



THE
GATEWAY
TO THE FUTURE OF PHARMACY



A Cascade of Updates: Hot Topics in Anticoagulation

Heather A. Powell, PharmD, BCPS
Assistant Professor of Clinical Sciences
Roosevelt University College of Pharmacy

Golden L. Peters, PharmD, BCPS
Associate Professor of Pharmacy Practice
St. Louis College of Pharmacy

Disclosure and Conflict of Interest

Heather Powell and Golden Peters declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.

Pharmacist Objectives

At the conclusion of this program, the pharmacist will be able to:

1. Identify situations where full therapeutic anticoagulation, pharmacologic venous thromboembolism prophylaxis, or no additional pharmacologic anticoagulant is indicated for bridging.
2. Select the most appropriate anticoagulant for patients requiring full therapeutic anticoagulation when given a patient case.
3. Compare and contrast reversal strategies for anticoagulation including warfarin, heparins, and the direct oral anticoagulants.

Technician Objectives

At the conclusion of this program, the technician will be able to:

1. Describe situations where anticoagulation bridging may be indicated.
2. Compare and contrast the oral anticoagulants when given a patient case.
3. Identify agents used for reversal of anticoagulants including warfarin, heparins, and the direct oral anticoagulants.

A Cascade of Updates: Hot Topics in Anticoagulation

Outline

- Anticoagulation Bridging
- Therapeutic Anticoagulants
- Anticoagulant Reversal

Anticoagulation Bridging

Pre-Test Question #1

A 75 year old, 80 kg patient undergoing a routine colonoscopy. PMH includes atrial fibrillation, DM, CHF, and HTN. Medications include warfarin, lisinopril, metoprolol succinate, and metformin. INR today is 1.4. CrCl is 75 ml/min. What is the most appropriate type of bridging this patient should receive peri-procedurally?

- A. Enoxaparin 80 mg SubQ q 12 h
- B. Heparin 5000 units SubQ q 8 h
- C. Warfarin should be continued
- D. Bridging is not indicated in this patient

Bridging

- When an oral anticoagulant is discontinued and replaced by a therapeutically dosed SubQ or IV anticoagulant before and/or after a procedure

Bridging Example

56 yo patient (100 kg) with mechanical mitral valve undergoing colonoscopy (Goal INR < 1.2)

Day	Bridging Agent Frequency (Enoxaparin 100 mg)	Warfarin (5 mg PO q PM)
-5	BID	HOLD
-4	BID	HOLD
-3	BID	HOLD
-2	BID	HOLD
-1	AM HOLD PM	HOLD
Procedure day	HOLD AM dose Resume PM dose	5 mg PO q PM
POD 1	BID	5 mg PO q PM
POD 2	BID	5 mg PO q PM
POD 3	BID	TBD (INR check)

Overall Considerations

- Bridging is not indicated on the label of any anticoagulants and is based solely on expert opinion
- New evidence supports the use of **less** bridging for patients who are:
 - Subtherapeutic on warfarin
 - Holding warfarin peri-procedurally

Circulation. 2012; 126:1630-1639
N Engl J Med. 2015; 379(9):823-833
JAMA Intern Med. 2015; 175:1163-1168
Curr Cardiol Rep. 2016; 18(101):1-7
J Am Coll Cardiol. 2017. 69(7): 871 -898

Overall Considerations

- Bridging is **not** recommended for patients who are receiving direct oral anticoagulants (DOACs)
- Therapy interruption for DOACs is based on renal function and drug pharmacokinetics

Overall Considerations

- Bridging decisions should be made on a **case-by-case** basis taking into account thrombotic and bleed risk of the patient and procedure in addition to evidence-based guidelines

CHADS₂ Score Refresher

- Stroke risk assessment tool for patients with atrial fibrillation

CHADS ₂	CHA ₂ Ds ₂ -VASC	Points
Congestive Heart Failure		1
Hypertension		1
Age 75 or older		1
Diabetes		1
Previous stroke or TIA		2
	Vascular disease	1
	Age 65 or older	1
	Sex (Female)	1

CHEST. 2012;141(2)(suppl):e531S-e575S

Bridging in Atrial Fibrillation

Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE trial)

Objective	Forgoing LMWH bridging peri-operatively for patients on warfarin for atrial fibrillation is non-inferior to bridging for thromboembolism prevention and superior for bleeding
Study Design	Non-inferiority, randomized, double-blind, placebo-controlled
Intervention	<ul style="list-style-type: none">• Warfarin was stopped 5 days prior to procedure and restarted within 24 hours• LMWH or matching placebo from 3 days until 24 hours pre-procedure and then for 5 to 10 days post-procedure• Follow-up was conducted over 30 days post-procedure

N Engl J Med. 2015; 379(9):823–833

Bridging in Atrial Fibrillation

BRIDGE (cont.)

Outcomes	<ul style="list-style-type: none">• Arterial thromboembolism (stroke, systemic embolism, or TIA)• Major bleeding
Enrollment	1884 patients enrolled <ul style="list-style-type: none">• 950 received no bridging• 934 received bridging
Results	<ul style="list-style-type: none">• Arterial thromboembolism (stroke, systemic embolism, or TIA)<ul style="list-style-type: none">○ 0.4% in no-bridge group vs 0.3% in bridge group (risk difference = 0.1%; 95% CI -0.6 to 0.8, P=0.01 for non-inferiority)• Major bleeding<ul style="list-style-type: none">○ 1.3% in no-bridge group vs. 3.2% in bridge group (relative risk = 0.41; 95% CI 0.20 to 0.78; P=0.005 for superiority)

N Engl J Med. 2015; 379(9):823–833

Bridging in Atrial Fibrillation

BRIDGE (cont.)

Limitations

Mean CHADS2 score for no-bridge group was 2.3 and 2.4 for bridging group

Only 3% of patients had CHADS2 scores of 5-6

Conclusions regarding bridging in a high risk population (CHADS2 of 5 or 6) cannot be made from this study

ARTICLE IN PRESS

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. ■, NO. ■, 2017
ISSN 0735-1097/\$36.00
<http://dx.doi.org/10.1016/j.jacc.2016.11.024>

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

J Am Coll Cardiol. 2017. 69(7): 871 -898

Bridging in Venous Thromboembolism

Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures

Objective	Compare clinically relevant bleeding and recurrent VTE rates for patients who did and did not receive bridge therapy during warfarin interruption for invasive procedures
Study Design	Retrospective, cohort study
Intervention	<ul style="list-style-type: none">• Bridging vs. no bridging peri-procedurally
Outcomes	<ul style="list-style-type: none">• 30-day clinically relevant bleeding, recurrent VTE, and all-cause mortality

Bridging in Venous Thromboembolism

Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures (cont.)

Enrollment

1812 procedures in 1178 patients between 6/1/2005 and 4/30/2012

- 1257 received no bridging
- 555 received bridging

Results

- Clinically relevant bleeding (clinically overt bleeding resulting in hospitalization or ED visit or that complicated the procedure)
 - 2.7% in bridge group vs 0.2% in no-bridge group (hazard ratio = 17.2; 95% CI 3.9 to 75.1, P=0.01)
- Recurrent VTE
 - 0.2% in no-bridge group vs 0% in bridge group (P=0.56)
- All-cause mortality
 - No events occurred in either group

Bridging Assessment

Low-Moderate Risk
($<10\%$ annual
thromboembolism risk)

Bridging generally not
recommended

High Risk
($>10\%$ annual
thromboembolism risk)

Consider bridging

High Thromboembolism Risk

- **Mechanical Heart Valve**
 - Any mitral mechanical valve
 - Any mechanical valve with h/o prior stroke or transient ischemic attack (TIA)
 - Older (caged ball or tilting disc) valve prosthesis, any position
 - Aortic mechanical valve with risk factors (i.e. Afib, LVEF < 35%)

High Thromboembolism Risk

- **Atrial fibrillation**

- CHADS₂ score of 5 or 6
- Prior stroke, TIA, or systemic embolus within the last 3 months
- Prior stroke, TIA, or systemic embolus with prior therapy interruption or while on therapy

JACC Decision Pathway equates high risk atrial fibrillation peri-procedurally necessitating bridging to be a CHA₂DS₂-VASC of 7+

High Thromboembolism Risk

- **VTE**

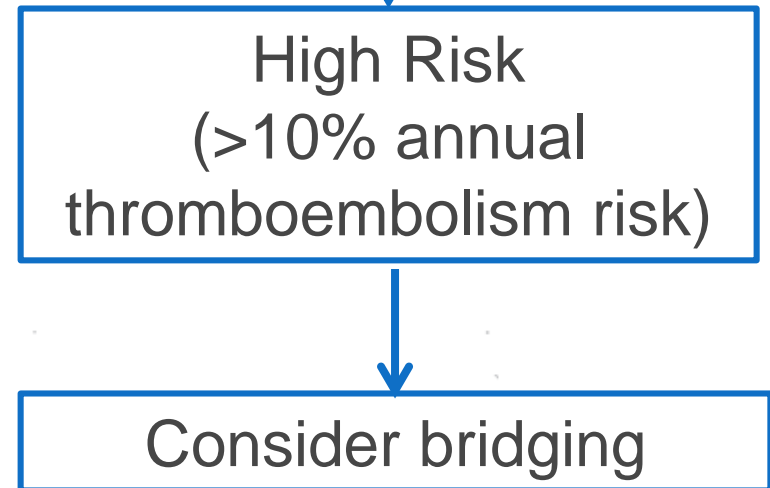
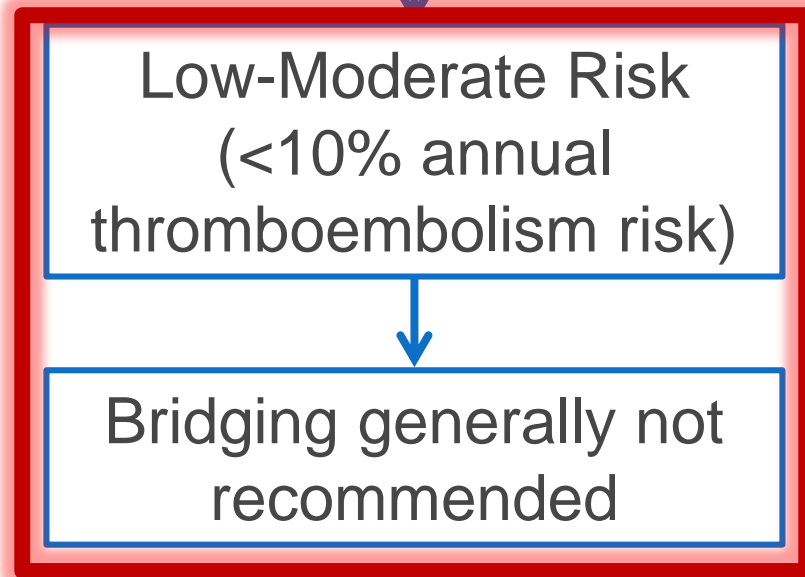
- VTE with severe thrombophilia
 - Thrombophilia = accurately diagnosed protein C/S or antithrombin deficiency, antiphospholipid antibody syndrome, or multiple thrombophilia
- Recent VTE (within the last 6 weeks)
- VTE with active cancer for the following high thrombotic risk cancer types: pancreatic, CNS, GI, lung, endocrine, head/neck
 - Active cancer = ongoing treatment, treatment completed within the last 6 months or palliative

High Thromboembolism Risk

- **VTE (cont.)**
 - History of recurrent VTE that occurred during short-term interruption of anticoagulation therapy
 - Undergoing a procedure with high inherent risk for VTE such as joint replacement surgery or major abdominal cancer resection

JAMA Intern Med. 2015; 175:1163–1168
CHEST. 2012;141(2)(suppl):e326S-e350S

Bridging Assessment



Low-Moderate Thromboembolism Risk

Any patient with mechanical heart valve, atrial fibrillation, or VTE¹ who does **not** meet HIGH risk criteria

1. *Prophylactic-dose LMWH may be considered for patients who experience unprovoked VTE between 6 to 12 weeks ago*

CHEST. 2012;141(2)(suppl):e326S-e350S
J Am Coll Cardiol. 2017. 69(7): 871 -898
JAMA Intern Med. 2015; 175:1163–1168

Post-Test Question #1

A 75 year old, 80 kg patient undergoing a routine colonoscopy. PMH includes atrial fibrillation, DM, CHF, and HTN. Medications include warfarin, lisinopril, metoprolol succinate, and metformin. INR today is 1.4. CrCl is 75 ml/min. What is the most appropriate type of bridging this patient should receive peri-procedurally?

- A. Enoxaparin 80 mg SubQ q 12 h
- B. Heparin 5000 units SubQ q 8 h
- C. Warfarin should be continued
- D. Bridging is not indicated in this patient

Post-Test Question #1

A 75 year old, 80 kg patient undergoing a routine colonoscopy. PMH includes atrial fibrillation, DM, CHF, and HTN. Medications include warfarin, lisinopril, metoprolol succinate, and metformin. INR today is 1.4. CrCl is 75 ml/min. What is the most appropriate type of bridging this patient should receive peri-procedurally?

- A. Enoxaparin 80 mg SubQ q 12 h
- B. Heparin 5000 units SubQ q 8 h
- C. Warfarin should be continued
- D. Bridging is not indicated in this patient**

Therapeutic Anticoagulants

Pre-Test Question #2

An 80 year old, 110 kg patient presents to your ED with lower right extremity swelling and erythema is diagnosed with an unprovoked DVT. PMH is significant for HTN, HLD, GERD, GI bleed (2013). Medications include atorvastatin, amlodipine, and omeprazole. SCr is 0.8 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Dabigatran
- B. Rivaroxaban
- C. Apixaban
- D. Warfarin (INR goal of 2-3)

Pre-Test Question #3

A 52 year old, 150 kg is diagnosed with Afib and requires therapeutic anticoagulation. PMH is significant for HTN, HFpEF, and DM. Medications include lisinopril, metoprolol tartrate, and metformin but patient is admittedly non-compliant. SCr is 1.1 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Rivaroxaban
- B. Apixaban
- C. Warfarin (INR goal of 2-3)
- D. Patient does not qualify for anticoagulation

Mechanism of Action

Injectables	Argatroban	Direct Thrombin Inhibitor
	Bivalirudin	Direct Thrombin Inhibitor
	Heparin	Thrombin and fibrin formation inhibitor
	LMWH	Factor Xa and thrombin inhibitor
	Fondaparinux	Factor Xa inhibitor

Orals	Apixaban	Factor Xa inhibitor
	Dabigatran	Direct Thrombin Inhibitor
	Edoxaban	Factor Xa inhibitor
	Rivaroxaban	Factor Xa inhibitor
	Warfarin	Vitamin K antagonist

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.

Anticoagulants by Use

Indication	IV	SubQ	PO
VTE treatment and reoccurrence prevention	Argatroban Bivalirudin Heparin	LMWH Fondaparinux	Apixaban Dabigatran Edoxaban Rivaroxaban Warfarin
VTE prophylaxis with atrial fibrillation or flutter	Argatroban Bivalirudin Heparin	LMWH Fondaparinux	Apixaban Dabigatran Edoxaban Rivaroxaban Warfarin
VTE prophylaxis and treatment with cardiac valve replacement	Argatroban Bivalirudin Heparin	LMWH Fondaparinux	Warfarin

CHEST 2016 VTE Updates

- For VTE and **no cancer**, as long-term anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban (all Grade 2B) **over** vitamin K antagonist (VKA) therapy, and suggest VKA therapy over LMWH (Grade 2C).
- For VTE **and cancer**, we suggest LMWH **over** VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

CHEST. 2016; 149(2):315-352.

Anticoagulants by Use

Indication	IV	SubQ	PO
VTE prophylaxis		LMWH Fondaparinux Heparin	
VTE prophylaxis following total hip arthroplasty		LMWH Fondaparinux Heparin	Apixaban Dabigatran Rivaroxaban
VTE prophylaxis following total knee arthroplasty		LMWH Fondaparinux Heparin	Apixaban Rivaroxaban
Hypercoagulable disorders	Argatroban Bivalirudin Heparin	LMWH Fondaparinux Heparin	Warfarin

CHEST. 2016; 149(2):315-352.

Anticoagulant Use in Dialysis

Anticoagulant	Recommendations
Argatroban	Restrict to those with HIT. No dose adjustment necessary.
Bivalirudin	Restrict to those with HIT. Initiate at lower rate.
Enoxaparin	Avoid
Fondaparinux	Contraindicated
Heparin	Drug of choice for short-term bridging or VTE prophylaxis. No dose adjustment necessary.
Apixaban	Avoid if possible. This population was excluded from VTE trials and Afib dosing is based on a single dose pharmacokinetic/dynamic study. Caution!
Dabigatran	Avoid. This population was excluded from all trials. Approx. 57% is removed over 4 hours of HD.
Edoxaban	Avoid. Use not recommended when CrCl < 15 ml/min
Rivaroxaban	Avoid
Warfarin	Drug of choice for long-term usage

Anticoagulant Use in Heparin-Induced Thrombocytopenia (HIT)

Anticoagulant	
Argatroban	Use if CrCl < 30 ml/min without hepatic impairment
Bivalirudin	Use if CrCl < 30 ml/min with hepatic impairment (LFTs > 3x ULN)
Enoxaparin	Contraindicated
Fondaparinux	Use if CrCl > 30 ml/min
Heparin	Contraindicated
Apixaban	No restrictions
Dabigatran	No restrictions
Edoxaban	No restrictions
Rivaroxaban	No restrictions
Warfarin	No restrictions

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.

Apixaban (Eliquis®): Clinical Pearls

- **Optimal:**

- Cannot or does not want to bridge with SubQ injections
- Difficulty traveling for INR monitoring
- History of GI bleed
- Age > 75 years old
- Low body weight (≤ 60 kg)
- Elevated SCr ≥ 1.5 mg/dL

- **Suboptimal:**

- Extensive liver disease and coagulopathy
- Poor compliance
- Need a reversal agent
- Severe renal disease (SCr >2.5 mg/dL)
- Combined strong CYP3A4 and P-gp inhibitors and inducers
- Once daily dosing preference (dosed BID)

Dabigatran (Pradaxa®): Clinical Pearls

- **Optimal:**

- Difficulty traveling for INR monitoring
- Need a reversal agent

- **Suboptimal:**

- Extensive liver disease and coagulopathy
- Poor compliance and/or require use of a pillbox
- History of GI bleed
- Age > 75 years old
- Difficulty with administration of SubQ injections for dabigatran initiation in VTE
- Significant dyspepsia at baseline
- Renal disease with CrCl < 30 ml/min
- Concomitant P-gp inducer or inhibitor administration
- Once daily dosing preference (dosed BID)

Edoxaban (Savaysa®): Clinical Pearls

- **Optimal:**

- Difficulty traveling for INR monitoring
- Once daily dosing preference (dosed q day)

- **Suboptimal:**

- Extensive liver disease and coagulopathy
- Poor compliance
- Need a reversal agent
- History of GI bleed
- Age >75 years old
- Difficulty with administration of SubQ injections for edoxaban initiation in VTE
- Renal disease with $\text{CrCl} \geq 95$ ml/min (if Afib) or $\text{CrCl} < 30$ ml/min

Rivaroxaban (Xarelto®): Clinical Pearls

- **Optimal:**

- Difficulty traveling for INR monitoring
- Once daily dosing (dosed q day)

- **Suboptimal:**

- Extensive liver disease and coagulopathy (Child Pugh B or C)
- Poor compliance
- Need a reversal agent
- History of GI bleed
- Age >75 years old
- Renal disease with CrCl < 30 ml/min
- Concomitant strong CYP3A4 and P-gp inhibitors or inducers

Rivaroxaban [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2014.

Warfarin (Coumadin®): Clinical Pearls

- **Optimal:**

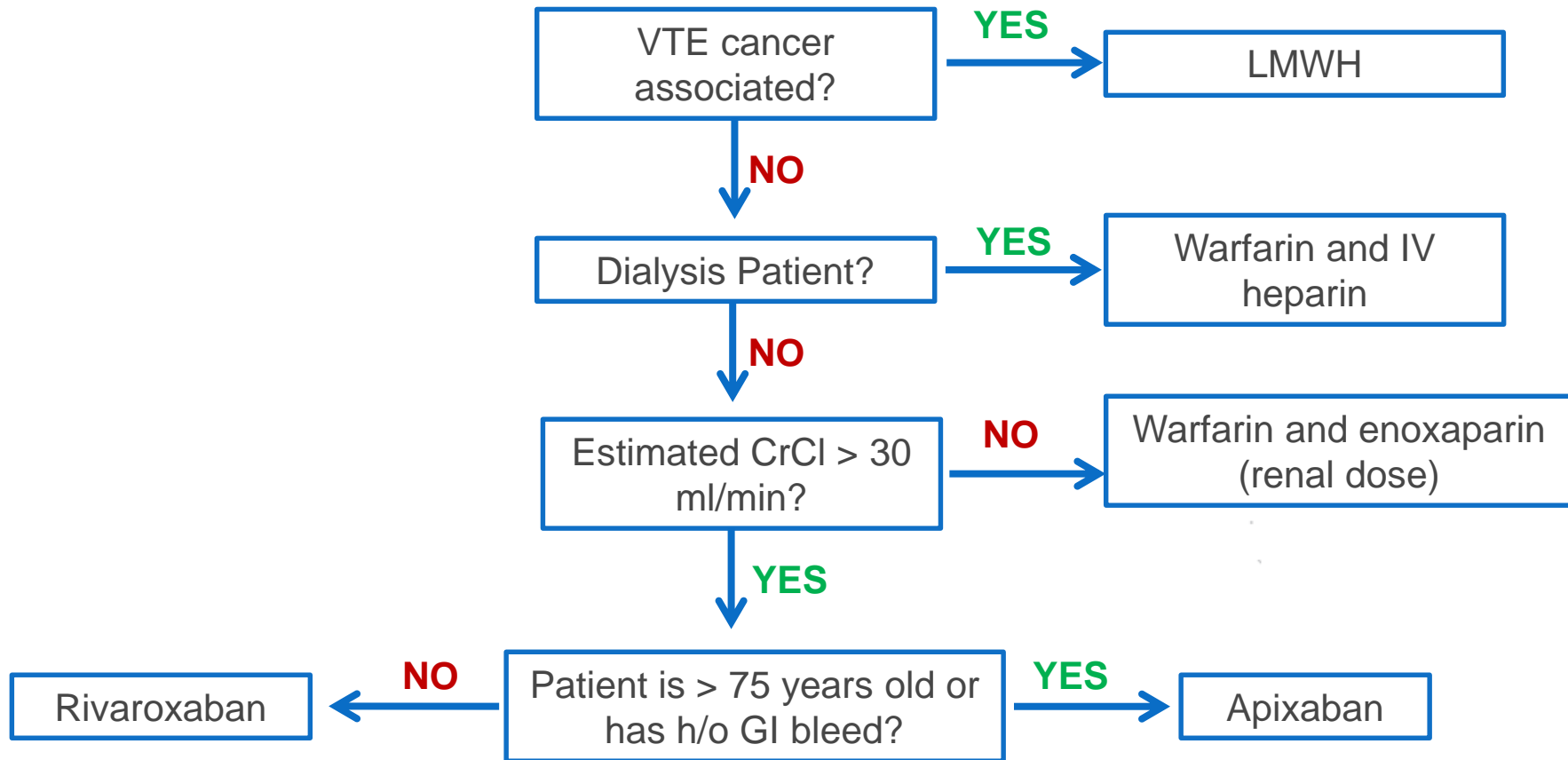
- Mechanical valve patients
- Obese patients (BMI > 40 or Wt > 120 kg)
- Once daily dosing preference (dosed q day)
- Renal disease with CrCl < 30 ml/min
- Need for a reversal agent
- Cost considerations

- **Suboptimal:**

- Extensive liver disease and coagulopathy
- Difficulty with administration of SubQ injections for warfarin initiation or bridging
- Poor nutrition or PO intake

Coumadin (warfarin) [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; September 2016.

New VTE Requiring Anticoagulation Decision Tree



Post-Test Question #2

An 80 year old, 110 kg patient presents to your ED with lower right extremity swelling and erythema is diagnosed with an unprovoked DVT. PMH is significant for HTN, HLD, GERD, GI bleed (2013). Medications include atorvastatin, amlodipine, and omeprazole. SCr is 0.8 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Dabigatran
- B. Rivaroxaban
- C. Apixaban
- D. Warfarin (INR goal of 2-3)

Post-Test Question #2

An 80 year old, 110 kg patient presents to your ED with lower right extremity swelling and erythema is diagnosed with an unprovoked DVT. PMH is significant for HTN, HLD, GERD, GI bleed (2013). Medications include atorvastatin, amlodipine, and omeprazole. SCr is 0.8 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Dabigatran
- B. Rivaroxaban
- C. Apixaban**
- D. Warfarin (INR goal of 2-3)

Post-Test Question #3

A 52 year old, 150 kg is diagnosed with Afib and requires therapeutic anticoagulation. PMH is significant for HTN, HFpEF, and DM. Medications include lisinopril, metoprolol tartrate, and metformin but patient is admittedly non-compliant. SCr is 1.1 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Rivaroxaban
- B. Apixaban
- C. Warfarin (INR goal of 2-3)
- D. Patient does not qualify for anticoagulation

Post-Test Question #3

A 52 year old, 150 kg is diagnosed with Afib and requires therapeutic anticoagulation. PMH is significant for HTN, HFpEF, and DM. Medications include lisinopril, metoprolol tartrate, and metformin but patient is admittedly non-compliant. SCr is 1.1 mg/dL, INR is 1.01, LFTs are WNL. Select the most appropriate anticoagulant for this patient.

- A. Dabigatran
- B. Apixaban
- C. Warfarin (INR goal of 2-3)**
- D. Patient does not qualify for anticoagulation

Anticoagulant Reversal

Pre-Test Question #4

A 57 year old male on warfarin for Afib presents to the ER for persistent, uncontrollable diarrhea for 3 days. INR is supratherapeutic at 7.6. No signs of bleeding are identified. What is the most appropriate anticoagulant reversal agent for this patient?

- A. Phytonadione (vitamin K)
- B. Protamine
- C. Idarucizumab (Praxbind®)
- D. 4-factor prothrombin complex concentrate (Kcentra®)
- E. No reversal agent is warranted

Anticoagulant

Reversal Options

Heparin
LMWH

Protamine

Warfarin

- Phytonadione (Vitamin K)
- Fresh frozen plasma (FFP)
- 4-Factor prothrombin complex concentrate (PCC) (Kcentra®)
- 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®)
- Recombinant coagulation factor VIIa (NovoSeven RT®)

Dabigatran

- Dialysis
- Idarucizumab (Praxbind®)

Apixaban
Rivaroxaban
Edoxaban

- 4-Factor prothrombin complex concentrate (PCC) (Kcentra®)
- 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®)
- Recombinant coagulation factor VIIa (NovoSeven RT®)

Heparin Reversal

- Average half-life of IV heparin is 1- 2 hours (dependent on obesity, renal function, malignancy, PE, and infection)
- Procedural or minor bleed management:
 - Stop heparin-containing drug
 - Hold heparin infusion for 4 or more hours prior to procedure (or per provider discretion)
- Emergent procedure or life-threatening bleed:
 - Stop heparin-containing drug
 - Administer protamine

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.
CHEST. 2012;141(2 Suppl):e44S-e88S

LMWH Reversal

- Average half-life of enoxaparin is 4.5 - 7 hours (dose independent)
- Procedural or minor bleed management:
 - Stop LMWH
 - Hold LMWH dose for 24 or more hours prior to procedure (or per provider discretion)
- Emergent procedure or life-threatening bleed:
 - Stop LMWH
 - Administer protamine

Protamine is unable to completely neutralize the anti-Xa activity of LMWH (maximum: ~60-75%)

Anticoagulant	Reversal Options
Heparin LMWH	Protamine
Warfarin	<ul style="list-style-type: none"> • Phytonadione (Vitamin K) • Fresh frozen plasma (FFP) • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)
Dabigatran	<ul style="list-style-type: none"> • Dialysis • Idarucizumab (Praxbind®)
Apixaban Rivaroxaban Edoxaban	<ul style="list-style-type: none"> • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)

CHEST Guidelines: Warfarin Reversal

INR	Recommendation
Above therapeutic range but <4.5 and no significant bleeding	Lower the dose of warfarin or omit dose
4.5-10 and no significant bleeding	Omit 1-2 doses of warfarin (no vitamin K) (Grade 2B)
≥10 and no significant bleeding (includes minor bleeding)	Hold warfarin and give 2.5-5mg PO Vitamin K (Grade 2C)
Major or life threatening bleed	<ul style="list-style-type: none">• PCC4 over plasma (2 units Fresh frozen plasma (FFP) IV over 30-45 minutes) (Grade 2C)• Hold warfarin, give 5-10mg Vitamin K by slow IV infusion (Grade 2C)

Phytonadione (Vitamin K)

Mechanism of Action	Restarts vitamin K dependent synthesis of active clotting factors II, VII, IX, X, and Proteins C & S
Onset of Action	
Oral	6-10 hours
IV	1-2 hours
Onset of Peak Effect	
Oral	24-48 hours
IV	12-14 hours
Monitoring	Draw PT/INR 24 hours post-phytonadione dose

- SubQ Vitamin K administration is not recommended
 - Absorption is erratic and unpredictable
- US Boxed Warning for IV Vitamin K
 - Severe reactions resembling hypersensitivity reactions have occurred during or immediately after IV administration

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.
CHEST. 2012;141(2 Suppl):e44S-e88S

FFP vs. 4-Factor PCC

	FFP	PCC
Blood typing required	YES	NO
Thawing time	30-45 minutes	0 minutes
Infection Risk	YES	YES (attenuated by heat treatment)
Thrombosis Risk	YES	YES
TACO/TRALI risk	YES	NO
Clotting factors contained	ALL	II, VII, IX, X, Proteins C & S, antithrombin III, and trace heparin

TACO: transfusion-associated circulatory overload

TRALI: transfusion-associated acute lung injury

***4-Factor PCC cannot be used if the patient has a history of HIT
[use 3-factor prothrombin concentrate (Profilnine SD®) instead]***

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.

FFP vs. 4-Factor PCC

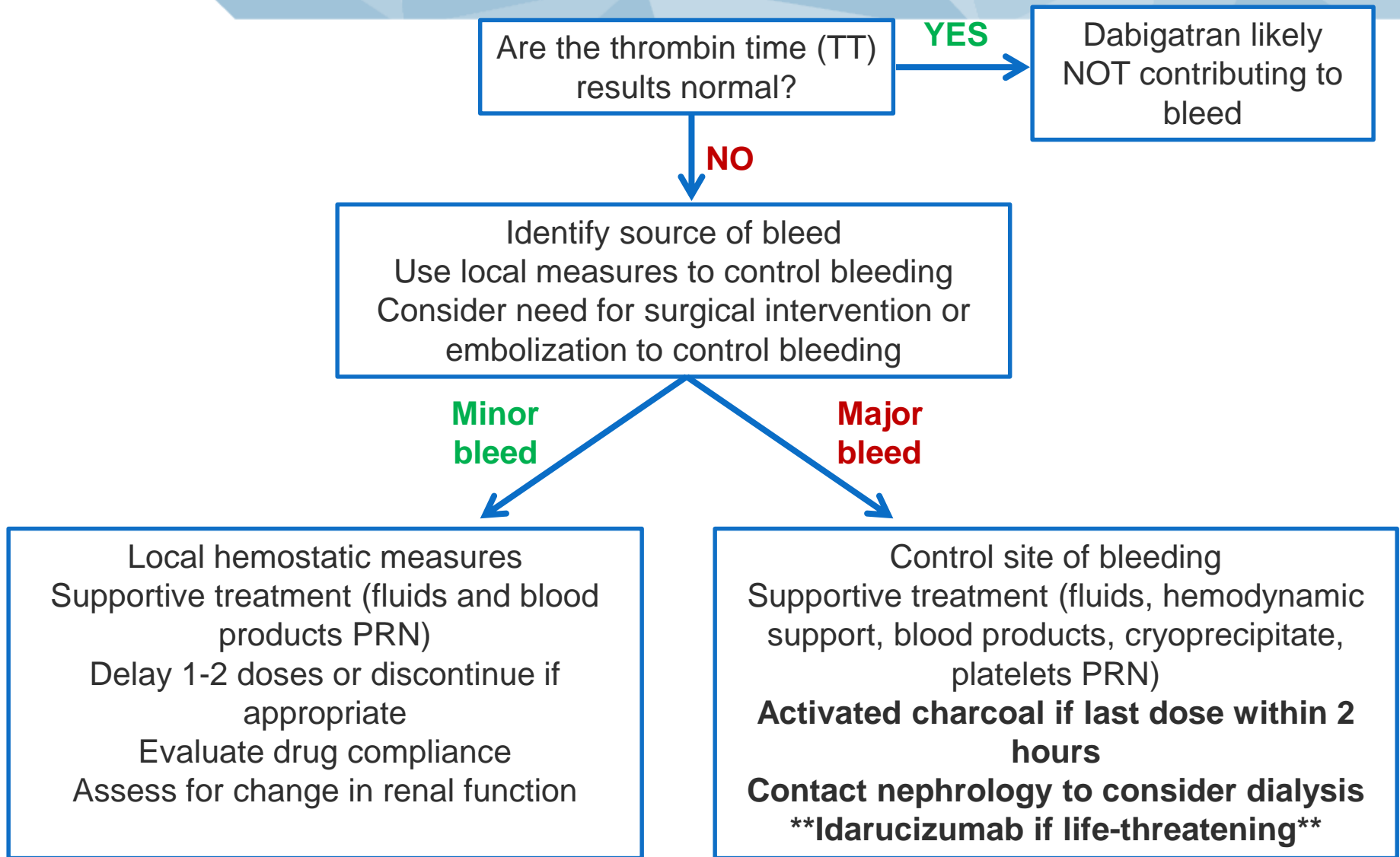
	FFP	PCC
Clotting factor concentration	LOW	HIGH
Infusion volume	1 unit = ~250 mL	<200 mL
Speed of INR correction	0.5 – 1 hour (Peak 1-2 hours)	Immediate (Peak 15 minutes)
Duration of INR correction	6 hours	≥24 hours
Extent of INR correction	Likely not to reduce <1.6 using FFP alone	Full
Expense	Moderate	High

Administer phytonadione (vitamin K) concurrently with clotting factors to resume clotting factor production for warfarin patients

J Thromb Haemost 2007; 98(4):790-797.
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.
Circulation. 2013;128:1234-1243

Anticoagulant	Reversal Options
Heparin LMWH	Protamine
Warfarin	<ul style="list-style-type: none"> • Phytonadione (Vitamin K) • Fresh frozen plasma (FFP) • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)
Dabigatran	<ul style="list-style-type: none"> • Dialysis • Idarucizumab (Praxbind®)
Apixaban Rivaroxaban Edoxaban	<ul style="list-style-type: none"> • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)

Dabigatran Reversal



Dabigatran Reversal

- Replacing clotting factors is NOT likely to be effective in reversing dabigatran
 - Dabigatran exerts its anticoagulant effect through direct clotting factor inhibition (free and fibrin-bound thrombin), not through clotting factor depletion

Idarucizumab (Praxbind®)

- A dabigatran-specific anticoagulant reversal to indicated for life-threatening or uncontrolled bleeding
- Received accelerated FDA approval in October 2015 through the ongoing REVERSE-AD trial

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2015.
Am J Health-Syst Pharm. 2017; 74:54-61

Idarucizumab (Praxbind®)

Mechanism of Action	A humanized monoclonal antibody fragment that binds specifically to dabigatran and its acylglucuronide metabolites with an affinity 350x stronger than that of thrombin
Onset of Action	Within minutes (hemostasis restored at a median of 11.4 hours)
Duration	At least 24 hours
Dosing	<ul style="list-style-type: none">• 5 g IV given as two separate 2.5 g doses no more than 15 minutes apart• If coagulation parameters re-elevate after doses have been given AND clinically relevant bleeding occurs OR if a second emergency surgery/urgent procedure is required, <i>may consider</i> administration of additional 5 g

Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2015.
Am J Health-Syst Pharm. 2017; 74:54-61

Idarucizumab (Praxbind®)

Monitoring	Thrombin Time (TT): <ul style="list-style-type: none">• Baseline (upon presentation)• 2 hours post-exposure (if known) or post-presentation• Every 12 hours thereafter until TT returns to normal
Adverse Reactions	<ul style="list-style-type: none">• Delirium (7%)• Headache (5%)• Hypokalemia (7%)• Constipation (7%)• Fever (6%)• Monoclonal antibody hypersensitivity reaction is possible• Thromboembolism

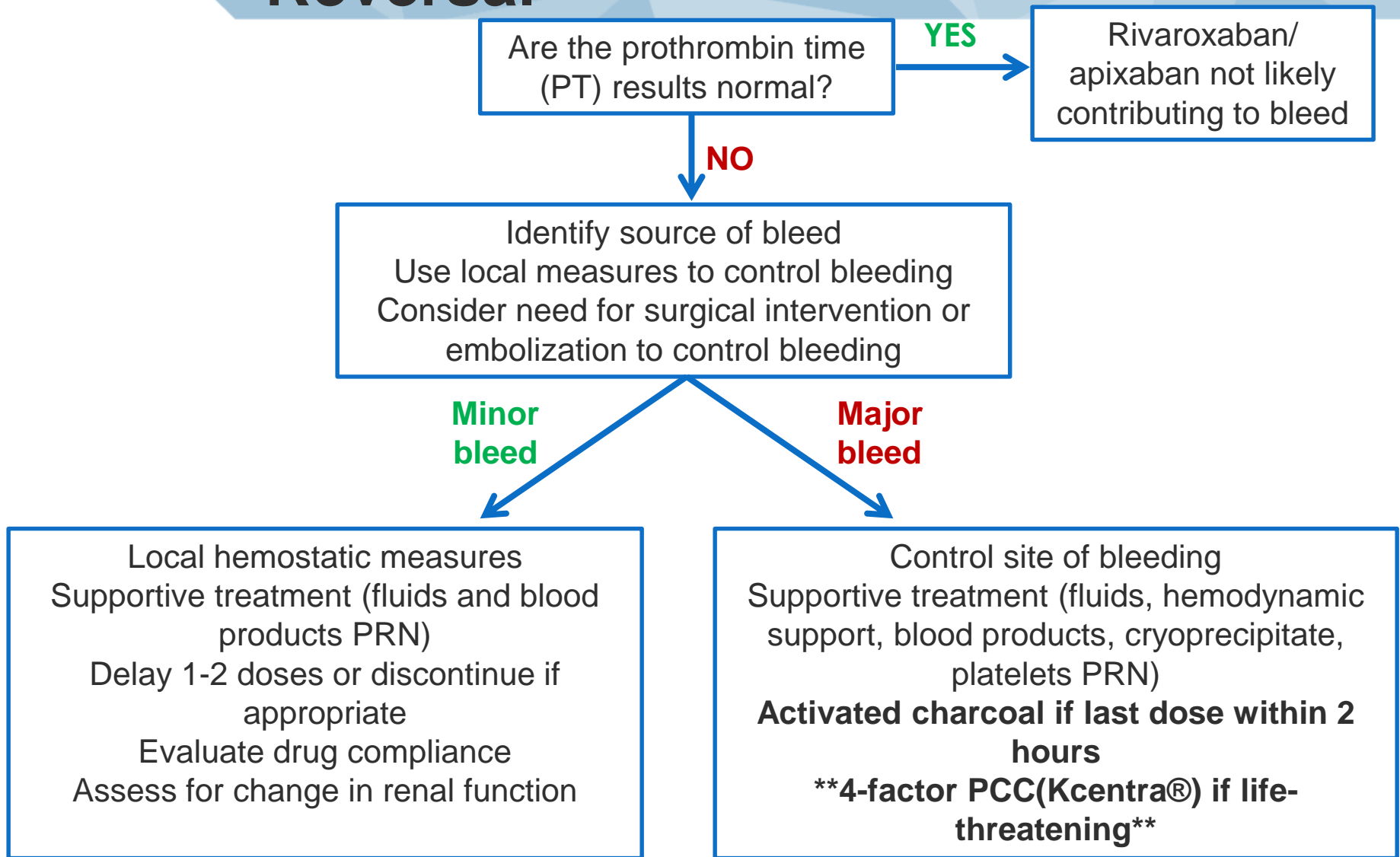
Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2015.
Am J Health-Syst Pharm. 2017; 74:54-61

Anticoagulant	Reversal Options
Heparin LMWH	Protamine
Warfarin	<ul style="list-style-type: none"> • Phytonadione (Vitamin K) • Fresh frozen plasma (FFP) • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)
Dabigatran	<ul style="list-style-type: none"> • Dialysis • Idarucizumab (Praxbind®)
Apixaban Rivaroxaban Edoxaban	<ul style="list-style-type: none"> • 4-Factor prothrombin complex concentrate (PCC) (Kcentra®) • 3-Factor prothrombin complex concentrate (PCC) (Profilnine SD®) • Recombinant coagulation factor VIIa (NovoSeven RT®)

Oral Direct Factor Xa Inhibitor Reversal

- There is currently **NO** FDA-approved specific reversal agent or antidote for apixaban, edoxaban, or rivaroxaban
- The strength and evidence of the following recommendations are weak and limited!!

Oral Direct Factor Xa Inhibitor Reversal



Andexanet alfa (AndexXa™)

- An investigational drug being studied as a reversal agent for life-threatening or uncontrolled bleeding associated with direct and indirect Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban, enoxaparin, and fondaparinux)
- FDA delayed the approval of andexanet alfa in August 2016
 - Requested more information related to manufacturing and additional data to support the inclusion of edoxaban and enoxaparin in the labeling

Ciraparantag (PER977)

- An investigational drug currently being studied as a potential specific reversal agent for dabigatran, direct and indirect Factor Xa inhibitors, and heparins
- A small synthetic molecule that directly binds to DOACS and heparins through noncovalent hydrogen bonding to neutralize anticoagulant activity

Post-Test Question #4

A 57 year old male on warfarin for Afib presents to the ER for persistent, uncontrollable diarrhea for 3 days. INR is supratherapeutic at 7.6. No signs of bleeding are identified. What is the most appropriate anticoagulant reversal agent for this patient?

- A. Phytonadione (vitamin K)
- B. Protamine
- C. Idarucizumab (Praxbind®)
- D. 4-factor prothrombin complex concentrate (Kcentra®)
- E. No reversal agent is warranted

Post-Test Question #4

A 57 year old male on warfarin for Afib presents to the ER for persistent, uncontrollable diarrhea for 3 days. INR is supratherapeutic at 7.6. No signs of bleeding are identified. What is the most appropriate anticoagulant reversal agent for this patient?

- A. Phytonadione (vitamin K)
- B. Protamine
- C. Idarucizumab (Praxbind®)
- D. 4-factor prothrombin complex concentrate (Kcentra®)
- E. No reversal agent is warranted**

Take Home Points

- A “less is more” approach is warranted for anticoagulation bridging in patients subtherapeutic on warfarin or who are holding warfarin peri-procedurally
- Subtle differences between the direct oral anticoagulants (DOACs) exist and patient specific factors (as well as patient preference) should be taken into account when choosing an anticoagulant
- Numerous reversal agents exist for the anticoagulants, however, an understanding of the mechanisms and benefits vs. risks of each is crucial to providing appropriate reversal

Resources & References

- Dougherty JU, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2017. 69(7): 871 - 898
- Siegal, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012; 126:1630-1639
- Douketis JD, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015; 379(9):823-833
- Witt DM, et al. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *JAMA Intern Med*. 2015; 175:1163-1168
- Krishnamoorthy A, et al. A bridge to nowhere? Benefits and risks for periprocedural anticoagulation in atrial fibrillation. *Curr Cardiol Rep*. 2016; 18(101):1-7
- You JJ, et al. American College of Chest Physicians antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012;141(2)(suppl):e531S-e575S
- Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2016; Dec 19, 2016.
- Kearon C, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *CHEST*. 2016; 149(2):315-352.
- Eliquis (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2016.
- Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2015.
- Savaysa (edoxaban) [prescribing information]. Parsippany, NJ: Daiichi Sankyo; September 2016.
- <http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=2196085>. Accessed May 2017.

Resources & References

- Rivaroxaban [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2014.
- Coumadin (warfarin) [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; September 2016.
- Glund S. A randomized study in health volunteers to investigate the safety, tolerability, and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *J Thromb Haemost* 2007; 98(4):790-797.
- Pollack Jr CV, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015; 373:511-520
- Riley TR, et al. Role of agents for reversing the effects of target-specific oral anticoagulants. *Am J Health-Syst Pharm*. 2017;74:54-61
- Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; September 2015
- Eerenberg ES, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: clinical perspective. *Circulation*. 2011;124:1573-1579.
- Kaatz S. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol*. 2012;87: S141-S145.
- Portola Pharmaceuticals Receives Complete Response Letter from FDA for Biologics License Application for AndexXa (andexanet alfa). Portoloa Pharmaceuticals, Inc; October 2016. <http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=2196085>. Accessed May 2017.

Speaker Contact Information

Heather Powell, PharmD, BCPS

- hpowell01@roosevelt.edu

Goldie Peters, PharmD, BCPS

- golden.peters@stlcop.edu