THE CLOT THICKENS…OR NOT: ANTICOAGULATION UPDATES FOR PHARMACISTS

Khyati Patel, PharmD, BCACP

Associate Professor – Rosalind Franklin University of Medicine and Science

Ambulatory Care Pharmacist – Advocate Aurora Medical Center, Kenosha, WI

DISCLOSURE

- Khyati Patel declares 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.

LEARNING OBJECTIVES

- At the end of this presentation, attendees should be able to…

1. List common health conditions that require use of anticoagulants for prevention or treatment of thrombosis.
2. Describe pharmacology, dosing, indications, adverse effects, contraindications, monitoring, reversal agents, and efficacy and safety outcomes for the available direct oral anticoagulants.
3. Discuss the latest guidance for management of anticoagulation in patients with venous thromboembolism and atrial fibrillation.
4. Explain strategies for perioperative management of direct oral anticoagulants.

PRE-ASSESSMENT QUESTION - 1

1. Which of the following conditions require use of anticoagulants for the treatment of thrombosis?
   A. Aortic stenosis
   B. Factor VIII deficiency
   C. Mechanical mitral valve placement
   D. Ventricular fibrillation

PRE-ASSESSMENT QUESTION - 2

2. Which of the following DOAC regimen has shown superiority against warfarin in preventing stroke and systemic embolism when studied in population with atrial fibrillation?
   A. Dabigatran 110 mg BID
   B. Apixaban 5 mg BID
   C. Rivaroxaban 20 mg daily
   D. Edoxaban 60 mg daily

PRE-ASSESSMENT QUESTION - 3

3. According to the 2021 CHEST Guidelines for Antithrombotic Therapy for VTE, which of the following anticoagulant is recommended for the treatment of venous thromboembolism in the setting of cancer?

   A. Fondaparinux
   B. Warfarin
   C. Enoxaparin
   D. Apixaban

PRE-ASSESSMENT QUESTION - 4

4. A 56-year-old female patient takes apixaban for treatment of atrial fibrillation (CHA_2DS_2-VASc = 3). The surgery team consults you to recommend perioperative management for upcoming hysterectomy. Which of the following represents the most appropriate approach based on the 2022 CHEST Guidelines for Perioperative Management of Antithrombotics?

   A. Stop apixaban 5 days before surgery, weight based dose of enoxaparin days 3-5 before surgery, resume the day after surgery

   B. Stop apixaban 2 day before surgery, resume 2 days after surgery

   C. Stop apixaban 1 day before surgery, resume 1 day after surgery

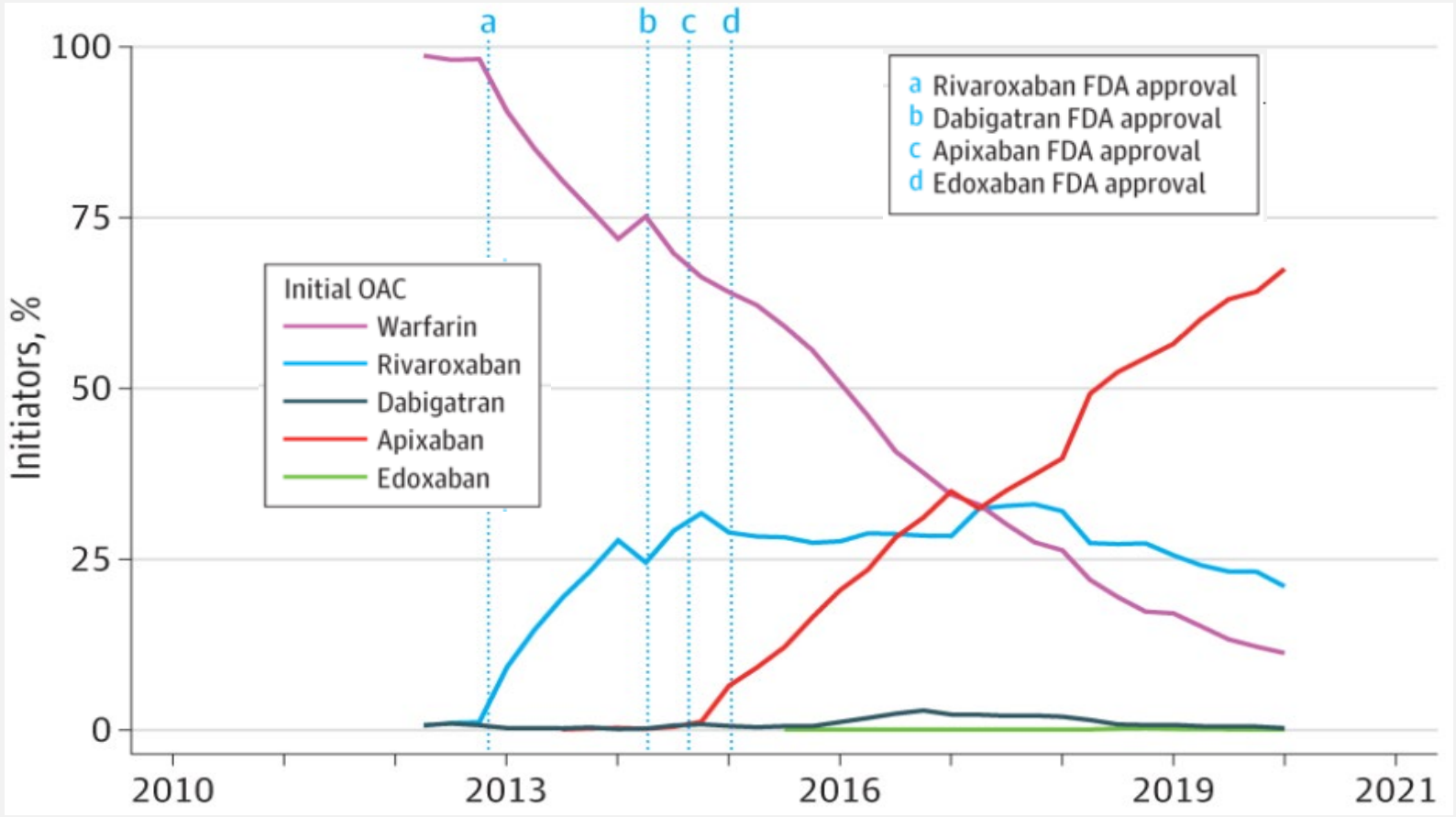
   D. Continue apixaban; no need to stop through the surgery

WHY THIS TOPIC?

- From 2011 to 2019
  - Medicare Part D beneficiaries using oral anticoagulants ⬆ from 9.2% to 11.5%
    - Use of direct oral anticoagulants (DOACs) ⬆ from 7.4% to 66.8%

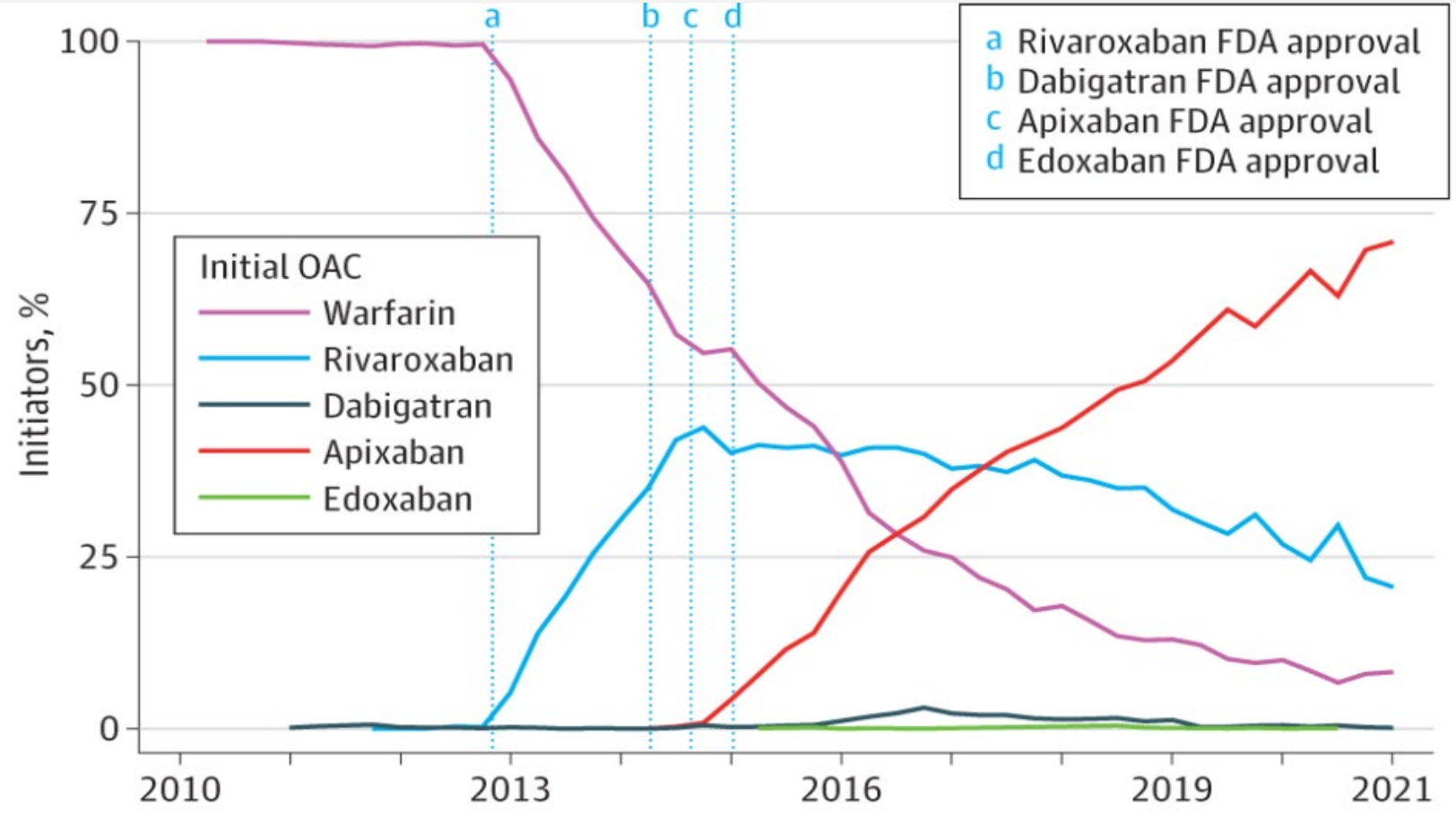
Troy A, Anderson TS. National Trends in Use of and Spending on Oral Anticoagulants Among US Medicare Beneficiaries From 2011 to 2019. *JAMA Health Forum.* 2021;2(7):e211693.

TRENDS IN DOACS USE – MEDICARE



Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the Use of Oral Anticoagulants for Adults With Venous Thromboembolism in the US, 2010-2020. *JAMA Netw Open.* 2023;6(3):e234059.

TRENDS IN DOACS USE – PRIVATE INSURANCE

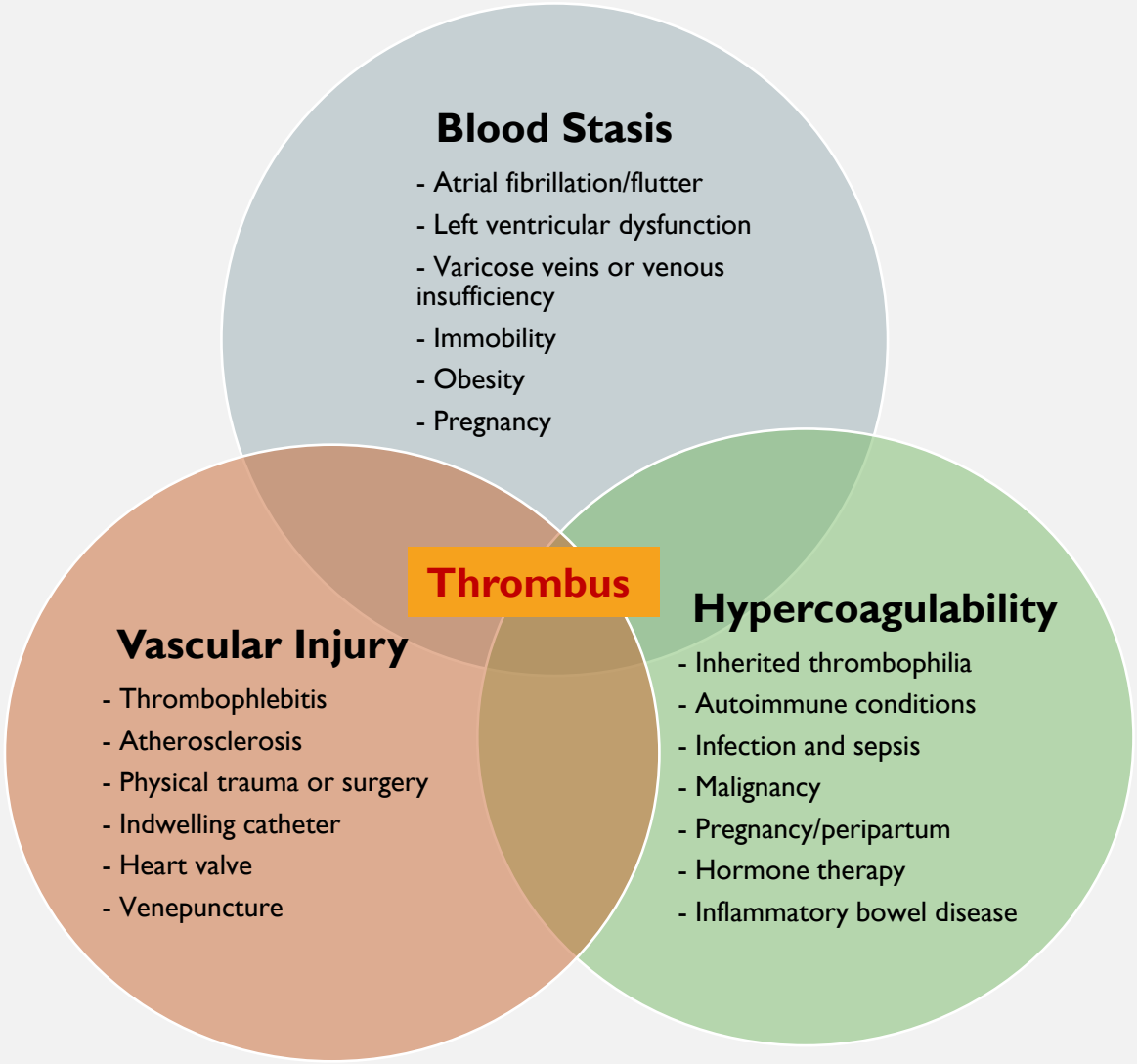


Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the Use of Oral Anticoagulants for Adults With Venous Thromboembolism in the US, 2010-2020. *JAMA Netw Open.* 2023;6(3):e234059.

USE OF ANTICOAGULANTS

LO 1: List common health conditions that require use of anticoagulants for prevention or treatment of thrombosis

VIRCHOW'S TRIAD



COMMON CONDITIONS REQUIRING ANTICOAGULANT USE

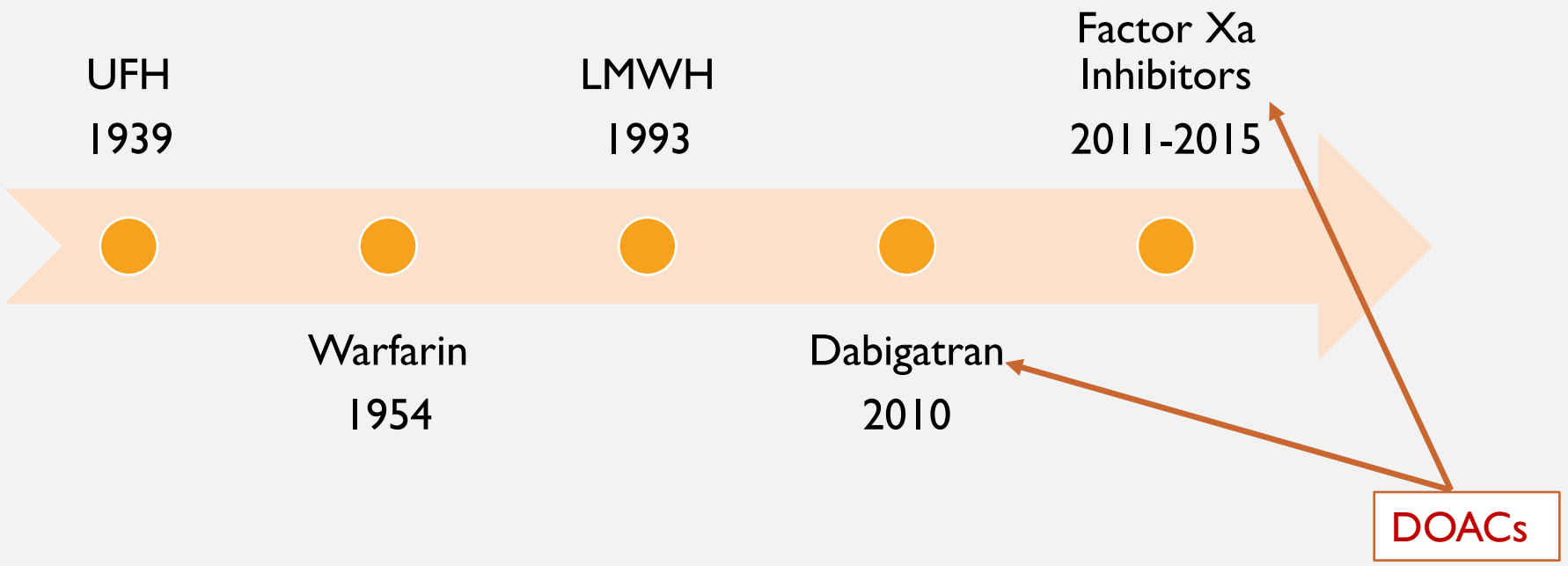
- Atrial fibrillation (AF) or flutter
- Deep vein thrombosis
- Pulmonary embolism
- Mechanical heart valves
- Stroke or transient ischemic attack
- Heart attack
- Coronary artery disease (CAD)
- Cardiomyopathy
- Peripheral artery disease (PAD)
- Recent surgery (e.g. hip or knee arthroscopy)
- Inherited thrombophilia (e.g. Factor V Leiden, protein S deficiency, antithrombin deficiency)
- Acquired thrombophilia (e.g. antiphospholipid syndrome)
- Prolonged immobility (e.g. longer hospital stay)

AVAILABLE ANTICOAGULANTS

Pharmacologic Category	Brand Names	Generic Names
Unfractionated heparin (UFH)	Hep-lock®	Heparin
Low-molecular weight heparin (LMWH)	Lovenox®	Enoxaparin
	Fragmin®	Dalteparin
Vitamin K antagonist (VKA)	Coumadin®, Jantoven®	Warfarin
Direct thrombin inhibitor	Pradaxa®	Dabigatran
Factor Xa inhibitors (oral)	Eliquis®	Apixaban
	Savaysa™	Edoxaban
	Xarelto®	Rivaroxaban
Factor Xa inhibitor (SC)	Arixtra®	Fondaparinux

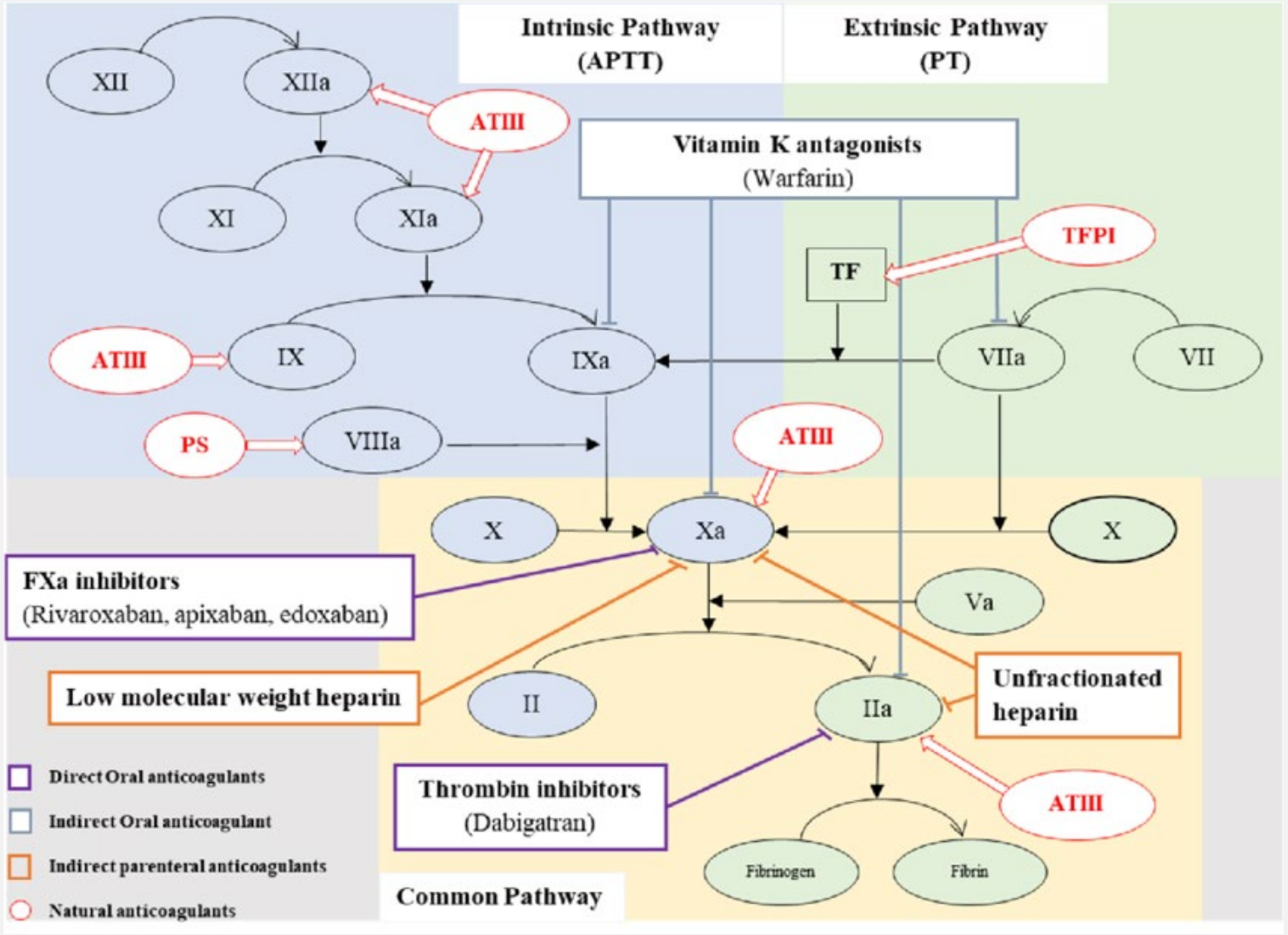
SC- subcutaneous

TIMELINE OF APPROVAL OF ANTICOAGULANTS



Milestones in Anticoagulant Drugs. American Society of Hematology. https://www.hematology.org/about/history/50-years/milestones-anticoagulant-drugs. November 30, 2008.

PHARMACOLOGY OF ANTICOAGULANTS



ATIII – antithrombin III
PS – Protein S
TF – tissue factor
TFPI – tissue factor pathway inhibitor
FXa – factor Xa

Chandika P, Tennakoon P, Kim T-H, et al. Marine Biological Macromolecules and Chemically Modified Macromolecules; Potential Anticoagulants. *Marine Drugs*. 2022; 20(10):654.

OLD VS. NEW

Warfarin

- Wider range of indications
- Longer onset and offset of anticoagulant effect
- Narrow therapeutic window
  - Frequent monitoring
- Many interactions
  - Drug-drug, drug-herbal, and drug-food
- Reversal with Vitamin K, FFP and/or 4F-PCC
- Periprocedure – may require bridging with LMWH
- Genetic polymorphism impacts dosing and safety
- $

DOACs

- Narrower range of indications
- Quicker onset and shorter half-life
- No routine efficacy monitoring
- Some safety monitoring
- Fewer drug/herbal interactions
- DOAC-specific reversal agents
- Periprocedure – do not require bridging with LMWH
- $$$

FFP – fresh frozen plasma; 4F-PCC – 4-factor prothrombin complex concentrate

DIRECT ORAL ANTICOAGULANTS

LO 2: Describe pharmacology, dosing, indications, adverse effects, contraindications, monitoring, reversal agents, and efficacy and safety outcomes for the available direct oral anticoagulants.

PHARMACOLOGY AND AVAILABILITY

Direct Thrombin Inhibitor

Inhibits activated factor IIa and prevents conversion of fibrinogen to fibrin

Factor Xa inhibitors

Inhibit factor Xa which then prevent activation of factor II and conversion of fibrinogen to fibrin

Agent	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Strengths	75 mg, 110 mg, 150 mg capsules -To be kept in original container -Good for 4 months once opened	2.5 mg,10 mg, 15 mg, 20 mg tablets 1 mg/mL suspension	2.5 mg, 5 mg tablets	15 mg, 30 mg, and 60 mg tablets

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

INDICATIONS* AND DOSING

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
VTE treatment	150 mg BID#	15 mg BID x 21 days then 20 mg daily with food	10 mg BID x 7 days then 5 mg BID	Wt > 60 kg: 60 mg once daily# Wt ≤ 60 kg: 30 mg once daily#
Prophylaxis of recurrent VTE	--	10 mg daily	2.5 mg BID	--
VTE prophylaxis	220 mg once daily for min 10 and max 35 days	10 mg daily for min 10 and max 39 days	2.5 mg BID for min 10 and max 35 days	--
Nonvalvular AF	150 mg BID	20 mg daily with the evening meal	5 mg BID If age > 80 years, wt ≤ 60 kg, or Scr of ≥ 1.5 mg/dL: 2.5 mg BID	60 mg once daily
CAD/PAD	--	2.5 mg BID + ASA 81 mg	--	--

* Listed are FDA-approved indications only # after 5-10 days of parenteral anticoagulant ASA – aspirin; wt – weight

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

RENAL DOSING

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
VTE treatment Prophylaxis of Recurrent VTE VTE prophylaxis	< 30 mL/min: Avoid use	< 30 mL/min or ESRD: Avoid use	Altered renal function or ESRD w/ HD: No dose adjustments needed	15-50 mL/min: 30 mg daily < 15 mL/min or HD: Avoid use
Nonvalvular AF	15-30 mL/min: 75 mg BID < 15 mL/min: Avoid use	15-50 mL/min: 15 mg daily < 15 mL/min: Avoid use	Scr ≥ 1.5 mg/dL AND age ≥ 80 years or wt ≤ 60 kg: 2.5 mg BID ESRD w/ HD: No dose adjustments needed	> 95 mL/min: not recommended 15-50 mL/min: 30 mg daily < 15 mL/min or HD: Avoid use
CAD/PAD	--	< 15 mL/min: Avoid use	--	--

ESRD – end-stage renal disease; HD – hemodialysis

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

HEPATIC DOSING

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
• No adjustments recommended	• Mild: No adjustment • Mod-severe: Avoid use	• Mild: No adjustment • Mod: use with caution • Severe: Avoid use	• Mild: No adjustment • Mod: use with caution • Severe: Avoid use

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

RECOMMENDED DOACS BASED ON WEIGHT

Low body weight (< 60 kg)	Normal body weight (60-120 kg)	Severe obesity (> 120 kg or BMI > 40 kg/m^2)
• Dose adjusted apixaban and edoxaban • Avoid dabigatran and rivaroxaban	• Any DOACs without dose adjustments	• Use apixaban and rivaroxaban with caution • Avoid dabigatran and edoxaban

Chen A, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc*. 2020;9(13):e017559.

PERTINENT PK/PD

Generic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Absorption	Rapid	Rapid*	Rapid	Rapid
Metabolism	Hydroxylation and glucuronidation	CYP 3A4/5 and CYP2J2	- Mainly via CYP 3A4/5 - Minimally via1A2, 2C8, 2C9, 2C19, 2J2	- Conjugation and oxidation by CYP3A4 - Minimally via hydrolysis
Time to peak	1 hr	2-4 hrs	3-4 hrs	1-2 hrs
Half-life (adults)	12-17 hrs	5-9 hrs	8-15 hrs	10-14 hrs
Excretion	Active in urine	Active and inactive in urine and feces	Mainly inactive in urine and feces	Active in urine

*Increased bioavailability of 20 mg dose when taken with food

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

EFFICACY OUTCOMES – ATRIAL FIBRILLATION TRIALS

- Active comparator = warfarin

DOAC	Trial	Number of patients	Efficacy (stroke/systemic embolism)	Efficacy (all-cause mortality)
Dabigatran	RE-LY	18,113	Superior (150 mg) Non-inferior (110 mg)	↓
Rivaroxaban	ROCKET-AF	14,264	Non-inferior	Similar
Apixaban	ARISTOTLE	18,201	Superior	↓
Edoxaban	ENGAGE AF-TIMI 48	21,105	Non-inferior (60 mg) Less effective (30 mg)	↓ (60 mg)

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151.
Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.
Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992.
Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104.

SAFETY OUTCOMES – ATRIAL FIBRILLATION TRIALS

DOAC	Trial	Number of patients	Safety (major bleeding)
Dabigatran	RE-LY	18,113	↑ GI bleed (150 mg) ↓ GI bleed (110 mg)
Rivaroxaban	ROCKET-AF	14,264	↑ GI and ↓ intracranial bleeding
Apixaban	ARISTOTLE	18,201	↓ major bleeding (especially intracranial bleeding)
Edoxaban	ENGAGE AF-TIMI 48	21,105	↓ bleeding

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151.
Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.
Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992.
Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104.

EFFICACY OUTCOMES – VTE TRIALS

- Active comparator = LMWH bridged to warfarin
- Both dabigatran and edoxaban studies included 5-10 days of initial parenteral anticoagulation

DOAC	Trial	Number of patients	Efficacy (recurrent symptomatic VTE/VTE-related death)
Dabigatran	RE-COVER I and II	~5,107	Non-inferior
Rivaroxaban*	EINSTEIN-DVT & EINSTEIN-PE	~8,281	
Apixaban	AMPLIFY	5,395	
Edoxaban	Hokusai-VTE	8,292	

* Only studied recurrent symptomatic VTE as primary outcome

Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352.
Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.
Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.
Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.
Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.
Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.

SAFETY OUTCOMES – VTE TRIALS

DOAC	Trial	Safety (major bleeding)
Dabigatran	RE-COVER I and II	Similar, possibly trending less with dabigatran
Rivaroxaban	EINSTEIN-DVT & EINSTEIN-PE	↓ major bleeding (especially in the DVT trial)
Apixaban	AMPLIFY	↓ major bleeding (significant finding)
Edoxaban	Hokusai-VTE	↓ major bleeding

Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352.
Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.
Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.
Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.
Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.
Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.

SAFETY CONCERNS

Common ADRs

- Major and minor bleeding including spinal or epidural hematomas
- Bruising
- Dabigatran specific – abdominal distress/pain, dyspepsia, esophagitis, gastritis, GERD

DDIs

- CYP3A4/P-gp inducers and inhibitors → Avoid use
  - E.g. ketoconazole, ritonavir, clarithromycin, carbamazepine, phenytoin, rifampin, St. John's Wort

Contraindications

- Active bleeding
- Presence of mechanical heart valve

GERD – gastroesophageal reflux disease

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

MONITORING

- Routine efficacy (coagulation) monitoring is NOT required/established
  - aPTT or PT may be measured at baseline and when clinically indicated
- Baseline weight needed for dosing for some agents
- Routinely evaluate – adherence, bleeding/clotting events, ADRs, medication changes for drug-drug interactions, health status

Hemoglobin/hematocrit	Liver Function	Renal Function
• Baseline • HAS-BLED = 0-2 → Every 6 months • HAS-BLED ≥ 3 → Every 3 months	• Baseline • Severe impairment → every 3 months • Moderate impairment → every 6 months • Mild impairment → every 12 months	• Baseline • CrCl < 30 mL/min → every 1-2 months • CrCl 30-59 mL/min → every 3 months • CrCl > 60 mL/min → every 6 months

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

REVERSAL AGENTS FOR DOACS

Anticoagulant	Specific reversal agent	Mechanism	Dose	Cost
Dabigatran	Idarucizumab (Praxbind®)	Humanized antibody fragment that binds to dabigatran and its metabolites with a greater affinity	Two doses of 2.5 mg IV no more than 15 minutes apart	$
Rivaroxaban Apixaban	Andexanet alfa (Andexxa®)	Binds and sequesters factor Xa inhibitors, inhibits activity of TFPI	Any dose DOAC < 8 hrs or low-dose DOAC < 8 hrs: 400 mg IV bolus, then 4 mg/min IV over 120 mins High-dose DOAC < 8 hrs: 800 mg IV bolus, then 8 mg/min IV over 120 mins	$$$

- 4F-PCC → off-label use for reversal of all DOACs
- Known ingestion within 2-4 hrs → activated charcoal
- No approved reversal agents for Edoxaban → andexanet alfa and 4F-PCC used off-label

Praxbind prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2021
Andexxa prescribing information. AstraZeneca Pharmaceuticals; 2024

TFPI – tissue factor pathway inhibitor
4F-PCC – 4-factor prothrombin complex concentrate

NOT RECOMMENDED FOR USE IN…

- Acquired thrombophilia
  - Antiphospholipid syndrome
- Inherited thrombophilia – lack of robust data
  - Protein S deficiency, protein C deficiency, antithrombin III deficiency
- Valvular atrial fibrillation
  - Presence of moderate-severe mitral stenosis or mechanical valves
- Arterial thrombosis
- Embolic stroke
- End-stage renal disease (and/or dialysis)
  - Data is limited, but apixaban may be used
- Severe liver disease
- Patients taking interacting medications

CONVERTING ORAL ANTICOAGULANTS

Conversion	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
From warfarin	D/c warfarin and start when INR < 2.0	D/c warfarin and start when INR < 3.0	D/c warfarin and start when INR < 2.0	D/c warfarin and start when INR ≤ 2.5
To warfarin	1) CrCl > 50 mL/min → start warfarin 3 days before stopping dabi 2) CrCl 31-50 mL/min → start warfarin 2 days before stopping dabi 3) CrCl 15-30 mL/min → start warfarin 1 day before stopping dabi	Stop the agent and start warfarin the same day along with parenteral anticoagulation until INR is within therapeutic range		
Between other DOACs	Start the new DOAC when the next dose of the previous DOAC was scheduled			

Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
Eliquis prescribing information. Bristol-Myers Squibb Company; 2021. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023

UPDATES IN GUIDELINE RECOMMENDATIONS

LO 3: Discuss the latest guidance for management of anticoagulation in patients with venous thromboembolism and atrial fibrillation.

UPDATES IN GUIDELINES

AHA/ACC Atrial Fibrillation Guidelines 2023

- Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2023;149(1). doi:10.1161/cir.0000000000001193

CHEST VTE Antithrombotic Therapy 2021

- Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease. CHEST Journal. 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055

CHEST Perioperative Management of Antithrombotics 2022

- Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. CHEST Journal. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025

AHA – American Heart Association; ACC – American College of Cardiology; CHEST – American College of CHEST Physicians

KEY RECOMMENDATIONS FROM 2023 AHA/ACC GUIDELINES FOR ATRIAL FIBRILLATION MANAGEMENT

Assess risk of thrombosis annually using the validated CHA_2DS_2VASc Score (COR 1, LOE B-NR)

Start anticoagulation in patients with CHA_2DS_2VASc score of ≥ 2 in men/≥ 3 in women to prevent stroke and/or systemic thromboembolism (COR 1, LOE A)

Reasonable to start anticoagulation in patients with CHA_2DS_2VASc score of 1 in men and 2 in women (COR 2a, LOE A)

DOACs are recommended over warfarin (COR 1)

- Warfarin preferred if mitral stenosis or mechanical heart valves are present

COR – class of recommendation; LOE – level of evidence

Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. *Circulation*. 2023;149(1).

KEY RECOMMENDATIONS FROM CHEST 2021 GUIDELINES FOR ANTITHROMBOTIC THERAPY FOR VTE – PREFERRED THERAPY

Diagnosis	Preferred Therapy	Strength of Recommendation, Level of Evidence
VTE	DOAC > warfarin	Strong, moderate
VTE w/ cancer	DOAC > LMWH	Strong, moderate
VTE w/ antiphospholipid syndrome	Warfarin (INR range 2.0-3.0) > DOAC	Weak, low
SVT w/ ↑ risk of DVT	Fondaparinux SC 2.5 mg daily > LMWH	Weak, low
SVT in those who refuse/unable to use parenteral anticoagulants	Rivaroxaban 10 mg daily	Weak, low
Extended-phase VTE treatment	Reduced dose apixaban or rivaroxaban > full dose Reduced dose apixaban or rivaroxaban > aspirin/no therapy Rivaroxaban > aspirin Aspirin* > no therapy	Weak, low Strong, low Weak, moderate Weak, low

*Unprovoked VTE, stopping anticoagulation, no aspirin contraindications

VTE – venous thromboembolism; SVT – superficial vein thrombosis; SC - subcutaneously

Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease. *CHEST Journal*. 2021;160(6):e545-e608.

KEY RECOMMENDATIONS FROM CHEST 2021 GUIDELINES FOR ANTITHROMBOTIC THERAPY FOR VTE – LENGTH OF THERAPY

Diagnosis	Length of Therapy	Strength of Recommendation, Level of Evidence
VTE w/o contraindications to anticoagulation	3-month treatment, assess for extended-phase tx	Strong, moderate
VTE w/ major transient risk factor	3-month treatment, avoid extended-phase tx	Strong, moderate
VTE w/ minor transient risk factor	3-month treatment, avoid extended-phase tx	Weak, moderate
Unprovoked VTE (or provoked by persistent risk factor)	Extended-phase tx with DOAC	Strong, moderate
Unprovoked VTE, cannot receive DOAC	Extended-phase tx with warfarin	Weak, moderate

Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease. *CHEST Journal*. 2021;160(6):e545-e608.

PERIOPERATIVE MANAGEMENT OF DOACS

LO 4: Explain strategies for perioperative management of direct oral anticoagulants.

KEY RECOMMENDATIONS FROM CHEST 2022 GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTICS

Procedural Bleed Risk Stratification

High (30-day bleed risk: ≥ 2%)

- Cancer surgery
- Major orthopedic surgeries
- Major thoracic surgeries
- Cardiac, intracranial or spinal surgeries
- Reconstructive plastic surgeries
- Urologic surgeries (bladder or prostate resection or tumor ablation)
- GI surgeries (bowel resection, colonic polyp resection)
- Nephrectomy, kidney biopsy
- Neuraxial anesthesia
- Epidural injection

Moderate (30-day bleed risk: 0-2%)

- Arthroscopy
- Shoulder, foot, hand surgery
- Coronary angiography
- GI scopes ± biopsy
- Laparoscopic cholecystectomy
- Abdominal hernia repair
- Hemorrhoidal surgery
- Abdominal hysterectomy
- Bronchoscopy ± biopsy
- Cutaneous/lymph node biopsy

Low (30-day bleed risk: ~0%)

- Minor dermatologic procedures
- Cataract procedures
- Minor dental procedures
- Dental cleaning and fillings
- Pacemaker or cardioverter-defibrillator implantation

GI - gastrointestinal

Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. *CHEST Journal*. 2022;162(5):e207-e243.

KEY RECOMMENDATIONS FROM CHEST 2022 GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTICS

Individual Bleed Risk Stratification

HAS-BLED Score

- Uncontrolled HTN
- Abnormal renal or liver function
- Stroke
- Bleeding predisposition
- Labile INRs
- Older age (> 65 years)
- Drugs with antiplatelet properties or excess alcohol use

HEMORR2HAGES Score

- Hepatic or renal disease
- Alcohol use
- Malignancy
- Older age (> 75 years)
- Reduced platelet count/function (ASA tx)
- Re-bleeding risk
- HTN
- Anemia
- Genetic factors
- Increased falls risk
- Stroke

VTE-BLEED Score

- Active cancer
- Male patient with uncontrolled HTN
- Anemia
- History of bleeding
- Kidney dysfunction
- Age ≥ 60 years

HTN – hypertension; INR – international normalized ratio; ASA – aspirin

Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. *CHEST Journal*. 2022;162(5):e207-e243.

DOAC-SPECIFIC APPROACH BASED ON PROCEDURAL BLEED RISKS

Agent	Pre-operative	Post-operative
Dabigatran	Stop for 1 day if low-to-moderate risk and CrCl ≥ 50 mL/min Stop for 3-5 days if low-to-moderate risk and CrCl < 50 mL/min Stop for 2 days for high risk and CrCl ≥ 50 mL/min Stop for 4 days for high risk and CrCl < 50 mL/min	Resume ≥ 24 hours for low-to-moderate risk Resume ≥ 48-72 hours for high risk
Rivaroxaban	Stop for 1 day for low-to-moderate risk, 2 days for high risk	
Apixaban		
Edoxaban		

Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. *CHEST Journal*. 2022;162(5):e207-e243.

PERIOPERATIVE APPROACH

- The recommendations are irrespective of the anticoagulation indication
- No need to:
  - Bridge using LMWH/UFH
    - DOACs have rapid onset and offset
    - Higher risk of bleeding when bridged with LMWH with no impact on stroke/systemic embolism
  - Measure DOAC levels to guide management

Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. *CHEST Journal*. 2022;162(5):e207-e243.

ROLE OF PHARMACISTS

- Selection of appropriate therapy
  - Agent, dose, and duration
- Monitoring and adjustment of anticoagulation therapy
- Navigating drug-drug interactions
- Converting anticoagulants
- Medication access
- Perioperative management
- Patient and provider education

SUMMARY

There is an established evidence and therefore a shift in use of DOACs comparted to traditional VKA therapy

VKA therapy still preferred in those with thrombophilia, mechanical heart valves, and arterial thrombosis

Less monitoring and perioperative bridging requirements with DOACs

- Some monitoring is still necessary

Pharmacists play a valuable role in therapy selection, monitoring, perioperative management, drug-drug interaction management, medication access, and education

POST-ASSESSMENT QUESTION - 1

1. Which of the following conditions require use of anticoagulants for the treatment of thrombosis?
   A. Aortic stenosis
   B. Factor VIII deficiency
   C. Mechanical mitral valve placement
   D. Ventricular fibrillation

POST-ASSESSMENT QUESTION - 2

2. Which of the following DOAC regimen has shown superiority against warfarin in preventing stroke and systemic embolism when studied in population with atrial fibrillation?
   A. Dabigatran 110 mg BID
   B. Apixaban 5 mg BID
   C. Rivaroxaban 20 mg daily
   D. Edoxaban 60 mg daily

POST-ASSESSMENT QUESTION - 3

3. According to the 2021 CHEST Guidelines for Antithrombotic Therapy for VTE, which of the following anticoagulant is recommended for the treatment of venous thromboembolism in the setting of cancer?

   A. Fondaparinux
   B. Warfarin
   C. Enoxaparin
   D. Apixaban

POST-ASSESSMENT QUESTION - 4

4. A 56-year-old female patient takes apixaban for treatment of atrial fibrillation (CHA_2DS_2-VASc = 3). The surgery team consults you to recommend perioperative management for upcoming hysterectomy. Which of the following represents the most appropriate approach based on the 2022 CHEST Guidelines for Perioperative Management of Antithrombotics?

   A. Stop apixaban 5 days before surgery, weight based dose of enoxaparin days 3-5 before surgery, resume the day after surgery

   B. Stop apixaban 2 day before surgery, resume 2 days after surgery

   C. Stop apixaban 1 day before surgery, resume 1 day after surgery

   D. Continue apixaban; no need to stop through the surgery

REFERENCES

1. Troy A, Anderson TS. National Trends in Use of and Spending on Oral Anticoagulants Among US Medicare Beneficiaries From 2011 to 2019. *JAMA Health Forum.* 2021;2(7):e211693. doi:10.1001/jamahealthforum.2021.1693
2. Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the Use of Oral Anticoagulants for Adults With Venous Thromboembolism in the US, 2010-2020. *JAMA Netw Open.* 2023;6(3):e234059. doi:10.1001/jamanetworkopen.2023.4059.
3. Milestones in Anticoagulant Drugs. American Society of Hematology. https://www.hematology.org/about/history/50-years/milestones-anticoagulant-drugs. November 30, 2008. Accessed April 9, 2025.
4. Chandika P, Tennakoon P, Kim T-H, Kim S-C, Je J-Y, Kim J-I, Lee B, Ryu B, Kang HW, Kim H-W, et al. Marine Biological Macromolecules and Chemically Modified Macromolecules; Potential Anticoagulants. *Marine Drugs*. 2022; 20(10):654. https://doi.org/10.3390/md20100654.
5. Pradaxa prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2023
6. Xarelto prescribing information. Janssen Pharmaceutical Companies; 2021
7. Eliquis prescribing information. Bristol-Myers Squibb Company; 2021
8. Savaysa prescribing information. Daiichi Sankyo, Inc.; 2023
9. Chen A, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc*. 2020;9(13):e017559. doi: 10.1161/JAHA.120.017559.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561
11. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891. doi:10.1056/NEJMoa1009638
12. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. doi:10.1056/NEJMoa1107039
13. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907
14. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352. doi:10.1056/NEJMoa0906598
15. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772. doi:10.1161/CIRCULATIONAHA.113.004450
16. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903
17. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297. doi:10.1056/NEJMoa1113572
18. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi:10.1056/NEJMoa1302507
19. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415. doi:10.1056/NEJMoa1306638
20. Praxbind prescribing information. Boehringer Ingelheim Pharmaceutical, Inc.; 2021
21. Andexxa prescribing information. AstraZeneca Pharmaceuticals; 2024
22. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease. *CHEST Journal.* 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055
23. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;149(1). doi:10.1161/cir.0000000000001193
24. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy. *CHEST Journal.* 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025

CPE CODE

THE CLOT THICKENS…OR NOT: ANTICOAGULATION UPDATES FOR PHARMACISTS

Khyati Patel, PharmD, BCACP

Khyati.patel@rosalindfranklin.edu