Transitioning Direct Oral Anticoagulants to IV Heparin in the Inpatient Setting

Sara Zochert
Pharm.D., BCPS, CACP
Pharmacist – Sanford USD Medical Center

Disclosure Statement

- I have nothing to disclose.

Pharmacist Learning Objectives

1. Given a list of labs match them to the appropriate Direct Oral Anticoagulant (DOAC) for monitoring.
2. Describe current literature available as reference material when transitioning patients from DOACs to parenteral therapy.
3. Explain how the Anti-Xa laboratory assay measures concentrations of various medications.
4. Identify appropriate lab monitoring to assess baseline DOAC effects when ECT/ECA or DOAC Anti-Xa levels are not available.

Technician Learning Objectives

1. Identify medications that are classified as Direct Oral Anticoagulants (DOACs)
2. Given a list of labs match them to the appropriate Direct Oral Anticoagulant (DOAC) for monitoring.
3. Explain how the Anti-Xa laboratory assay measures concentrations of various medications.

Technician Learning Assessment #1:

- True or False – Apixaban, Dabigatran, Edoxaban, Rivaroxaban, and Warfarin are all Direct Oral Anticoagulants?

Increase in use of Direct Oral Anticoagulants (DOACs)

Drug Name	Rx's 2015 Q4	Rx's 2016 Q4	Percent Change	Market Share
Apixaban	1,315,213	2,183,821	66%	19.2%
Dabigatran	487,527	486,176	-0.3%	4.3%
Edoxaban	23,563	23,886	1.4%	0.2%
Rivaroxaban	1,948,201	2,209,216	13.4%	19.4%
Warfarin	7,332,251	6,488,962	-11.5%	57%
Total Oral Anticoagulants	11,106,755	11,392,061	**2.6%**	

Pharmacist Learning Assessment #1/Technician Learning Assessment #2:

Match the following labs to the appropriate DOAC for monitoring (labs may have more than one answer)

Activated partial thromboplastin time (aPTT)

Anti-Xa level

Ecarin clotting time (ECT) / Ecarin clotting assay (ECA)

Prothrombin Time (PT)

Thrombin Time (TT)

Apixaban

Dabigatran

Edoxaban

Rivaroxaban

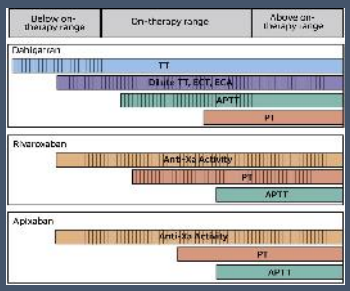
Lab	Dabigatran		Rivaroxaban/Edoxaban		Apixaban	
	Sensitivity	Interpretation	Sensitivity	Interpretation	Sensitivity	Interpretation
ECT/ECA	Sensitive ↑↑	Linear relationship, *Quantitative* lab	N/A	N/A	N/A	N/A
PT / INR	Low ↑	Normal at therapeutic levels, elevated at supratherapeutic levels	Low ↑↑	Normal levels do not exclude clinically relevant drug conc.	Low ↑/no effect	Even less than riva/edox, normal levels do not exclude clinically relevant drug conc.
aPTT	Low ↑↑	Better option than PT, normal levels do not exclude clinically relevant drug conc.	Low ↑	Less sensitive than PT	Low ↑/no effect	Less sensitive than PT
TT	Highly ↑↑↑	Overly sensitive, if measurable dabigatran level likely low	N/A	N/A	N/A	N/A
Anti-Xa level	N/A	N/A	Highly ↑↑	*Quantitative* if calibrated to specific drug (not edoxaban)	Highly ↑↑	*Quantitative* if calibrated to specific drug

ECT = ecarin clotting time, ECA = ecarin clotting assay, PT = prothrombin time, aPTT = activated partial thromboplastin time, TT = thrombin time

Conway SE et.al., Pharmacotherapy 2017; 37(2): 236-248. Miyares MA et.al., Am J Health-Syst Pharm. 2012; 69: 1473-84. Faust AC. Am J Health-Syst Pharm. 2016; 73: 2037-41. Kassim NA. J Appl Hematol 2015;6: 141-7. Favaloro EJ et.al. Current Drug Metabolism. 2017 18(7):595-608.

Lab monitoring

- Vertical hatching represents the approximate range of detectability/sensitivity for each assay based on various levels of therapy.
- Ranges are approximate and vary based on the choice of reagent.



ECT = ecarin clotting time, ECA = ecarin clotting assay, PT = prothrombin time, aPTT = activated partial thromboplastin time, TT = thrombin time

Cuker A et al. J Am Coll Cardiol 2014; 64: 1128-39.

Pharmacist Learning Assessment #2

What resources are available as references when transitioning patients from DOACs to parenteral therapy?

A. No references exist
B. Only the package insert
C. The package insert plus published generic recommendations
D. The package insert, plus published generic recommendations, plus pharmacokinetic data
E. The package insert, plus published generic recommendations, plus pharmacokinetic data, plus clinical trial data

Transition based on Package Insert

DOAC	FROM a parenteral anticoagulant	TO a parenteral anticoagulant
Dabigatran	Begin 0 to 2 hrs before time of next dose, or at time of discontinuation of IV heparin infusion	Wait 12 hrs after last dose (CrCl ≥ 30 ml/min) Or 24 hrs after last dose (CrCl < 30 ml/min) to begin parenteral therapy
Rivaroxaban	Begin 0 to 2 hrs before time of next evening administration of the drug, or at the time of discontinuation of IV heparin infusion	Begin at the time of next dose
Apixaban	Begin at the time of next dose	Begin at the time of next dose
Edoxaban	Begin at the time of next dose, or discontinue IV heparin and begin edoxaban 4 hrs later	Begin at the time of next dose
Betrixaban	???	???

Dabigatran [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 7/2017. Rivaroxaban [package insert]. Titusville, NJ: Janssen Pharmaceutical Companies; 10/2017. Apixaban [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 7/2016. Edoxaban [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2017.

Case #1 - Rivaroxaban to IV heparin

- RB – 59 yo, 91 kg, male admitted for chest pain, unstable angina
- PMH: CAD, DM2, HTN, HLD, Hx of DVT/PE more than 5 years ago
- Rivaroxaban 20 mg PO daily – last dose morning of admission
- SCr = 0.87, CrCl > 100 ml/min

Day/Time	PT / INR	aPTT	Rivaroxaban Anti-Xa	Heparin Anti-Xa	
1 - 1440	13.1 / 1				
2 - 0730		24.6	< 25		No IV heparin bolus, Heparin infusion initiated at 12 units/kg/hr, max of 1000 units/hr at 0900
1518				<0.1	Stress test was negative and discharge orders placed at 1630.

Summary / Take Home Message

- Case #1 - Good example of transition from rivaroxaban to IV heparin in younger patient with good renal function
- No IV heparin bolus given, but could have considered
- Consider delaying initiation of IV heparin until next due time for lower thrombosis risk
- Based on it's shorter half life and longer dosing interval (q 24 hrs for most patients) switching from rivaroxaban to IV heparin should be less challenging

Kassim NA. J Appl Hematol 2015; 6: 141-7

What if clearance is prolonged?

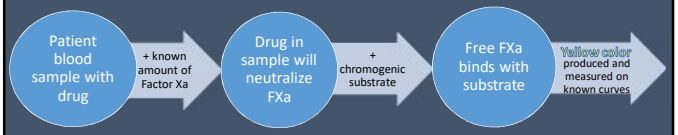
- Acute kidney injury
- Acute liver failure
- Patient on incorrect dose
- Drug interactions

Pharmacist/Technician Learning Assessment #3

How does the Anti-Xa laboratory assay measure the concentration of a medication?

A. Based on how much time passes before the blood sample forms a clot
B. I have no idea
C. A known amount of FXa is added to the blood sample, the remaining FXa produces a color that correlates to the drug concentration
D. Liquid chromatography/mass spectrometry is used to determine the concentration

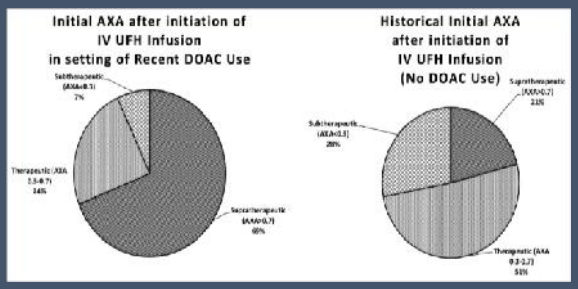
Anti-Xa Assay



More yellow color indicates low concentration of drug.
The curve used to measure the concentration is drug specific, but the rest of the test is not.

Dager WE et.al. (2011) Bethesda, MD: ASHP.

Effects of Apixaban/Rivaroxaban on initial *HEPARIN* Anti-Xa level



Macedo KA et al. Ann Pharmcother. 2018 Feb; 52(2): 154-159.

Potential Recommendations

1. Determine the last administration time of factor Xa inhibitor.
2. Begin IV heparin infusion without a bolus, ~2 hrs prior to the time the next dose would have been given.
3. Monitor infusion via an aPTT assay every 6-8 hrs for the first 48 hrs (may need to extend to 72 hrs if significant renal/hepatic impairment)
4. After 48-72 hrs may use Anti-Xa assay for monitoring, return to aPTT scale if 2 consecutive Anti-Xa levels are over 1.1 units/mL.

Faust AC et.al., Am J Health-Syst Pharm. 2016; 73: 2037-41.

Potential for Over-Anticoagulation

- Changing to aPTT scale does not remove the factor Xa inhibitor from the patient
- Using an aPTT scale may mask the presence of factor Xa inhibitors and patient may then be over anticoagulated
- Conversely, continued use of Anti-Xa monitoring scale could lead to under anticoagulation, especially in the setting of acute thrombosis

Macedo KA et. al., Ann Pharmcother. 2018 Feb; 52(2): 154-159.

Factors to consider when transitioning patients

- Timing of last dose
- Indication for anticoagulation (thrombosis risk)
- Bleeding risk factors
- Renal function
  - Dabigatran > edoxaban > apixaban > rivaroxaban
- Labs

Kassim NA. J Appl Hematol 2015; 6: 141-7.

Case #2 - Apixaban to IV heparin with AKI

- JS – 55 yo male, 111 kg admitted for AKI
- PMH: metastatic esophageal cancer, DVT 1 month prior to admission
- Home medication:
  - Apixaban 5 mg PO BID – last dose AM of admit
- SCr = 8.68
- Apixaban was continued on admission, pharmacist intervened
- Recommendation to check ***apixaban*** Anti-Xa level prior to transition to IV heparin infusion

Laboratory Monitoring

Day / Time	PT / INR	aPTT	Apixaban Anti-Xa	SCr	
1 – 2053			261	8.68	
2 – 0433			206	9.14	
3 – 0431	17.4 / 1.43	36.1	127	8.28	No IV bolus, Initiate IV heparin infusion at 12 units/kg/hr, max of 1000 units/hr at 1545
2148		52.3			Goal aPTT = 50-70, continue at 1000 units/hr
4 – 0549		41.6		9.19	IV heparin bolus of 15 units/kg, Increase IV infusion to 1200 units/hr
1409		57.2			Continue 1200 units/hr
2044		53.6			Continue 1200 units/hr
5 – 0537		58.5		7.24	Continue 1200 units/hr

DOAC level interpretation

Drug	Dose	Trough plasma level (ng/ml)		Peak plasma level (ng/ml)	
		Median (Mean)	5^{th}-95^{th} percentile	Median (Mean)	5^{th}-95^{th} percentile
Dabigatran	150 mg BID	90	31-225	184	64-443
Rivaroxaban	20 mg daily	26	6-87	270	189-419
Apixaban	5 mg BID	103 (50)	41-230	171 (129)	91-321
Edoxaban	60 mg daily	22	10-40[a]	170	120-250[a]

[a] interquartile range

*Note that DOAC Anti-Xa levels are NOT FDA approved.

Ezekoitz MD et al., Am J Cardiol 2007;100:1419; Mueck W et al., Clin Pharmacokinet 2014;53:1; Kowalski et al., J Pharmacokinet 2014;41 (Supp 1): 319; Weltz JI et al., Thromb Haemost 2010;104:633. Cuker A et al. J Am Coll Cardiol 2014; 64: 1128-39.

Summary / Take Home Message

- Case #2 - Example of utilizing quantitative labs to determine appropriate initiation of IV heparin infusion in patient with AKI
  - Without a bolus dose
  - Heparin initial rate of 18 units/kg/hr could have been considered
- Appropriate use of aPTT monitoring scale to adjust IV heparin

Pharmacist Learning Assessment #4

How can baseline effects of DOACs be assessed without the use of quantitative labs (ECT / ECA / DOAC Anti-Xa levels)?

A. Use INR levels
B. Use *HEPARIN* Anti-Xa levels
C. Baseline effects of DOACs should never be assessed
D. Transfer patient to another facility that uses measurable labs

Case #3 - Utilization of qualitative labs

- RB – 55 yo female, 155 kg (BMI = 59), admitted for unstable angina
- PMH: Afib, gastric bypass surgery
- CHA_2DS_2-VASc = 2
- Home medication:
  - Apixaban 5 mg PO BID – last dose the AM of admission
- SCr = 0.59 (baseline)
- Apixaban held for planned angiogram, IV heparin infusion ordered

Lab Monitoring

Day / Time	PT / INR	aPTT	Heparin Anti-Xa	
1 – 1913	14.1 / 1.1	30.3	1.3	IV heparin infusion 12 units/kg/hr started at 2130, with IV bolus dose (max 4000 units), at max of 1000 units/hr
2 – 0333		40.9	0.6	Goal aPTT = 50-70, increase of 2 units/kg/hr to 1300 units/hr
1026		47.1	0.55	Increase of 2 units/kg/hr to 1600 units/hr
1738		55.3	0.52	Continue 1600 units/hr, changed order to Anti-Xa scale after this
2355			0.35	Continue 1600 units/hr
3 – 0557			0.24	Increase of 2 units/kg/hr to 1900 units/hr
1122			0.65	Continue 1900 units/hr, IV heparin discontinued after angiogram and patient discharge. Resumed apixaban at home after discharge.

Use of baseline HEPARIN Anti-Xa levels

DOAC	Expected steady state *HEPARIN* Anti-Xa level	
	Trough	Peak
Apixaban	0.7 to 1.1 units/mL	1.8 to 2.2 units/mL
Rivaroxaban	0.6 to 1 units/mL	3.8 to 6.2 units/mL

*Study utilized STA liquid heparin kit (Diagnostica Stago, Parsippany, NJ)

Beyer J et. al. Clin Appl Thromb Hemost. 2016; 22: 423-428.

Recent Potential Recommendations

1. Assess risk vs. benefit on a patient by patient basis.
2. Consider initiation of IV heparin infusion without bolus with heparin Anti-Xa level:
   - Less than 1 – high clot risk
   - Less than 0.7 – lower clot risk
   - Authors did not define clot risk in article
3. Lower IV heparin infusion rates may be required if baseline Anti-Xa levels are elevated
4. Use of an aPTT monitoring scale may be considered
   - Requires up-to-date calibration of aPTT ranges based on available reagents

Macedo KA et. al., Ann Pharmcother. 2018 Feb; 52(2): 154-159.

Future / Further Considerations

- Transition of dabigatran to IV heparin infusion utilizing an aPTT monitoring scale
  - Biophen direct thrombin inhibitor (BDTI) assay
- Additional research on utility of baseline heparin Anti-Xa levels (greater upper limits of detectability) for evaluation of rivaroxaban, apixaban, edoxaban
- Transition of betrixaban to parenteral therapy
  - Elimination half life of 19-27 hours
  - Consider utilization of aPTT monitoring scale like other factor Xa inhibitors
  - Very little information available regarding effects on labs

Poli S et.al., Thromb Haemost. 2017 Dec;117(12):2369-2375

Summary / Take Home Message

- Time of last DOAC administration is important
- Most patients can be transitioned to IV heparin by following package insert
- Baseline labs should be considered for most patients
  - Especially patients with AKI
- Delayed initiation of parenteral therapy may be appropriate based on indication for anticoagulation and baseline lab monitoring
- Utilization of an aPTT dosing scale for IV heparin monitoring will prevent under anticoagulation, but may also cause over anticoagulation

Recommended Additional Reading

- Clinical trial:

1. Macedo KA, Tatarian P, Eugenio KR. Influence of direct oral anticoagulants on anti-factor Xa measurements utilized for monitoring heparin. Ann Pharmacother. 2018 Feb; 52 (2): 154-159.

- Laboratory Monitoring:

1. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014; 64: 1128-39.
2. Favaloro EJ, Pasalic L, Curnow J, Lippi G. Laboratory monitoring or measurement of direct oral anticoagulants (DOACs): advantages, limitations and future challenges. Current Drug Metabolism 2017 18(7): 595-608.

- Utilization of HEPARIN Anti-Xa levels

1. Beyer J, Trujillo T, Fisher S, Ko A, Lind SE, Kiser TH. Evaluation of heparin calibrated antifactor Xa assay for measuring the anticoagulant effect of oral direct Xa inhibitors. Clin Appl Thromb Hemost. 2016; 22: 423-428.
2. Gosselin RC, Francart SJ, Hawes EM, Moll S, Dager WE, Adcock DM. Heparin-Calibrated Chromogenic Anti-Xa activity measurements in patients receiving rivaroxaban: can this level be used to quantify drug level? Ann Pharmacother. 2015; 49(7): 777-783.

Questions?

References

- ISMP newsletter. Volume 22, Issue 15. July 27, 2017.
- Dabigatran [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmceuticals, Inc; 7/2017.
- Rivaroxaban [package insert]. Titusville, NJ: Janssen Pharmaceutical Companies; 10/2017.
- Apixaban [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 7/2016.
- Edoxaban [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2017.
- Wendte J, Voss G, VanOverschelde B. Influence of apixaban on antifactor Xa levels in a patient with acute kidney injury. Am J Health-Syst Pharm. 2016; 73: 563-7.
- Faust AC, Kanyer D, Wittkowsky AK. Managing transitions from oral factor Xa inhibitors to unfractionated heparin infusions. Am J Health-Syst Pharm. 2016; 73: 2307-41.
- Macedo KA, Tatarian P, Eugenio KR. Influence of direct oral anticoagulants on anti-factor Xa measurements utilized for monitoring heparin. Ann Pharmacother. 2018 Feb; 52 (2): 154-159.
- Beyer J, Trujillo T, Fisher S, Ko A, Lind SE, Kiser TH. Evaluation of heparin calibrated antifactor Xa assay for measuring the anticoagulant effect of oral direct Xa inhibitors. Clin Appl Thromb Hemost. 2016; 22: 423-428.

References

- Dager WE, Gulseth MP, Nutescu EA. (2011). *Anticoagulation Therapy: A Point of Care Guide*. Bethesda, MD: American Society of Health-System Pharmacists.
- Byron M, **Zochert S**, Hellwig T, Gavozdea-Barna M, Gulseth MP. "Successful Use of Laboratory Monitoring to Facilitate an Invasive Procedure for a Patient on Dabigatran." AJHP 2017; 74:e96-100.
- Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and Clinical Monitoring of direct acting oral anticoagulants: what clinicians need to know. Pharmacotherapy 2017; 37 (2): 236-248.
- Miyares MA and 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: 1473-84
- Hellerslia V and Mehta P. Transitions of Anticoagulants 2016. Hospital Pharmacy. PDF available at [illegible]
- Kassim NA. The new, direct, target-specific oral anticoagulants. J Appl Hematol 2015;6: 141-7.
- Favaloro EJ, Pasalic L, Curnow J, Lippi G. Laboratory monitoring or measurement of direct oral anticoagulants (DOACs): advantages, limitations and future challenges. Current Drug Metabolism 2017 18(7): 595-608.
- Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014; 64: 1128-39.
- Poli S, Hartig F, Spencer C, Ebner M, Birschmann I, Kuhn J, Faix S, Zeimann U, Haring HU, Lehmann R, Peter A, Horber S. Diagnostic Accuracy of a Novel Chromogenic direct thrombin inhibitor assay: clinical experiences for dabigatran monitoring. Thromb Haemost. 2017 Dec; 117 (12): 2369-2375.

Answers

- Technician #1 = False, warfarin is not a DOAC
- Pharmacist #1/Technician #2 – see next slide
- Pharmacist #2 = E, although the amount of data is still limited
- Pharmacist/Technician #3 = C
- Pharmacist #4 = B

Pharmacist Learning Assessment #1/Technician Learning Assessment #2:

Match the following labs to the appropriate DOAC

(may have more than one answer)