Direct Xa Inhibitor Levels

A subset of direct oral anticoagulants (DOACs) directly inhibit coagulation factor Xa. These direct Xa inhibitors, including rivaroxaban, apixaban, and edoxaban, do not require routine laboratory monitoring. There are some clinical scenarios in which efficacy or safety may be a concern and a measurement of direct Xa inhibitor activity may be useful. Drug-specific anti-Xa activity assays calibrated for a single direct Xa inhibitor may be used to make quantitative measurements of drug level. There is currently no definitive clinical trials evidence for adjusting apixaban, rivaroxaban, or edoxaban dose based on an anti-Xa activity result.

Testing Strategy

Possible Appropriate Scenarios for Ordering DOAC-specific Anti-Xa Assays[a]

Testing Scenario	Type of Level	Timing	Indication	Target
Concern for efficacy (to ensure adequate absorption)	Peak (steady state)	2-3 hours after DOAC dose	Severe obesity (BMI >40)	Peak >5th percentile
			Questionable impaired absorption (eg, gastric bypass)	
			Use of a p-glycoprotein and/or CYP3A4 inducer	
	Random level	Any time in the dosing interval	Suspected DOAC treatment failure	N/A[b]
Concern for safety (to ensure no DOAC accumulation)	Trough (steady state)	Right before a scheduled DOAC dose	Moderate to severe renal impairment (defined as CrCl <30 mL/min)	Trough <95th percentile
			Use of a p-glycoprotein and/or CYP3A4 inhibitor	

[a]If initial testing is performed while as an inpatient, consider repeating as an outpatient.

[b]A random level trough <5th percentile may indicate that a failure occurred in the setting of significantly reduced drug concentrations (eg, due to noncompliance, drug interaction, etc.) and could represent an inability to maintain an on-therapy drug level.

CrCl, creatinine clearance

Test Interpretation

Clinical and/or Analytical Sensitivity

Lower limit of assay detection by drug:

- Apixaban: 23 ng/mL

Tests to Consider

Apixaban Level 3004090

Method: Chromogenic Assay

Use to measure apixaban concentration

Edoxaban Level 3004092

Method: Chromogenic Assay

Use to measure edoxaban concentration

Rivaroxaban Level 3004094

Method: Chromogenic Assay

Use to measure rivaroxaban concentration

- Edoxaban: 20 ng/mL
- Rivaroxaban: 25 ng/mL

Results

- Because laboratory monitoring of direct Xa inhibitors is not required, there are no established therapeutic ranges for these drugs.
- Expected on-therapy ranges are published in the literature and derived from direct Xa inhibitor clinical trials. These on-therapy ranges:
  - Are specific to a given drug dose and treatment indication.
  - Describe observed peak and trough drug levels during clinical trials.
- ARUP reports will include on-therapy ranges from published clinical trials for on-therapy peak and trough levels observed with specified drug doses for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Select on-therapy range information is included in the table below. Further on-therapy range information, including information about on-therapy ranges with adjusted dosing for renal impairment, may be found in the listed references.

On-Therapy Range Information[a]

Drug	Dose	Indication	Peak	Trough
Apixaban	5 mg twice daily	Treatment of DVT and PE	59-302 ng/mL (5th-95th percentile)	22-177 ng/mL (5th-95th percentile)
	5 mg twice daily	Stroke prevention in nonvalvular atrial fibrillation	91-321 ng/mL (5th-95th percentile)	41-230 ng/mL (5th-95th percentile)
	2.5 mg twice daily	Prevention of VTE following elective hip or knee replacement surgery	41-146 ng/mL (5th-95th percentile)	23-109 ng/mL (5th-95th percentile)
Edoxaban	60 mg daily	Treatment of DVT and PE	149-317 ng/mL (interquartile range)	10-39 ng/mL (interquartile range)
	60 mg daily	Stroke prevention in non-valvular atrial fibrillation	125-245 ng/mL (1.5 X interquartile range)	19-62 ng/mL (interquartile range)
Rivaroxaban	20 mg daily	Treatment of DVT and PE	189-419 ng/mL (5th-95th percentile)	6-87 ng/mL (5th-95th percentile)
	20 mg daily	Stroke prevention in non-valvular atrial fibrillation (CrCl >50 mL/min)	184-343 ng/mL (5th-95th percentile)	12-137 ng/mL (5th-95th percentile)
	10 mg daily	Prevention of VTE following hip replacement surgery	91-196 ng/mL (5th-95th percentile)	1-38 ng/mL (5th-95th percentile)

[a]For more details, including information about on-therapy ranges with adjusted dosing for renal impairment, see Additional Resources.

VTE, venous thromboembolism

Sources: European Medicines Agency, 2021[1]; Mueck, 2014[2]; Ruff, 2015[3]; Weitz, 2010[4]

Limitations

- Anti-Xa activity assays can only be used to accurately measure the specific drug for which they are calibrated (eg, apixaban can only be accurately measured in an anti-Xa assay that includes an apixaban calibrator).
- Anti-Xa activity results are not reliable when more than one drug with anti-Xa activity is present in a plasma sample. Any drug with activity against factor Xa (eg, unfractionated heparin, low molecular weight heparin, fondaparinux, apixaban, edoxaban, rivaroxaban) will show effect in any of the anti-Xa activity assays. That is, if more than one drug is present (eg, unfractionated heparin and rivaroxaban), the effects of both drugs will be detected in the anti-Xa activity assay, regardless of the drug for which the assay is calibrated.
- Grossly hemolyzed specimens are not suitable for testing due to potential coagulation factor activation and chromogenic assay interference.
- Grossly icteric samples are not suitable for testing as bilirubin may interfere with chromogenic assays.

References

1. European Medicines Agency. Eliquis: summary of product characteristics. [Accessed: July 2021]

2. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53(1):1-16.

3. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet. 2015;385(9984):2288-2295.

4. Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost. 2010;104(3):633-641.

Additional Resources

Douxfils J, Adcock DM, Bates SM, et al. 2021 update of the International Council for Standardization in Haematology recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost. 2021;121(8):1008-1020.

Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018;16(2):209-219.

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ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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