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Update on Anticoagulation Agents and Reversals

Carolyn Ruiz
West Kendall Baptist Hospital, carolynr@baptisthealth.net

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Update on anticoagulation agents and reversals

Carolyn M. Ruiz Rodríguez
PGY-1 Pharmacy Resident
West Kendall Baptist Hospital

Abbreviations

- Acute Coronary Syndrome (ACS)
- Activated prothrombin complex concentrate (aPCC)
- Body mass index (BMI)
- Coronary artery disease (CAD)
- Deep vein thrombosis (DVT)
- Direct oral anticoagulants (DOAC)
- Gastrointestinal (GI)
- Hip fracture surgery (HFS)
- Intracranial hemorrhage (ICH)
- Low molecular weight heparin (LMWH)
- Myocardial infarction (MI)
- Non-valvular atrial fibrillation (NVAF)
- Peripheral artery disease (PAD)
- Prothrombin complex concentrate (PCC)
- Pulmonary embolism (PE)
- Total hip arthroplasty (THA)
- Total knee arthroplasty (TKA)
- Unfractionated heparin (UFH)
- Venous thromboembolism (VTE)
- Vitamin K antagonist (VKA)

Objectives

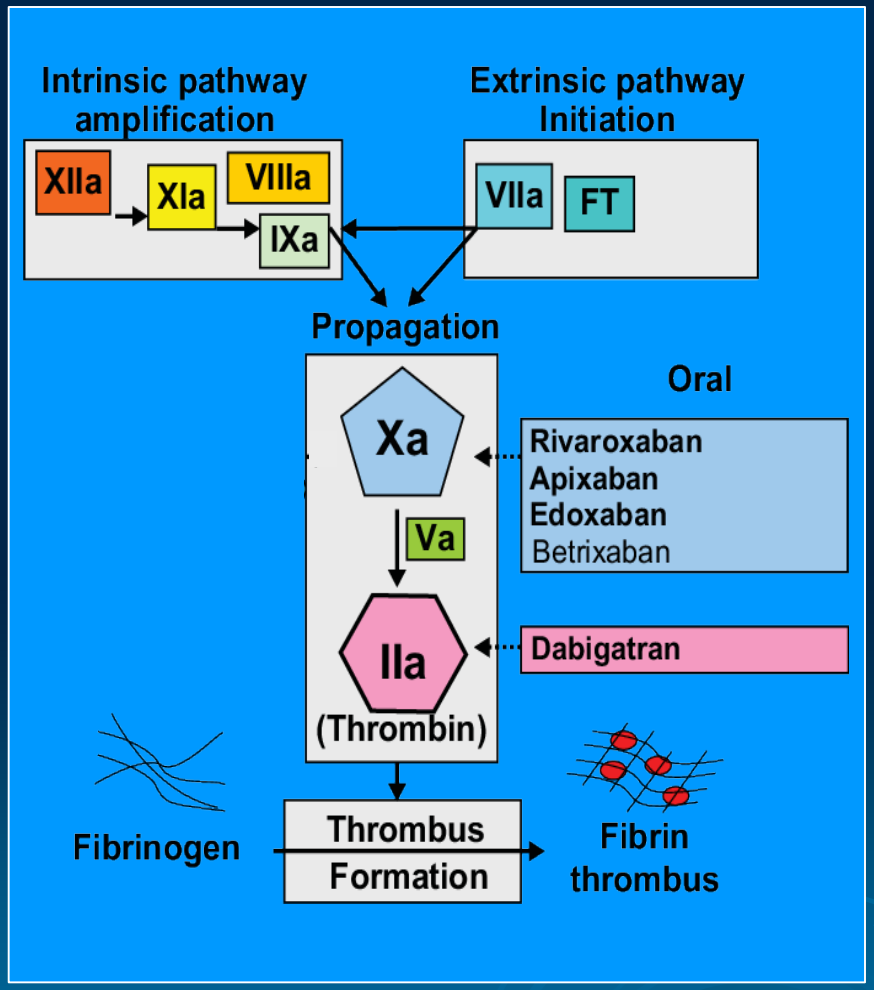
1. Review direct oral anticoagulants (DOACs)
2. Discuss the place in therapy for DOACs
3. Describe agents available for the reversal of bleeding associated with the use of DOACs
4. Define the pharmacist's role in the selection/monitoring of anticoagulation and reversal agents

Anticoagulation Agents

Traditional	Novel
Vitamin K Antagonist (VKA)	**Direct Thrombin Inhibitors**
Warfarin (Coumadin®)	Dabigatran (Pradaxa®)
Unfractionated Heparin (UFH) & Heparinoids	Argatroban
Heparin	Bivalirudin (Angiomax®)
Dalteparin (Fragmin®)	**Direct Factor Xa Inhibitors**
Fondaparinux (Arixtra®)	Rivaroxaban (Xarelto®)
Low Molecular Weight Heparin (LMWH)	Apixaban (Eliquis®)
Enoxaparin (Lovenox®)	Edoxaban (Savaysa®)
	Betrixaban (Bevyxxa®)

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.

Anticoagulation Cascade



- Warfarin
  - Inhibits vitamin K and factors VII, IX, X, IIa
- Dabigatran
  - Inhibits factor IIa
- Rivaroxaban, apixaban, edoxaban and betrixaban
  - Inhibit factor Xa

Gomez A, et al. Vasc Health Risk Manag. 2013.

Direct Oral Anticoagulants (DOACs)

	dabigatran	rivaroxaban	apixaban	edoxaban	betrixaban
Site of action	Factor IIa (Thrombin)	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Indication	• Prevention (hip or knee) and treatment of VTE • NVAF	• Prevention (hip or knee) and treatment of VTE • NVAF • CAD or PAD	• Prevention (hip or knee) and treatment of VTE • NVAF	• Treatment of VTE • NVAF	• Prevention of VTE
Half-life (hours)	12-17	5-9 (elderly 11-12)	9-14	10-14	19-27
Frequency	Once daily	Once daily	Twice daily	Once daily	Once daily
Renal excretion	80 %	33 %	25 %	35-50 %	18 %

NVAF-non-valvular atrial fibrillation; VTE-venous thromboembolism; CAD-coronary artery disease; PAD-peripheral artery disease

Arterioscler Thromb Vasc Biol. 2008 Mar;28(3):380-6.
Bevyxxa (betrixaban), Savayza (edoxaban) prescribing information.

DOACs Compared to Warfarin

Advantages	Disadvantages
As effective as warfarin	Expensive
Lower overall risk of major bleeding	Increased gastrointestinal bleeding
Less intracranial hemorrhage (ICH)	Shorter half-lives
No monitoring required	Limited ability to assess effectiveness
No diet restrictions	Limited data in end-stage renal/hepatic impairment
Less drug interactions	Costly antidote

Lawrence, LK. Direct oral anticoagulants and parenteral direct thrombin inhibitors, UpToDate, Waltham, MA, 2018.

ICH with DOACs

- Incidence varies between 0.6% to 1%
- VTE treatment
  - 52% reduction in ICH compared with warfarin
  - Van Der Hulle, et al (2014)
    - Meta-analysis of 5 trials (n=24,555)
    - Non-fatal ICH
      - DOACs 0.09% vs. warfarin 0.25%

Ruff CT, et al. Lancet 2014;383(9921):955-962.
Van Der Hulle T, et al. J Thromb Haemost, 2014.

ICH with DOACs

- AF
  - Lower risk of ICH for the treatment of stroke prevention

DOAC vs. warfarin	Percentage (%)
Rivaroxaban	0.80 vs. 1.2
Apixaban	0.33 vs. 0.80
Edoxaban	0.39 vs. 0.85
Dabigatran	0.10 vs. 0.39

Connolly SJ, et al. *N Engl J Med.* 2009; Patel MR, et al. *N Engl J Med.* 2011; Giugliano RP, et al. *N Engl J Med*. 2013; Granger CB, et al. *N Engl J Med.* 2011; Ruff CT, el al. *Lancet*. 2014.

GI Bleeding with DOACs

- DOACs associated with 25—30% increased risk when compared to warfarin
  - Apixaban has shown to have a favorable profile

Apixaban vs. dabigatran	Apixaban vs. rivaroxaban
1.38 vs. 2.73 %/year	1.34 vs. 3.54 %/year
P < 0.001	P < 0.001

  - Rivaroxaban associated with highest risk among DOACs

Abraham NS, et al. *Gastroenterology*. 2017;152:1014-1022.
Graham DJ, et al. *Circulation*. 2015;131(2):157-164.

GI Bleeding with DOACs

- Rate of GI bleeding increases with age among patients using DOACs
  - Higher risk in patients 65 years or older

- Co-therapy with proton pump inhibitors (PPI) or H2 antagonists has shown to reduce the incidence of GI bleed

Abraham NS, et al. *BMJ*. 2015;350:1857.
Ray WA, et al. *JAMA*. 2018;320(21):2221-2230.

PLACE IN THERAPY

Indications

1. Prophylaxis of Venous Thromboembolism (VTE)
2. Treatment of VTE
3. Non-valvular Atrial Fibrillation (AF)
4. Acute Coronary Syndrome (ACS)

VTE Prophylaxis in Medical Patients

- CHEST Guidelines (2012)
  - Recommended agents for at risk patients
    - LMWH, UFH, fondaparinux, intermittent pneumatic compression and/or graduated compression stockings
    - Limited guidance on DOACs
- Betrixaban (Bevyxxa®) is the only FDA approved DOAC for medical VTE prophylaxis

Gould MK, et al. *CHEST.* 2012.

VTE Prophylaxis in Medical Patients

- American Society Hematology (ASH) recommendation (2018)
  - LMWH over DOACs
  - Alternatives
    - Unfractionated heparin
    - Fondaparinux
  - Inpatient only treatment recommended, rather than inpatient plus extended duration outpatient

Schunemann HJ, et al. *Blood Advances*. 2018.

VTE Prophylaxis in Surgical Orthopedic Patients

- Total hip arthroplasty (THA) or total knee arthroplasty (TKA)
  - LMWH
  - Fondaparinux
  - Warfarin
  - Aspirin
  - Heparin
  - Rivaroxaban
  - Dabigatran
  - Apixaban

Treatment duration—Minimum 10 to 14 days

Falck-Ytter, et al. *CHEST*. 2012.

VTE Prophylaxis in Surgical Orthopedic Patients

- Hip fracture surgery (HFS)
  - LMWH
  - Heparin
  - Fondaparinux
  - Warfarin
  - Aspirin
- DOACs not recommended

Treatment duration—Minimum 10 to 14 days

Falck-Ytter, et al. *CHEST*. 2012.

Aspirin Role in VTE Prophylaxis in Surgical Patients

- Bawa, et al. (2018)
  - Retrospective review of post-op medication claims of patients who received aspirin, warfarin or enoxaparin within 6 months of THA and TKA
  - DVT rates
    - Aspirin 2.20%, warfarin 4.74%, enoxaparin 3.73%
- Anderson, et al. (2018)
  - Compared rivaroxaban 10 mg PO daily for 5 days followed by aspirin 81 mg PO daily versus rivaroxaban
  - VTE occurrence
    - Aspirin/rivaroxaban 0.64% vs. 0.70% rivaroxaban alone ($p<0.001$)

Anderson DR, et al. *N Engl J* Med. 2018.
Bawa H, et al. *J Am Acad Orthop Surg.* 2018.

VTE Prophylaxis in General Surgical Patients

- CHEST Guidelines (2012)
  - General and abdominal-pelvic surgery
    - Low risk of VTE
      - Mechanical over pharmacological prophylaxis
    - Moderate and high risk of VTE in patients with low risk of bleeding
      - Unfractionated heparin
      - LMWH
    - High risk of VTE and high risk of bleeding
      - Mechanical prophylaxis

DOACs not recommended

Gould MK, et al. *CHEST*, *2012; 141 (2):e227S-e277S.*

VTE Prophylaxis Dosing

Name	Dose
Heparin	5000 units subQ Q12h (low risk) Q8h (high risk)
Enoxaparin	40 mg subQ Q24h 30 mg Q24h (renal impairment)
Dabigatran	220 mg PO daily (hip surgery only)
Rivaroxaban	10 mg PO daily (hip or knee surgery only)
Apixaban	2.5 mg PO twice daily (hip or knee surgery only)
Betrixaban	160 mg PO on day 1 then 80 mg PO daily

VTE TREATMENT

VTE Treatment

- Initial treatment (first 5 days of therapy)
  - Unfractioned heparin
  - LMWH
  - Fondaparinux
  - Rivaroxaban
  - Apixaban

Can be given without initial parenteral anticoagulation (in hemodynamically stable pts without extensive clot burden)

- Maintenance
  - DOACs preferred over warfarin (except betrixaban)

Kearon C, et al. *CHEST, 2016.*
Xarelto (rivaroxaban) & Eliquis (apixaban) prescribing information.

VTE Treatment

Type	Duration of therapy
Proximal provoked VTE	3 months
Isolated distal DVT	3 months
Unprovoked VTE	3 months
First unprovoked VTE	• Extended treatment (low-moderate risk of bleeding) • 3 months (high bleeding risk)
Second unprovoked VTE	
Cancer	3 months Independent of risk of bleeding

Extended treatment – no stop date

Kearon C, et al. *CHEST, 2016.*

VTE Extended Treatment with Aspirin

- CHEST Guidelines (2016)
  - Recommend aspirin to prevent recurrence of VTE
    - Dose: 100 mg once daily (low dose)
    - Criteria:
      - Unprovoked proximal DVT/PE
      - No contraindication to aspirin use
      - Stopped oral anticoagulation or completed anticoagulation treatment
      - Low risk of bleeding

Kearon C, et al. *CHEST, 2016.*

VTE Treatment in Special Population

- CHEST Guidelines (2016)
  - Cancer
    - LMWH recommended over warfarin or DOACs (long term therapy)
  - Pregnancy
    - LMWH recommended
    - Duration of therapy: 3 to 6 months
    - Not recommended:
      - DOACs (insufficient safety information)
      - Warfarin
      - Fondaparinux

Kearon C, et al. *CHEST,* 2016.
Bates AM, et al. *CHEST, 2016.*

VTE Treatment Dosing (Initial)

- Enoxaparin 1mg/kg subQ Q12h (reduce to Q24h in renal impairment)
  - Alternative: 1.5 mg/kg subQ Q24h
- Fondaparinux 5 – 10 mg subQ daily
  - Dependent on weight
- Heparin infusion
  - 80 units/kg IV bolus then 18 units/kg/h infusion

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.

VTE Treatment Dosing

- Rivaroxaban 15 mg PO Q12h for 21 days followed by 20 mg PO daily
- Apixaban 10 mg PO Q12h for 7 days followed by 5 mg PO Q12h
- Dabigatran 150 mg PO Q12h*
- Edoxaban 60 mg PO Q24h (>60 kg)*
  30 mg PO Q24h (≤60 kg)*

*At least 5 days of initial therapy with parenteral anticoagulation

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL

STROKE PREVENTION IN ATRIAL FIBRILLATION

Stroke Prevention in AF

- DOACs shown to be at least as safe and effective as warfarin for the prevention of stroke and systemic embolism
- Reduced events by 19% compared to warfarin ($p<0.0001$)
- Safety

Major Bleeds	Reduced by 14% ($p=0.06$)
Intracranial hemorrhage	Reduced by 52% ($p<0.0001$)
GI Bleeds	Increased ($p=0.04$)

Lip GYH, et al. *CHEST*, 2018.
Ruff CT, et al. *Lancet.* 2014.

Assessment Tools in AF

- $CHADS_2$ ⟶ **CHA_2DS_2—VASc**
  - Used to determine stroke risk

- HAS—BLED score
  - Developed originally for warfarin
  - Predicts serious bleeding
    - Only score predictive of intracranial bleeding

Both scores complement each other

Lip GYH, et al. *CHEST*, 2018; 154(5):1121-1201.
Ruff CT, et al. *Lancet,* 2014;383(9921):955-962.

Stroke Risk Assessment Tool

CHA_2DS_2—VASc

- Congestive Heart Failure
- Hypertension
- Age ≥ 75 years*
- Diabetes
- Stroke*
- Vascular disease
- Age (> 65 years)
- Sex (Female)

Score	Risk	Therapy
0 male 1 female	Low	None
≥ 1 male ≥ 2 female	Moderate	No therapy or DOAC or warfarin
≥ 2	Moderate or High	DOAC or warfarin

*Two (2) points assigned to these parameters

Lip GYH, et al. *CHEST,* 2018; 154(5):1121-1201.

Bleeding Risk Assessment Tool

- **HAS—BLED** used to address modifiable bleeding risk factors
- Performed at every patient contact

HAS-BLED	Score
Hypertension	1 point
Abnormal renal/liver function	1 point each
Stroke	1 point
Bleeding tendency (i.e. gastric ulcer disease)	1 point
Labile INR	1 point
Age	1 point
Drugs (i.e NSAIDs or aspirin)	1 point
Score >3 (high risk): warrant more frequent monitoring	

Lip GYH, et al. *CHEST,* 2018; 154(5):1121-1201.

AF Treatment

CHEST Guidelines (2018)

- Treatment of choice
  - DOACs over warfarin (strong recommendation)
- Prior unprovoked bleeding, warfarin-associated bleeding or high risk of bleeding (weak recommendation)
  - Apixaban
  - Edoxaban
  - Dabigatran

Lip GYH, et al. *CHEST,* 2018; 154(5):1121-1201.

AF Treatment in Mechanical Heart Valves

- DOACs not recommended–limited studies
- RE-ALIGN trial (n=252)
  - Studied dabigatran vs. warfarin
    - Stroke occurrence: 5% vs. 0%
    - Bleeding: 27% vs. 12% (p<0.01)
    - Study terminated prematurely due to safety concerns
- Treatment of choice: LMWH or UFH until stable on warfarin

Whitlock RP, et al. CHEST. 2012.
Eikelboom JK, et al. *N Engl J Med. 2013.*
Nishimura RA, et al. *JACC*. 2017.

AF Treatment in Elderly

- Age increases risk of intracranial hemorrhage (ICH) and mechanical falls

Study	Methods	Findings
Sardar, et al. (2014)	• Meta-analysis of pts ≥75 yo • Compared DOACs (rivaroxaban, apixaban and dabigatran) vs. warfarin	DOACs: • No excess bleeding • Equal or greater efficacy
Chao, et al. (2018)	• Cohort study in the very elderly (≥90 yo) • Evaluated the risk of ICH and stroke in patients in 2 groups (DOACs vs. warfarin)	Risk of ICH: • DOACs 0.42% vs. warfarin 1.63%; p<0.044)

Chao TF, et al. *Circulation*. 2018;138:37-47.
Sardar P, et al. *J Am Geriatr Soc.* 2014 May;62(5):857-64.

AF Treatment in Elderly

- Risk of falls
  - Individual risk assessment prior to starting DOACs
  - A patient would have to fall 295 times per year for the risk from falls to outweigh the benefits of anticoagulation
- Conclusion
  - DOACs rarely considered a contraindication

Fear the clot, not the bleed

Man-Son-Hing M, et al. *Arch Intern Med*. 1999.
Sardar P, et al. *J Am Geriatr Soc*. 2014.
Lip GYH, et al. *CHEST*. 2018.

AF Treatment in End-Stage Renal Disease (ESRD)

- **Dias, et al. (2016)**
  - Rivaroxaban (15 mg PO daily)
    - Single-dose study resulted in similar exposure to patients studied who had CrCl 15 to 49 mL/minute
- **Siontis, et al. (2018)**
  - Apixaban (5 mg PO twice daily)
    - Lower risk of stroke, major bleeding and death vs. VKA
- Limited studies available– use with caution

Dias C, Moore KT, et al. *Am J Nephrol.* 2016;43(4):229-236.
Siontis KC, et al. *Circulation.* 2018;138:1519-1529.

AF Treatment in Special Population

CHEST Guidelines (2018)

- Pregnancy
  - Treatment of choice: LMWH Q12h
  - Avoid use of DOACs
- Breast feeding
  - Use LMWH, unfractionated heparin, or warfarin
  - DOACs not recommended

Kearon C. et al. *CHEST.* 2016; 149:315-52.
Lip GYH. Et al. *CHEST*. 2018; 154 (5): 1121-1201.

AF Treatment in Obese Patients

- International Society of Hemostasis and Thrombosis (2016) Guidelines
  - Patients with BMI >40 kg/m^2 or >120 kg
    - Limited clinical data available
    - Warfarin preferred agent
    - DOACs not recommended
      - No FDA approved dosage recommendation

Martin K, et al. *J Thromb* Haemost. 2016;14(6):1308-1313.

Treatment Based on Patient Characteristics

Patient characteristics	Therapeutic options
Recurrent stroke/SE/TIA	dabigatran
Moderate-severe renal impairment*	apixaban, dabigatran, edoxaban, rivaroxaban
High risk of GI bleeding	apixaban, dabigatran
Major GI symptoms or dyspepsia	apixaban, rivaroxaban, edoxaban
High risk of bleeding**	apixaban, dabigatran, edoxaban
Low pill burden	edoxaban, rivaroxaban, warfarin

TIA-transient ischemic attack; GI-gastrointestinal
*CrCl 15-49 mL/min
**Defined as a HAS-BLED of ≥3 points

Lip GYH, et al. *CHEST.* 2018; 154(5):1121-1201.

AF Treatment Dosing

Name	Dose	Renal impairment
Acute treatment		
Enoxaparin	1 mg/kg subQ Q12h	1 mg/kg subQ Q24h
Chronic treatment		
Warfarin	Dose to INR goal of 2-3	No dose adjustment
Aspirin	75—100 mg PO daily	No dose adjustment
Acute and chronic treatment		
Apixaban	5 mg PO Q12h	2.5 mg PO Q12h
Rivaroxaban	20 mg PO daily	15 mg PO daily
Dabigatran	150 mg PO Q12h	75 mg PO Q12h

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL.

ACUTE CORONARY SYNDROME

Acute Coronary Syndrome

ATLAS ACS 2–TIMI 51 Trial

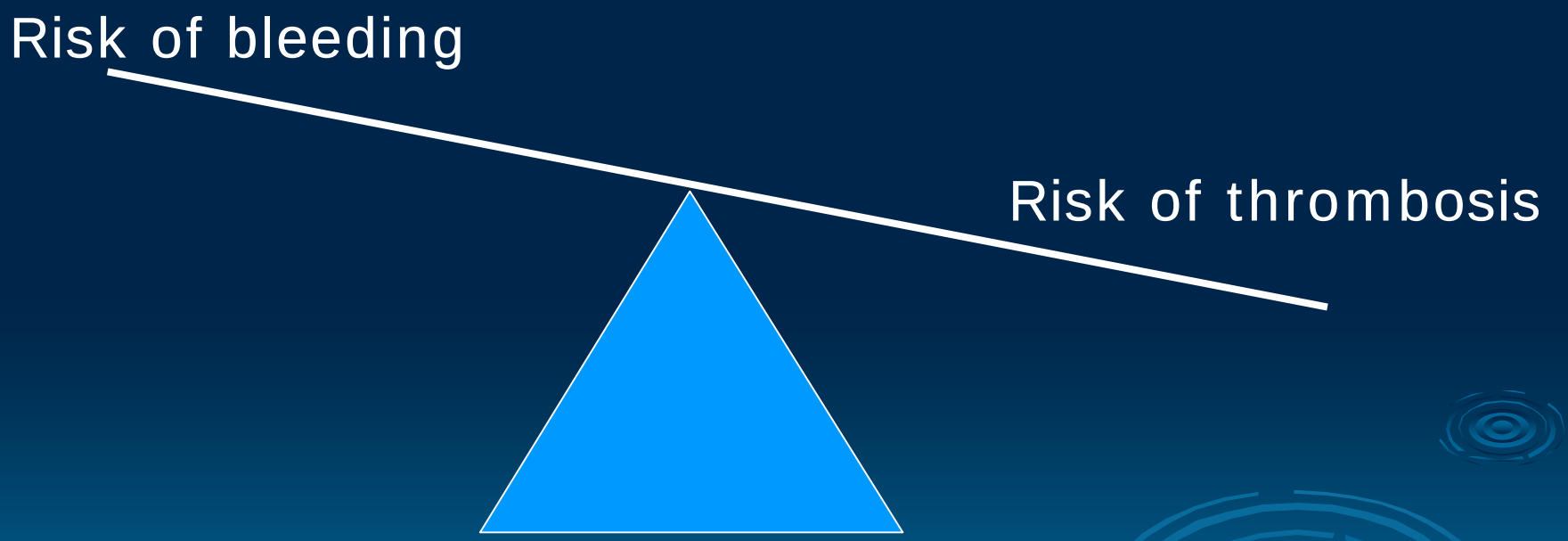
- Compared placebo vs. rivaroxaban 2.5 mg PO Q12 h vs. rivaroxaban 5 mg PO Q12 h

- Conclusion
  - Reduced death from cardiovascular causes, MI, or stroke (rivaroxaban 8.9 vs. placebo 10.7%; $p<0.008$)
  - Rivaroxaban 2.5 mg PO twice daily may be considered in patients with low risk of bleeding not requiring chronic anticoagulation for other indications

Mega ML, et al. *N Engl J Med*. 2012.

PERIOPERATIVE MANAGEMENT

To Bridge or Not to Bridge?



Perioperative Bleeding Risk Assessment

Minimal risk	Low risk	High risk
Endoscopy without surgery	Dental procedures	Major surgery (duration >45 min)
Central venous catheter removal	Hand/foot/shoulder surgery	Cardiac surgeries (coronary artery bypass)
Abscess incision	Cardiac procedures (i.e. implantable devices and catheter ablation)	Dental procedures (i.e. multiple teeth extraction)
Glaucoma or cataract intervention	Cholecystectomy	Major orthopedic surgeries (i.e. joint arthroplasty)

Burnett AE, et al. J Thromb Thrombolysis. (2016) 41:206–232.

Perioperative Bleeding Risk Assessment

Calculated CrCl (mL/min)	Timing of Last Dose Before Surgery	
	Low Risk of Bleeding	High Risk of Bleeding
Dabigatran		
> 50	Minimum 24 hours	2 days
31-50	2 days	5 days
< 30	4 days	5-6 days
Rivaroxaban, apixaban, edoxaban		
> 50	1 day	2 days
31-50	1-2 days	3-4 days
< 30	2 days	4 days

Anticoagulation Therapy 2nd edition. ASHP; 2018

When to Restart DOACs?

- Delay until adequate hemostasis

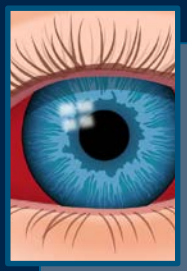
Procedural Bleed Risk	DOAC Resumption time
Minimal	May not require interruption of DOAC therapy
Low	24 hours post-operative
High	48-72 hours post-operative

Burnett AE, et al. J Thromb Thrombolysis (2016) 41:206–232.

RISK OF BLEEDING

Bleeding

- Critical sites



Intraocular

Retroperitoneal

GI tract

Brain

Tomaselli GF, et al. JACC. 2017;70(24)3042-67.
https://www.Medscape.com; https://www.allaboutvision.com;
https://renalfellow.org; http://gitract.ccfa.org/detail.

BLEEDING MANAGEMENT AND REVERSAL AGENTS

General Measures of Bleeding

- Assessment:
  - Determine the urgency of event
  - Assess the risk of bleeding and thrombosis
  - Obtain accurate medication history
- Discontinue/hold anticoagulation
  - Provide supportive measures
- Pharmacological intervention
  - Specific reversal agents
- Replace blood losses

Reversal Agents

Name	Reversal
Heparin	Protamine sulfate
Enoxaparin	Protamine sulfate
Fondaparinux	No specific reversal Fresh Frozen Plasma (FFP); PCC (Kcentra®); Recombinant Factor VIIa
Warfarin	Vitamin K (Mephyton®)—PO or IV FFP; PCC (Kcentra®); Recombinant Factor VIIa
Dabigatran	Idarucizumab (Praxbind®) aPCC (FEIBA®) Activated charcoal (within 2 h of ingestion) Antifibrinolytic (i.e. tranexamic acid)
Apixaban, Rivaroxaban	PCC (Kcentra®) Andexanet alfa (Andexxa®) Activated charcoal (within 2 h of ingestion) Antifibrinolytic (i.e. tranexamic acid)

UpToDate. Waltham, MA, 2018.

Management of ICH

- American Heart Association/American Stroke Association Guidelines (2015)
  - Dabigatran, rivaroxaban or apixaban induced
    - Activated PCC or other type of PCC
    - Activated charcoal if last dose within <2 hrs
  - Optimal time to resume anticoagulation
    - 4 weeks (reduces risk of ICH recurrence)
      - Exception: patients with mechanical heart valves

Hemphill III JC, et al. *Stroke.* 2015; 46:2032-2060.

Management After GI Bleed

- Based on available evidence
  - Warfarin may be restarted 7 to 14 days following a GI bleed
  - DOAC resumption after a GI bleed
    - Data is limited, consider the following
      - Faster onset of action
        - Delay restarting therapy for a few more days (compared to warfarin)
      - Select DOAC with less GI bleed risk (i.e. apixaban)

Abraham NS, et al. *Gastroenterology*. 2017;152:1014-1022.

Reversal of DOAC with Prothrombin Complex Concentrates (PCC)

- Plasma derived products of human clotting factors
- Preferred non-hemostatic agent for DOAC reversal
- Weight based dosing more effective than standard dosing
- Adverse effect– hypercoagulability

Kcentra (4FPCC), Profilnine (3FPCC), Feiba (aPCC) prescribing information.

Reversal of DOAC with PCC

Types	Factors	Dosage (units/kg)	Target	Cost
4 factor PCC (Kcentra®)	II (prothrombin), VII, IX, and X	50 (off label use)	apixaban rivaroxaban edoxaban betrixaban	$9,695*
3 factor PCC (Profilnine®)	II, IX, and X (not contain factor VII)	50	apixaban rivaroxaban edoxaban betrixaban	$3,930*
activated PCC (Feiba®)	II, VIIa, IX and X	• ICH: 50 • Life threating bleed:25 to 100 (off label use)	dabigatran	$3,100 to 11,630*

*Assuming 70 kg patient, and recommended dose range
*Based on hospital acquisition cost

Kcentra (4FPCC), Profilnine (3FPCC), Feiba (aPCC) prescribing information.
Tomaselli GF, et al. JACC. 2017;70(24)3042-67.

Reversal of DOAC with PCC

Low grade evidence

- Indications
  - Use only in life-threatening circumstances or urgent surgery/procedures
- PCC recommended over aPCC
  - Higher incidence of thrombosis with aPCC

Garcia DA, Management of bleeding in patients receiving DOACs, UpToDate. Waltham, MA, 2018.

When to Use PCC?

- First line agent
  - Apixaban, edoxaban and rivaroxaban
  - 4 factor-PCC most extensively studied
- Second line agent
  - Dabigatran
    - Reversal agent not available
    - Use aPCC
      - May consider PCC

Tomaselli GF, et al. JACC. 2017;70(24)3042-67.

Idarucizumab (Praxbind®)

- Humanized monoclonal antibody fragment (Fab)
- First line agent for reversal of dabigatran (Pradaxa®)
  - Binds irreversibly to free and thrombin-bound dabigatran
- Onset of action: reverses within 10 minutes of administration

Idarucizumab (Praxbind®)

- Supplied: 2.5 g/50 mL ($2,100 per dose*)
- Administration (within 1 hr of removal from vial)

2.5 g IV bolus over 5-10 min → Within 15 minutes → 2.5 g IV bolus over 5-10 min

Consider additional 5 g if re-elevated aPTT and/or clinically relevant bleeding

*Based on hospital acquisition cost

Praxbind (idarucizumab) prescribing information.

Idarucizumab (Praxbind®)

- RE-VERSE AD study (n=503)
  - Predominant sites of bleeding
    - GI (45.5%)
    - ICH (32.6%)
  - Cessation of bleeding
    - Median time 2.5 h
  - Conclusion
    - More than 98% of the patients achieved complete and rapid reversal of anticoagulation
    - Idarucizumab is effective for patients with uncontrolled bleeding or undergoing urgent surgery

Pollack, CV, et al. N Engl J Med. 2017;377(5):431.

Idarucizumab (Praxbind®)

- Adverse effects
  - Pyrexia
  - Bronchospasm
  - Hyperventilation
  - Rash and pruritis
- Monitoring Parameters
  - Coagulation parameters
    - aPTT, TT and ECT normalized
  - Signs and symptoms of re-bleeding

Praxbind (idarucizumab) prescribing information.

Andexanet alfa (Andexxa®)

- Recombinant modified human factor Xa decoy protein
  - Temporary shuts down the activity of factor Xa
- FDA approved May 2018
  - Indications (rivaroxaban or apixaban):
    - Life threatening bleeding

Andexxa (andexanet alfa) prescribing information.

Andexanet alfa (Andexxa®)

- Dosing regimen

Dose	Initial IV Bolus	Follow-up IV infusion	Cost
Low dose	400 mg at a rate of 30 mg/min	4 mg/min for up to 120 minutes	$25,000*
High dose	800 mg at a rate of 30 mg/min	8 mg/min for up to 120 minutes	$50,000*

The safety and efficacy of more than one dose has not been evaluated
*Cost includes bolus plus the follow-up infusion
*Based on hospital acquisition cost ($2,750 per 100 mg vial)

Andexxa (andexanet alfa) prescribing information.

Andexanet alfa (Andexxa®)

FXa inhibitor	Last dose	Timing of FXa Inhibitor Last Dose Before Andexanet alfa initiation	
		<8 h or unknown	≥8 h
Apixaban	< 5 mg	Low dose	Low dose
	> 5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High dose	

Andexxa (andexanet alfa) prescribing information.

Andexanet alfa (Andexxa®)

- ANNEXA-4 Trial (n=67)
  - Assessed acute major bleeding within 18 h after administration of a factor Xa inhibitor
    - GI: 33 patients (49%)
    - Intracranial: 28 patients (42%)
    - Other: 6 patients (9%)
  - Clinical hemostasis
    - Reached in 53 patients (79%)
    - 12 h after the end of the infusion
  - Conclusion
    - Andexanet rapidly reversed anti-factor Xa activity

Conolly, MD, et al. *N Engl J Med. 2016.*

Andexanet alfa (Andexxa®)

- Adverse effects
  - Urinary tract infections
  - Pneumonia
  - Infusion site reactions
- Monitoring
  - Signs and symptoms
    - Arterial and venous thromboembolic events
    - Re-bleeding
    - Cardiac arrest

Andexxa (andexanet alfa) prescribing information.

Reversal Pipeline

- Ciraparantag (PER977®)
  - Investigational agent specifically for direct thrombin inhibitors, factor Xa inhibitors, and heparin (including LMWH)
  - Dose: 100—300 mg (single IV dose)
  - Exception
    - Argatroban
    - Warfarin (Coumadin®)

Gregory YH, et al. *CHEST*. 2018; 154(5):1121-1201.
Anticoagulation Therapy 2nd edition. ASHP; 2018.

Pharmacist's Role in Therapy

- Review
  - Medication history
  - Laboratory parameters
  - Appropriate reversal agent
- Prevent delays
  - Establish protocol for use of reversal agents
  - Develop order sets
- Collaborate with prescribers to determine when to restart anticoagulation therapy

Pharmacist's Role in Therapy

- Role in transitions of care
  - Assure appropriate therapy
  - Ensure medication access
  - Provide patient and caregiver education
- Follow-up is critical in order for patients to know when to restart therapy

Take Home Points

- DOACs
  - First line treatment for
    - Stroke prevention in AF patients
    - Patients with DVT of the leg or PE and no cancer
  - Alternative agents for
    - Prophylaxis
      - Orthopedic surgical patients
      - Medical patients (hospitalized/non-hospitalized)

Take Home Points

- PCC's are non-hemostatic reversal agents used as
  - First line for DOACs
  - Second line for dabigatran (Pradaxa®)
- Idarucizumab (Praxbind®)
  - Specific reversal agent for dabigatran (Pradaxa®)
- Andexanet alfa (Andexxa®)
  - Specific reversal agent for rivaroxaban (Xarelto®) and apixaban (Eliquis®) in life threatening bleeding

Assessment

1. True or False: Andexanet alfa (Andexxa®) is approved as a reversal agent for apixaban (Eliquis®) or rivaroxaban (Xarelto®).
2. True or False: The betrixaban (Bevyxxa®) dose for atrial fibrillation is 160 mg PO twice daily.
3. True or False: Direct oral anticoagulants (DOACs) may not be used in patients with valvular atrial fibrillation.

Thank You!