Management of Inpatient Anticoagulation Therapy

Liya Johnson, PharmD
PGY1 Pharmacy Resident

A presentation for HealthTrust Members
May 7, 2020

Disclosures

The presenter has no financial relationships with any commercial interests pertinent to this presentation

This program may contain the mention of drugs, brands or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand or supplier.

Pharmacist Learning Objectives

1. Describe the coagulation cascade and identify where anticoagulation therapies act in the cascade.
2. Differentiate the pharmacokinetics and pharmacodynamics between current anticoagulation therapies
3. Identify parameters to monitor efficacy and toxicity of therapy and to appropriately dose anticoagulant therapy.
4. List agents and indications for anticoagulation reversal.

Pharmacy Technician Learning Objectives

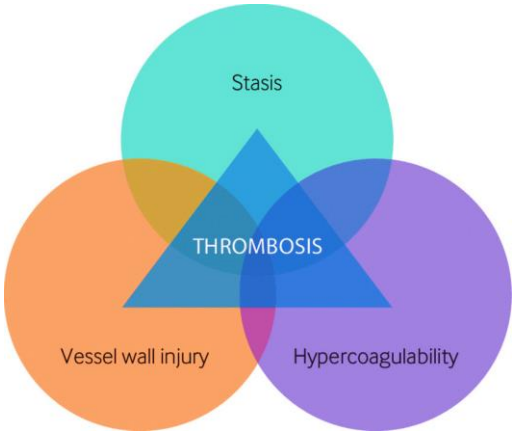
1. List reversal agents that require special handling
2. Understand reversal agents and storage requirements
3. Identify safety warnings for anticoagulation therapy and reversal
4. Demonstrate understanding of timeline for providing reversal in emergent situations

Acronyms

- LMWH = Low molecular weight heparin
- NOAC = Novel Oral anticoagulant
- VKA = Vitamin K antagonist
- LVAD = Left ventricular assist device
- VTE = Vascular thromboembolism
- PCI = Percutaneous intervention
- ACS = Acute coronary syndrome
- DVT = Deep vein thrombosis
- PE = Pulmonary embolism
- HIT = Heparin induced thrombocytopenia
- CRRT = Continuous renal replacement therapy
- MI = Myocardial infarction
- CAD = Coronary artery disease
- TIA = Transient ischemic attack
- aPTT = Activated partial thromboplastin time
- INR = International normalized ratio
- CrCl = Creatinine clearance
- HD = Hemodialysis
- BMI = Body mass index
- CKD = chronic kidney disease

Introduction: Why Anticoagulate?

- Thrombosis - hemostasis of blood clotting and dissolution is disrupted
  - Virchow's Triad – factors predisposing to thrombosis are present
- VTE
  - Coagulopathies acquired vs genetic

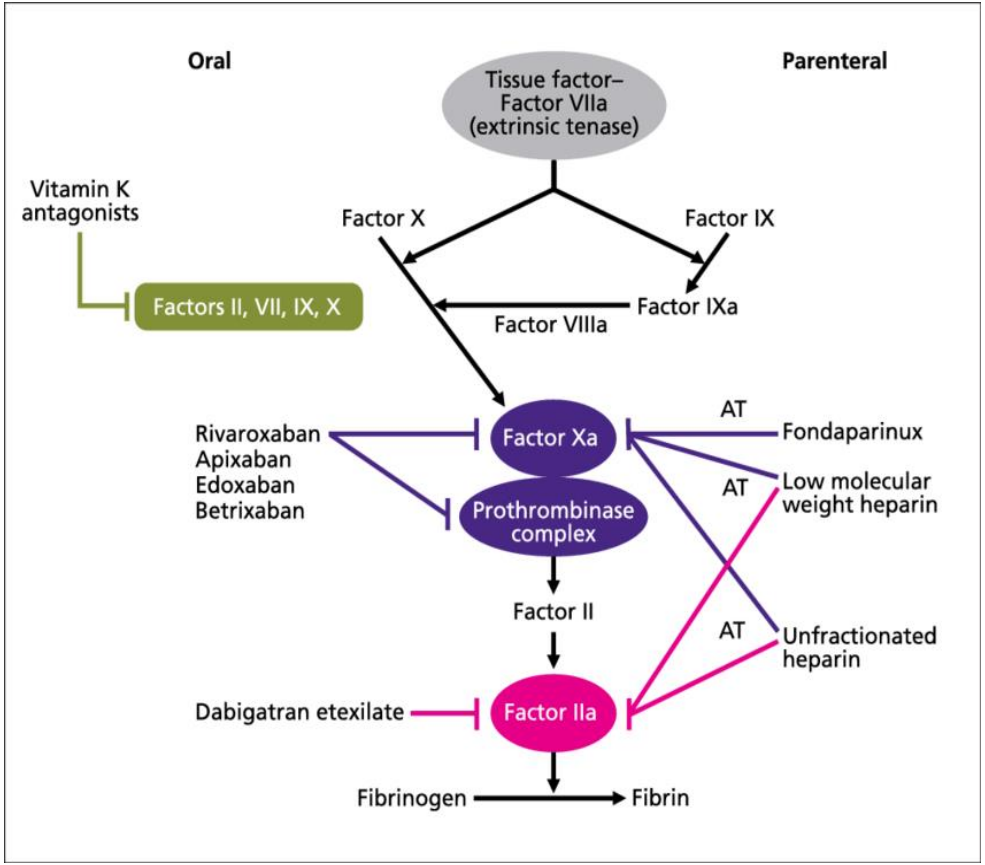


- Disease states
  - Atrial fibrillation
  - Acute coronary syndrome
- Artificial devices
  - Heart valves
  - LVAD
- DVT prophylaxis
  - Non-critical/Critically ill
  - Surgical prophylaxis

Image from: https://www.researchgate.net/figure/rchows-triad-of-the-three-broad-categories-of-factors-that-are-thought-to-contribute-to_fig1_317266064

Targets of Anticoagulants

- **Heparins**
  - Unfractionated Heparin
  - LMWH (ex. enoxaparin)
- **Vitamin K Antagonist**
  - Warfarin (Coumadin®)
- **Direct Thrombin Inhibitors**
  - Dabigatran (Pradaxa®)
  - Argatroban
- **Factor Xa Inhibitors**
  - Apixaban (Eliquis®)
  - Rivaroxaban (Xarelto®)
  - Edoxaban (Savaysa®)
  - Betrixaban (Bevyxxa®)
  - Fondaparinux (Arixtra®)



Pharmacokinetics & Pharmacodynamics

Parenteral Agents

	Unfractionated Heparin	Enoxaparin	Fondaparinux	Argatroban
Absorption	Immediate	100% bioavailability	100% bioavailability	X
Protein binding	Highly bound	X	94%	54%
Metabolism	No enzymatic degradation	Liver by de-sulfation	Eliminated unchanged	CYPA4/5
Elimination	Cleared from the circulation by uptake into extravascular space	8-20% in urine	77% in urine	Primarily feces
Half-life	0.5–2 hours	4.5–7 hours	17–21 hours	39–51 minutes
Peak	IV: Immediate SubQ: ~20 to 30 minutes	SubQ: 3 to 5 hours	SubQ: ~2 to 3 hours	Immediate

Oral Agents

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	Betrixaban
Absorption	Completely absorbed	3–7% bioavailability	50% bioavailability	80–100% bioavailability	62% bioavailability	34% bioavailability
Protein binding	99%	35%	87%	92–95%	55%	60%
Metabolism	CYP2C9	Esterase-catalyzed hydrolysis to active agent 7% in urine, 86% feces	CYP3A4 25% urine and feces	CYP3A4/5 and hydrolysis 30% urine, 1% feces	Cyp3A4 hydrolysis, conjugation, and oxidation	Minimal via CYP-independent hydrolysis
Elimination	92% urine	80% renal	27% renal	1/3 via urine	50% renal	85% feces, 11% urine
Half-life	20–60 hours	12–17 hours	12 hours	5–9 hours	10–14 hours	19–27 hours
Peak	3–4 days	1 hour	3–4 hours	2–4 hours	1–2 hours	3–4 hours

Monitoring of Anticoagulant Therapy

Anticoagulation Assays

	Lab	Ranges	Monitoring Frequency
Unfractionated Heparin	aPTT (23–37 secs)	aPTT = 1.5 to 2.5 x baseline DVT/PE*= 65–100 Afib/ACS* = 55–75	Every 6 hours
Enoxaparin	Anti-factor Xa	Mechanical heart valve (bridging): 0.5 to 1 units/mL VTE: 1-2 units/mL (once-daily dosing) 0.6-1 units/mL (twice-daily dosing)	Routine monitoring not recommended; May be considered in extremes of weight or impaired renal function. Take 4 to 6 hours after 3rd or 4th dose (steady state)
Fondaparinux	Anti-factor Xa	Therapeutic anti-Xa activity range not established	Routine monitoring is not recommended
Warfarin	INR (0.9–1.2)	INR = 1.5–2.5 (Idiopathic or inherited PAH) INR = 2–3 (MI, atrial fibrillation, VTE, etc.) INR = 2.5–3.5 (Mechanical valve)	Inpatient: Every 24 hours Outpatient: Weekly when out of range Every 4 weeks when stable
Argatroban	aPTT (23–37 secs)	1.5 to 3 x baseline, not exceeding 100 seconds	Daily

*Therapeutic range for aPTT must be established at each individual laboratory

Anticoagulation Assays

	Coagulation Markers Effected *Not used for monitoring does not reflect intensity of anticoagulation	**Anti-Xa Essays** ***Routine monitoring not recommended**
Dabigatran	aPTT	N/A
Rivaroxaban	PT/INR	Accurately estimates the plasma concentrations Therapeutic ranges not established
Edoxaban	PT/INR	
Apixaban	n/a	
Betrixaban	n/a	

Using anticoagulation in special populations

Evaluating Patient Characteristics – Selecting Anticoagulant Therapy

- **Age**
- **Weight**
- **Renal function**
  - CrCl
  - Urine output
  - Hemodialysis
- **Hepatic function**
- **Hematology markers**
  - Hemoglobin/hematocrit
  - Platelets
- **Co-morbidities**
  - Cardiovascular disease
  - Cancer
- **Drug interactions**
  - Antiplatelets
  - Herbal supplements
  - Hepatic enzyme inhibitors/inducers
- **Dietary intake**
  - Gut absorption

Geriatric Patients

Patient Case

- AB is an 76 y/o female with new onset of Atrial fibrillation
- **PMH**: hypertension (controlled), arthritis, depression
- **Labs**: Cr 1 mg/dL, BUN 19, CrCl 65 mL/min, Hgb 12.9 mg/dL, Hmct 39 %, INR 1, Plt 290, AST 15 U/L, ALT 11 U/L
- Weight – 70 kg, Height 5’4”
- **Medications:** Aspirin 81 mg daily, hydrochlorothiazide 25 mg daily, valsartan 160 mg daily, diltiazem CD 120 mg daily, ibuprofen 200 mg PRN pain, sertraline 25 mg daily
- Patient needs to be started on an anticoagulant

Geriatric Patients & Anticoagulation

- Risk of bleeding increases with age
  - Age > 65 y/o, > 75 y/o, > 85 y/o
  - Falls, low muscle mass, increased fatty tissue, reduced renal function
- Risk of stroke/thrombosis increase with age
  - CHA_2DS_2VAsc score $\geq$65 y/o 1 point, $\geq$75 y/o 2 points
- Balance risk of bleeding and thrombosis
- Select anticoagulant with demonstrated safety
- Adjust doses based on manufacturer recommendations

Geriatric Patients PK/PD

	Considerations

Dabigatran	Age ≥65 years and normal renal function:
	• Half-life of dabigatran is increased by approximately 1 hour
	  ○ 13.8 hours for age >65 years
	  ○ 12.9 hours for age <65 years
	• Clearance reduced by 4 L/h
	  ○ 66 L/h for age >65 years
	  ○ 70–140 L/h for age <65 years
	Total drug exposure is greater:
	• 1116 ng*h/mL for age <65 years

Rivaroxaban	In patients age ≥75 years, the half-life increased (11-13 hours) and total body clearance is slower Age does not appear to be a major determinant of pharmacokinetics.

Patients Age in Landmark Trials

	Rivaroxaban	Edoxaban	Betrixaban	Dabigatran	Apixaban
Trial and Age y/o	ROCKET-AF 73 (65–78) 40% over 75y/o	ENGAGE 72 (64–78)	APEX 76.6±8.46	RE-LY 71.4 +/- 8.6 (110 mg) 71.5 +/1 8.8 (150 mg) 40% over 75y/o	ARISTOTLE 70 (63–76) 31% over 75y/o
	EINSTEIN 55.8±16.4 16% over 75y/o			RE-COVER 56 (18–93)	

Post-Hoc Analysis - Age

Trial – Post-Hoc	Anticoagulant	Age	Thromboembolic events	Major Bleeding
RE-LY	Dabigatran 150 mg BID 110 mg BID vs. warfarin	≥ 75 y/o	D110 vs. W: HR 0.88 (0.66–1.17) D150 vs. W: HR 0.67 (0.49–0.90)	D110 4.4% yr / D150 5.1% yr vs. W 4.4% yr D110 vs. W: *P*=0.89 D150 vs. W: *P*=0.07
ROCKET AF	Rivaroxaban 20 mg daily vs. warfarin	≥ 75 y/o	HR 0.80 (0.63–1.02)	4.9% yr vs. 4.4% yr HR 1.11 (0.92–1.34)
ARISTOTLE	Apixaban 5 mg BID vs. Warfarin	≥ 75 y/o	HR 0.71 (0.53–0.95)	3.3% yr vs. 5.2% yr *P*<0.05
ENGAGE AF	Edoxaban 60 mg daily vs. warfarin	≥ 75 y/o	HR 0.83 (0.66–1.04)	4.0% yr vs. 4.8% yr *P*<0.05

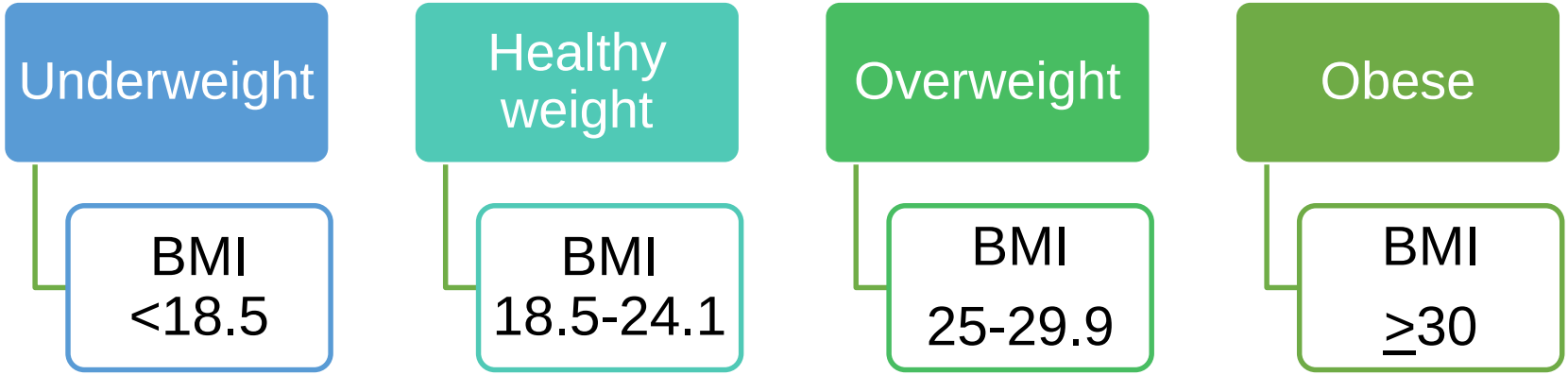
Patient Case

- AB is an 76 y/o female with new onset of Atrial fibrillation
- **Allergy**: NKA
- **PMH**: hypertension (controlled), arthritis, depression
- **Labs**: Cr 1 mg/dL, BUN 19, CrCl 65 mL/min, Hgb 12.9 mg/dL, Hmct 39 %, INR 1, Plt 290, AST 15, ALT 11
- Weight – 70 kg, Height 5’4”
- **Medications:** Aspirin 81 mg daily, hydrochlorothiazide 25 mg daily, valsartan 160 mg daily, diltiazem CD 120 mg daily, ibuprofen 200 mg PRN pain, sertraline 25 mg daily
- Patient needs to be started on an anticoagulant - NOAC

Case – Discussion

- Risk of bleeding vs risk of thrombosis
  - CHA_2DS_2VAsc score = 4 points
  - HASBLED score = 3 points
- Reduce risk of bleeding
  - Discontinue aspirin – no indication
  - Ibuprofen – use alternative
- Dabigatran – not preferred
  - In patients ≥75 years: Use with extreme caution or consider other treatment options
- NOAC selection (CrCl 65 mL/min)
  - Rivaroxaban 20 mg daily/Apixaban 5 mg BID/Edoxaban 60 mg daily

Extremes of Body weight



National Institute of Health Categories

Obesity PK/PD of NOACs

	Package Insert Comments
Dabigatran	None
Apixaban	Total exposure decreases due to an obesity-related increase in clearance
Rivaroxaban	Overall exposure is reduced with increased body weight despite a reduction in total body clearance
Edoxaban	Total exposure in patients with median low body weight (55 kg) was increased by 13% as compared with patients with median high body weight (84 kg)
Betrixaban	None

Patients Weight in Landmark Trials

	Rivaroxaban	Edoxaban	Betrixaban	Dabigatran	Apixaban
Trial and Weight	ROCKET-AF BMI = 28.3 (25.2–32.1)	ENGAGE < 60 kg= 10%	APEX 79.84 kg BMI =29.21±6.60	RE-LY 82.9 +/- 19.9 (110 mg) 82.5 +/- 19.4 (150 mg)	ARISTOTLE 82 kg (70–96)
	EINSTEIN ≤50 kg (2.1%) >50–100 kg (83.4%) >100 kg (14.2%) Missing data (0.3%)			RE-COVER 84 kg (38–175) BMI: 28.9 +/- 5.7	

NOACs- Weight

Trial	Anticoagulant	Weight	Outcome
RE-LY	Dabigatran	< 50 kg >100 kg > 110 kg	No excess bleeding reported No loss of efficacy reported Limited experience
RE-COVER	Dabigatran	> 100 kg	Greater risk of VTE
Upreti, et al.	Apixaban	< 50 kg 50- 85 kg 120 kg	≥120 kg group had a 31% to 23% lower apixaban cmax and AUC No need to adjust the dose of apixaban in patients weighing > 120 kg
Yin, et al.	Edoxaban	31- 165 kg	Non-renal clearance is effected by body weight

Recommendations

The International Society on Thrombosis and Haemostasis (ISTH) 2016 guideline suggests:

1. BMI < 40 kg m^2 and weight < 120 kg:
    a. Standard dosing of the DOACs
2. BMI of > 40 kg m^2 or a weight of > 120 kg:
    a. Avoid DOAC use due to limited clinical data available
    b. PK/PD: decreased drug exposures, reduced peak concentrations and shorter half-lives with increasing weight, concerns for underdosing
3. BMI of > 40 kg m^2 or a weight of > 120 kg: check a drug-specific peak and trough level
    a. Anti-FXa: apixaban, edoxaban, and rivaroxaban
    b. Ecarin time or dilute thrombin time with appropriate calibrators for dabigatran or mass spectrometry drug level for any of the DOACs
    c. Expected range: continue therapy
    d. Below the expected range: change to VKA rather than adjusting the dose of the DOAC.

Patient Case

- AF is a 45 y/o male with new Pulmonary Embolism. Patient has been admitted to the hospital and is getting ready to get discharged.
- **Allergy**: NKA
- Weight – 130 kg (286lb), height 5’9”, BMI – 42.2 kg/m^2
- **PMH:** hypertension, hypercholesteremia
- **Labs:** Cr 1 mg/dL, BUN 15, CrCl 85 mL/min, Hgb 14 mg/dL, Hmct 45 %, INR 1, Plt 350, AST 19 U/L, ALT 20 U/L
- **Current Medications** : amlodipine 10 mg daily, atorvastatin 40 mg daily, enoxaparin 130 mg BID
- Patient needs to be transitioned to an oral anticoagulant and refused warfarin, which agent would you recommend?

Patient Case

- Extreme Obesity - BMI > 40 kg/m^2 and Weight > 120 kg
- Dabigatran and Edoxaban
  - Post-marketing data is lacking, not clear evidence for safety/efficacy
  - PK/PD studies indicate possibility of effect on efficacy with weight increase
- Rivaroxaban and Apixaban
  - Robust clinical data is lacking
  - Based on PK/PD weight may not be a significant factor
  - Use either agent with recommendation to monitor anti-Xa levels

Renal Impairment

Renal impairment PK/PD

	Considerations
Dabigatran	T ½ increased: Mild-to-moderate renal impairment: 15 to 18 hours; Severe renal impairment: 28 hours
Apixaban	ESRD, the AUC of apixaban was 17% greater compared to those with normal renal function.
Rivaroxaban	Exposure increased by approximately 44 to 64% in subjects with renal impairment.Increases in pharmacodynamic effects were also observed
Edoxaban	Blood levels are increased in patients with poor renal function compared to those with higher renal function

Patients Renal Function in Landmark Trials

	Rivaroxaban	Edoxaban	Betrixaban	Dabigatran	Apixaban
Trial and CrCl	**ROCKET-AF** 67 mL/min (52-88)	**ENGAGE** Dose reduction with CrCl < 50 mL/min 19.3% (CrCl<50 mL/min, bw <60 kg and those who were using a Pgp inhibitor received an edoxaban dose at 50% less)	**APEX** <15 mL/min= <0.1% 15 to <30 mL/min= 4.6% 30 to <60 mL/min= 42.6% 60 to <90 mL/min= 34.6% ≥90 mL/min= 17.9% Missing data= 0.3%	**RE-LY** Excluded CrCl ≤30 mL/min	**ARISTOTLE** >80 mL/min =41.2% >50 to 80 mL/min = 41.9% >30 to 50 mL/min= 15% ≤30 mL/min= 1.5% Excluded scr >2.5 mg/dL or CrCl <25 mL/min
	EINSTEIN <30 mL/min (0.3%) 30–49 mL/min (6.6%) 50–79 mL/min (22.7%) ≥80 mL/min (68.9%) Missing data (1.4%)			**RE-COVER** 105.8±40.7 mL/min Excluded CrCl ≤30 mL/min	

Post-Hoc Analysis – Renal Function

Trial – Post-Hoc	Anticoagulant	CrCl mL/min	Outcomes
RE-LY	Dabigatran 150 mg BID 110 mg BID vs. warfarin	30 to 50	Plasma concentration increased with both dosages
ROCKET AF	Rivaroxaban 20 mg daily or 15 mg daily vs. warfarin	30-49	GI bleeding greater than warfarin
ARISTOTLE	Apixaban 5 mg BID, Apixaban 2.5 mg BID vs. Warfarin	50 to 25	Lower risk of major bleeding vs warfarin

Recommendations

	Adjustment	Indication
Dabigatran	CrCl 15 to 30 mL/minute: 75 mg twice daily unless receiving concomitant P-gp inhibitor, then avoid concurrent use (based solely on PK data)	Nonvalvular Atrial fibrillation
Apixaban	Serum creatinine ≥1.5 mg/dL and either ≥80 years of age or body weight ≤60 kg: 2.5 mg twice daily	Nonvalvular Atrial fibrillation
Rivaroxaban	CrCl 15 to 50 mL/minute: 15 mg once daily with food CrCl 30 to 50 mL/minute: 10 mg once daily with food in combination with clopidogrel	Nonvalvular atrial fibrillation PCI
Edoxaban	CrCl 15 to 50 mL/minute: Oral: 30 mg once daily	DVT/ PE treatment & Nonvalvular Atrial fibrillation
Betrixaban	CrCl ≥15 to <30 mL/minute: Initial: 80 mg single dose, followed by 40 mg once daily for 35 to 42 days Concomitant P-gp inhibitor, avoid use	VTE prophylaxis

CHEST Guidelines: Renal Dysfunction—VTE

In patients with Renal disease and CrCl <30 mL/min, VKA is the preferred anticoagulant

- NOACs and LMWH contraindicated with severe renal impairment
- Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions

ASH Guidelines: Renal Dysfunction—VTE

Avoid DOACs in favor of VKA for:	• Very elderly, those with compromised renal function, and situations where multiple drugs affecting P-gp and/or CYP enzymes are co-prescribed
>50 mL/min receiving DOAC therapy for treatment of VTE	• Good practice includes renal function monitoring every 6 to 12 months
<50 mL/min receiving DOAC therapy for treatment of VTE	• Good practice includes renal function monitoring approximately every 3 months

CHEST Guidelines: Renal Dysfunction—Afib

Moderate to severe : consider treatment with reduced doses	• Serum creatinine ≥ 1.5: apixaban • 15-30 mL/min: dabigatran • ≤50 mL/min: rivaroxaban • 15-50 mL/min: edoxaban
CKD (CrCl <15mL/min) or dialysis	• Warfarin (INR goal 2-3) • Apixaban • Dabigatran, Rivaroxaban, Edoxaban NOT recommended due to a lack of clinical evidence

Hemodialysis (HD)

Hemodialysis in Landmark Trials

	Rivaroxaban	Edoxaban	Betrixaban	Dabigatran	Apixaban
Trial and CrCl	**ROCKET-AF** Excluded CrCl ≤30 mL/min Not studied	**ENGAGE** Excluded CrCl ≤30 mL/min Not studied	**APEX** Not studied	**RE-LY** Excluded CrCl ≤30 mL/min Not studied	**ARISTOTLE** Excluded scr >2.5 mg/dL or CrCl <25 mL/min Not studied
	EINSTEIN Not studied			**RE-COVER** Excluded CrCl ≤30 mL/min Not studied	

Recommendations

	Dialyzed	Considerations
Dabigatran	Hemodialysis removes ~57% over 4 hours	Avoid use
Apixaban	Not dialyzable to minimally dialyzable	According to the manufacturer, no dosage adjustment necessary
Rivaroxaban	Not dialyzable	Avoid use
Edoxaban	Not dialyzable	Avoid use
Betrixaban	Not studied	Not studied

Apixaban HD trials

	Trial 1	Trial 2	Trial 3
Design	• Open-label, parallel group, single dose study	• Single-center, investigator-driven, open label cohort study	• Retrospective cohort study
Objective	• Assess safety of apixaban in subjects with end-stage renal disease on hemodialysis	• Determine apixaban pharmacokinetics at steady state in patients on HD: effect of 4 hour dialysis session on 1 single dose	• Determine patterns of apixaban use and associated outcomes in patients with ESRD on HD
Population	• 8 patients ESRD on HD vs 8 subjects with normal renal function. • 3/8 patients with ESRD were functionally anuric	• 6 patients • RRT 5+/-3 years • Urine output <200 mL/24h	• n=2351 • 51% dialysis > 3 years
Dosing	• 5-mg dose administered once to heathy subjects • 5 mg administered twice to ESRD patients, each dose separated by >7 day	• Effect of 4 hour dialysis session on 1 single dose	• Apixaban 2.5 mg BID: 1,317 • Apixaban 5 mg BID: 1,034
Conclusions	• Differences in anti-FXa activity were similar to differences in apixaban concentration • A single oral dose of apixaban was safe and well	• AUC increased by 2-5.4 x at steady state during the first phase of study • Apixaban 2.5 mg BID results in similar PK indices in patients on HD as 5 mg BID with preserved renal function	• Standard dose of apixaban was associated with lower risks of stroke/SE and death compared with the reduced dose • Both groups had fewer major bleeding events when compared to warfarin. Only apixaban 5 mg BID had fewer thromboembolic events

Reversal

Drug & Reversal Agent

Unfractionated Heparin • Protamine	Enoxaparin • Protamine	Warfarin • Vitamin K, 4F-PCC (Kcentra®)	Dabigatran • Idarucizumab (Praxbind®)
Apixaban • Andexanet alfa (ANDEXXA®) • 4F-PCC (Kcentra®)*	Rivaroxaban • Andexanet alfa (ANDEXXA®) • 4F-PCC (Kcentra®)*	Edoxaban • 4F-PCC (Kcentra®)*	Betrixaban • 4F-PCC (Kcentra®)*

*Off-label

Antidote	MOA	Temperature	Preparation for administration
Protamine	• Forms stable salt with heparin	• 20°C to 25°C • Do not freeze	• May be further diluted in D5W or NS
Vitamin K	• Promotes liver synthesis of clotting factors (II, VII, IX, X)	• 20°C to 25°C • Excursions permitted to 15°C to 30°C (59°F to 86°F)	• Protect from light • Dilute injection solution in preservative-free NS, D5W, or D5NS
4F-PCC (Kcentra®)	• Purified Vitamin -K dependent factors II, VII, IX, and X	• 2°C to 25°C • Do not freeze.	• Protect from light • Reconstitute with provided diluent (SWFI)
Idarucizumab (Praxbind®)	• Monocolonal antibody fragment binds specifically to dabigatran and its metabolite	• 2ºC to 8ºC • Do not freeze	• Protect from light • Do not shake
Andexanet alfa (ANDEXXA®)	• Binds and sequesters drug • Inhibits the activity of Tissue Factor Pathway Inhibitor (TFPI), increasing tissue factor-initiated thrombin generation	• 2°C to 8°C	• Reconstitute each 100 mg vial with 10 mL SWFI or each 200 mg vial with 20 mL SWFI • Use ≥20 mL syringe and ≥20 gauge needle • Slowly inject SWFI onto the inside wall of the vial to minimize foaming • Gently swirl vial until complete dissolution of powder • Do not shake.

Considerations for Reversal: Protamine

Unfractionated Heparin

- Consider:
  - Time (half life: 0.5–2 hours)
  - Amount ingested
  - Patient age, weight and renal function

	Time since dose	Recommendation
IV bolus or SC	< 30 mins	1 mg for every 100 units of heparin given
	30-60 mins	0.5 mg for every 100 units of heparin
	> 60 mins	0.25 mg for every 100 units of heparin
IV infusion	2-3 hours	1 mg for every 100 units of heparin over last 2–3 hours

Enoxaparin

- Consider:
  - Time (3–5 ½ lives, reversal not needed)
  - Amount ingested
  - Patient age, weight and renal function
  - Incomplete neutralization of anti-Xa activity

Time since dose	Recommendation
≤ 8 hours	1 mg for every 1 mg given
> 8 hours	0.5 mg for every 1 mg given

Considerations for Reversal: Vitamin K

- Vitamin K:
  - Not an acute reversal agent: used in non-major bleed or planned surgery
  - May repeat in 12–24 hours if INR elevated

Reversal non-major bleeding	
INR	**Recommendation**
Greater than therapeutic but <4.5	Hold until INR goal
4.5–7	Hold until INR goal OR Vit K PO 1.25–2.5 mg
> 7	Hold until INR goal AND Vit K PO 2.5- 5 mg PO or 1 mg slow IV if NPO

Reversal Prior to Surgery	
INR	**Recommendation**
Greater than therapeutic but < 7	Vit K PO 2.5 mg PO or 1 mg slow IV if NPO
> 7	Hold warfarin AND Vit K PO 2.5–5 mg PO or 1 mg slow IV if NPO

Considerations for Reversal: 4F-PCC

- 4F-PCC (Kcentra®)
  - Major life threating bleed or emergent surgery
  - Avoid in patients with history of HIT
  - Dosed on factor IX
  - For warfarin therapy: monitor INR at baseline and 30 minutes post dose
  - Give with 10 mg IV vitamin K
  - Dose is based on ACTUAL body weight and if body weight is greater than 100 kg, use 100 kg

Reversal major bleeding, Emergent surgery		
4F-PCC (Kcentra®)	INR	Recommendation
	2-4	25 units/kg (max 2,500 units)
	> 4-6	35 units/kg (max 3,500 units)
	> 6	50 units/kg (max 5,000 units)

Considerations for Reversal: Idarucizumab

- Consider:
  - Time since last dose
  - Amount ingested
  - Renal/hepatic function
  - Drug interactions
- Idarucizumab (Praxbind)
  - 5 g IV once, give in 2.5 g doses no more than 15 mins apart
  - IV push undiluted over no more than 5 mins

Considerations for Reversal: Andexanet alfa

- Consider:
  - Time since last dose
  - Amount ingested
  - Renal/hepatic function

Dose	<8 hours	8-18 hours	≥18 hours or unknown
Apixaban ≤ 5 mg	Low dose	Andexanet low dose	Standard of Care
Apixaban > 5 mg	High dose		
Rivaroxaban ≤10 mg	Low dose		
Rivaroxaban >10 mg	High dose		

Procedural Reversal

Agent	Renal function (Crcl mL/min)	Interval between last dose and procedure	Resume therapy
Dabigatran	≥ 50	1-2 days	• Resume 24 hours after if low risk bleeding • Resume 48-72 hours after if high risk bleeding
	<50	3-5 days	
Apixaban	>60	1-2 days	
	50-59	3 days	
	<30-49	5 days	
Rivaroxaban	Normal	1 day	
	60-90	2 days	
	30-59	3 days	
	15-29	4 days	
Edoxaban		1 day	As soon as appropriate hemostasis is achieved

Assessment Question 1

Which factors in the coagulation cascade does warfarin inhibit?

A. VII
B. II
C. IX
D. X
E. All of the above

Assessment Question 1 Response

Which factors in the coagulation cascade does warfarin inhibit?

A. VII
B. II
C. IX
D. X
E. All of the above

Assessment Question 2

When are the peak effects of warfarin expected to be seen?

A. 15 minutes
B. 1-2 hours
C. 1-2 days
D. 3-4 days

Assessment Question 2 Response

When are the peak effects of warfarin expected to be seen?

A. 15 minutes
B. 1-2 hours
C. 1-2 days
D. 3-4 days

Assessment Question 3

When should you monitor INR when giving 4F-PCC for warfarin reversal

A. Check INR at baseline
B. 2 hours post dose
C. 30 minutes post dose
D. A &C

Assessment Question 3 Response

When should you monitor INR when giving 4F-PCC for warfarin reversal

A. Check INR at baseline
B. 2 hours post dose
C. 30 minutes post dose
D. A &C

Assessment Question 4

Which of the following is the reversal agent for Dabigatran?

A. 4F-PCC (Kcentra®)
B. Recombinant Factor VIIa (NovoSeven®)
C. Idarucizumab (Praxbind®)
D. Andexanet Alfa (Andexxa®)

Assessment Question 4 Response

Which of the following is the reversal agent for Dabigatran?

A. 4F-PCC (Kcentra®)
B. Recombinant Factor VIIa (NovoSeven®)
C. Idarucizumab (Praxbind®)
D. Andexanet Alfa (Andexxa®)

Assessment Question 5

When monitoring the efficacy of a Heparin drip with an indication for atrial fibrillation, what is considered goal aPTT?

A. 39-54
B. 55-75
C. 76-100
D. 65-100

Assessment Question 5 Response

When monitoring the efficacy of a Heparin drip with an indication for atrial fibrillation, what is considered goal aPTT?

A. 39-54
B. 55-75
C. 76-100
D. 65-100

Technicians Assessment Question 1

Which of the following reversal agents should not be shaken to minimize the risk of foaming?

A. Protamine
B. Vitamin K
C. 4F-PCC
D. Andexanet Alfa

Technicians Question 1 Response

Which of the following reversal agents should not be shaken to minimize the risk of foaming?

A. Protamine

B. Vitamin K

C. 4F-PCC

D. **Andexanet Alfa**

Technicians Assessment Question 2

Which of the following reversal agents does not need to be protected from light?

A. Protamine
B. Vitamin K
C. 4F-PCC
D. Idarucizumab

Technicians Question 2 Response

Which of the following reversal agents does not need to be protected from light?

A. **Protamine**

B. Vitamin K

C. 4F-PCC

D. Idarucizumab

Technicians Assessment Question 3

4-Factor PCC should be avoided in a patient with a history of?

A. Labile INR
B. HIT (Heparin induced thrombocytopenia)
C. Stroke
D. Hemophilia

Technicians Question 3 Response

4-Factor PCC should be avoided in a patient with a history of?

A. Labile INR
B. HIT (Heparin induced thrombocytopenia)
C. Stroke
D. Hemophilia

Technician Assessment Question 4

Which of the following agents is incompletely reversed regardless of administration time of indicated antidote?

A. Heparin (Fragmin®)
B. Enoxaparin (Lovenox®)
C. Rivaroxaban (Xarelto®)
D. Apixaban (Eliquis®)

Technician Question 4 Response

Which of the following agents is incompletely reversed regardless of administration time of indicated antidote?

A. Heparin (Fragmin®)

B. Enoxaparin (Lovenox®)

C. Rivaroxaban (Xarelto®)

D. Apixaban (Eliquis®)

References

- Ashorobi D, Fernandez R. Thrombosis. [Updated 2019 May 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430
- Turpie, Alexander & Esmon, Charles. (2011). Venous and arterial thrombosis - Pathogenesis and the rationale for anticoagulation. Thrombosis and haemostasis. 105. 586-96. 10.1160/TH10-10-0683.
- Lexicomp Online®, Lexi-Drugs® Unfractionated Heparin, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Enoxaparin, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Fondaparinux, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020.
- Lexicomp Online®, Lexi-Drugs® Argatroban, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020.
- Lexicomp Online®, Lexi-Drugs® Warfarin, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Dabigatran, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Apixaban, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Rivaroxaban, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Edoxaban, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020.
- Lexicomp Online®, Lexi-Drugs® Betrixaban, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020.
- Unfractionated Heparin [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation; 1939.
- Enoxaparin [prescribing information]. Bridgewater, NJ : sanofi-aventis; 2009.
- Fondaparinux [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
- Argatroban [prescribing information]. Princeton, NJ: Sandoz Inc; 2011.
- Warfarin [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 1954.
- Dabigatran [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2019.
- Apixaban [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2012.
- Rivaroxaban [prescribing information]. Titusville,NJ: Janssen Pharmaceuticals, Inc; 2016.
- Edoxaban [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc; 2015.
- Betrixaban [prescribing information]. South San Francisco, Ca: Portola Pharmaceuticals, Inc; 2017.

References

- Cavallari I, Patti G. Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. Anatol J Cardiol. 2018;19(1):67–71. doi:10.14744/AnatolJCardiol.2017.8256
- Buckley LF, Rybak E, Aldemerdash A, Cheng JW, Fanikos J. Direct oral anticoagulants in patients with atrial fibrillation and renal impairment, extremes in weight, or advanced age. Clin Cardiol 2017;40:46–52
- Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial. Circulation. 2011;123:2363–2372.
- Halperin JL, Hankey GJ, Wojdyla D, et al; ROCKET AF Steering Committee and Investigators . Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism (ROCKET AF). Circulation. 2014;130:138–146.
- Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol. 2013;76(6):908–916. doi:10.1111/bcp.12114
- Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure–response analysis in patients with nonvalvular atrial fibrillation. Eur J Clin Pharmacol. 2014; 70:1339–51. [PubMed: 25168620]
- Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-1083. doi: 10.1345/aph.1L194.[PubMed 19458109]
- Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(6):1308-1313
- Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014;129:961–970.
- Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32:2387–2394
- Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012;33:2821–2830.
- Kearon C, Akl EA, Omelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-352.
- Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257–3291. doi:10.1182/bloodadvances.2018024893
- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019 January 21.
- Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56(5):628-636. doi: 10.1002/jcph.628
- Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017;28(7):2241-2248. doi: 10.1681/ASN.2016090980
- Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States [published correcton appears in Circulation. 2018]. Circulation. 2018;138(15):1519-1529. doi: 10.1161/CIRCULATIONAHA.118.035418
- Lexicomp Online®, Lexi-Drugs® Protamine, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Phytonadione, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020
- Lexicomp Online®, Lexi-Drugs® Prothrombin Complex Concentrate, Hudson, Ohio: Lexi-Comp, Inc.; March 30, 2020.
- Praxbind®.[package insert]. Ridgefield. CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2015.
- ANDEXXA®.[package insert]. South San Francisco. CA: Portola Pharmaceuticals, Inc; 2017.
  Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th edition: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012;141(2 Suppl):e326S-e350S.
- Baron TH, Kamath PS, and McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. NEJM 2013;368:2113-24.

Thank You!

Liya Johnson, PharmD, PGY1 Pharmacy Resident
Morristown Medical Center, Atlantic Health System
Liya.Johnson@atlantichealth.org