantitative/Qualitative Platelet Abnormality (i.e., aspirin use)*	Recent (≤3 months) Major Bleed or ICH*	Reduced Platelet Count/Function

Not an all-inclusive list. Thorough review of each patient's individual risk factors for bleeding is required in each situation. Consider risk factors for oral FXaI accumulation/delayed clearance from Table 1 in conjunction with these patient-specific factors increasing overall risk for bleeding

* Denotes patient-specific factors that the American College of Cardiology Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation has deemed bleed risk to be "increased"

Table 3: Patient-Specific Factors associated with Increased Thrombotic Risk	
HIGH Risk for thromboembolic events	**High Risk Atrial Fibrillation:** - $CHADS_2$ score of 5 or 6 - CHA_2DS_2-VaSc score of 7 – 9 - Recent (within 3 months) stroke, TIA, or systemic embolism **High Risk Venous Thromboembolism:** - Recent (within 3 months) venous thromboembolic event - Severe underlying thrombophilia ▪ Antiphospholipid antibodies ▪ Deficiency of protein C ▪ Deficiency of protein S
MODERATE Risk for thromboembolic events	**Moderate Risk Atrial Fibrillation:** - $CHADS_2$ score of 3 or 4 - CHA_2DS_2-VaSc score of 5 – 6 - Prior (≥3 months) stroke, TIA, or peripheral arterial embolism **Moderate Risk Venous Thromboembolism:** - Active malignancy treated within 6 months or palliative - History of recurrent venous thromboembolic events - Venous thromboembolic event within the past 3-12 months - Non-severe underlying thrombophilia ▪ Heterozygous factor V Leiden mutation ▪ Heterozygous factor II mutation
LOW risk for thromboembolic event	**Low Risk Atrial Fibrillation:** - $CHADS_2$ score of 0 – 2 without any prior history of stroke or TIA - CHA_2DS_2-VaSc score ≤ 4 without any prior history of stroke, TIA, or systemic embolism **Low Risk Venous Thromboembolism:** - History of a single venous thromboembolic event occurring >12 months ago in the absence of any additional risk factors

Adapted from 2017 American College of Cardiology Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation and 2022 CHEST guidelines for Perioperative Management of Antithrombotic Therapy.
Not an all-inclusive list. Thorough review of each patient's individual risk factors for thrombosis is required in each situation.

d. **Pathway C**: anti-Xa Apixaban or Rivaroxaban Concentration >200 ng/mL‡
   i. Consider HOLDING transition to parenteral anticoagulation. Check a repeat anti-Xa apixaban or rivaroxaban concentration in 12-24-hour intervals
      - If the repeat anti-Xa apixaban or rivaroxaban concentration is ≤100 ng/mL, move to Pathway A and initiate the appropriate parenteral anticoagulant
      - If the repeat anti-Xa apixaban or rivaroxaban concentration is 101-200 ng/mL, move to Pathway B and perform interdisciplinary comprehensive assessment of patient-specific bleeding/thrombotic risks, along with indication for parenteral anticoagulation, to optimize transition approach

‡There are unique, specific clinical scenarios (i.e., ST-segment elevation myocardial infarction, active pulmonary embolism with/without hemodynamic collapse) where initiation of parenteral anticoagulation therapy may be warranted despite an anti-Xa apixaban/rivaroxaban concentration ≥200 ng/mL. In these situations, initiation of parenteral anticoagulation with close monitoring for bleeding may be appropriate following collaborative interdisciplinary discussion amongst the treatment team.