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Objectives

- List current FDA indications for direct oral anticoagulant (DOAC) agents.
- Identify the appropriate weight at which DOACs should be avoided.
- Given a patient case, select appropriate anticoagulation therapy for a patient being discharged from the emergency department.
- Recall current reversal strategies and doses of reversal agents for anticoagulants.

*I have no financial interests to disclose.

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Overview of Presentation

- ACT 1:
  - FDA indications
  - Oral Anticoagulants
    - Warfarin
    - DOACs
  - Selecting an oral anticoagulant
- ACT 2:
  - Reversal strategies for oral anticoagulants

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Assessment Question

1. Which of the following anticoagulants can be successfully removed by hemodialysis in an emergency situation?

A. apixaban
B. warfarin
C. dabigatran
D. rivaroxaban

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Assessment Question

2. Direct acting oral anticoagulants like rivaroxaban and apixaban should be held if the patient weighs over _____ kg.

A.80
B. 100
C. 120
D. 140

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Assessment Question

3. Based on the studies by Amin and Yao (et al), which DOAC causes statistically significantly higher rates of GI bleeding?

A. apixaban
B. warfarin
C. dabigatran
D. rivaroxaban

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Assessment Question

4. What is the dose of 4-factor PCC when treating a life-threatening bleed due to a DOAC?

A. 25 mg/kg
B. 35 mg/kg
C. 45 mg/kg
D. 50 mg/kg

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Current FDA Indications (Dates)

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Afib						
-Valvular	1954					
-Non-valvular	1954	10/2010	11/2011	12/2012	1/2015	
VTE Prophylaxis*	1954		7/2011	3/2014		6/2017
VTE Treatment						
-DVT	1954	4/2014	11/2012	8/2014	1/2015	
-PE	1954	4/2014	11/2012	8/2014	1/2015	
-Recurrent DVT/PE	1954	4/2014	11/2012	8/2014		

*VTE prophylaxis refers to anticoagulation during hip/knee surgeries, however betrixaban indications are left more broad

Accessed from http://www.fda.gov/Drugs

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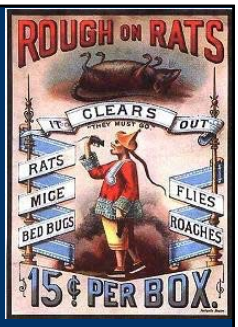
Warfarin



THE GOOD

- Most common po anticoagulant in the U.S.
- Multiple indications with high efficacy
- Long history of successful use
- Low cost

THE BAD, THE UGLY

- Food and drug/drug interactions
- Lifestyle issues
- Dosing variability
- Routine monitoring needed
- Bleeding

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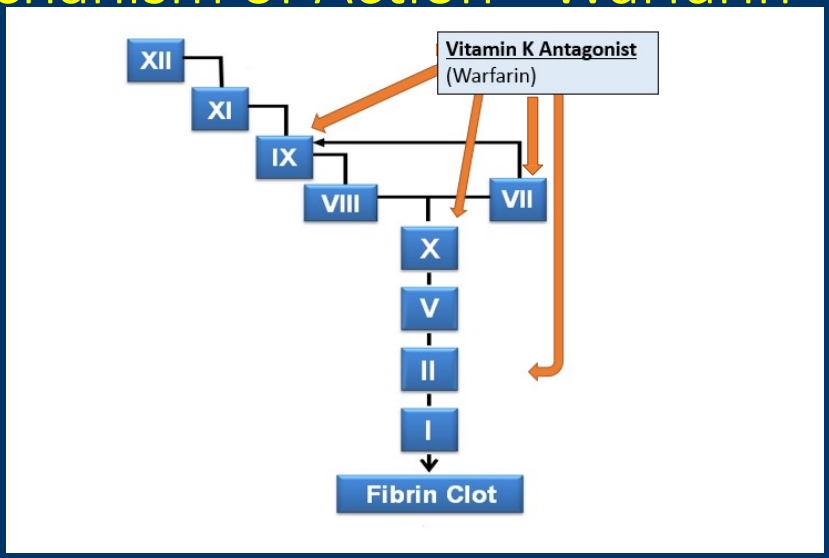
Mechanism of Action - Warfarin



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Initial Warfarin Dosing

[Goal INR (2-3)]

Day 1

- 5mg

Day 2

INR	Dose
<1.5	5mg
1.5-1.9	2.5mg
2.0-2.5	1-2.5mg
>2.5	0mg

Day 3

INR	Dose
<1.5	5-7.5mg
1.5-1.9	2.5-5mg
2.0-2.5	0-2.5mg

Warfarin is bridged with a parenteral anticoagulant like enoxaparin

Ansell AM, et al. Vitamin K antagonists. Amer Coll of Chest Phys 2008;133(6) Suppl:160S-198S. USPHS Pawhuska Indian Clinic Anticc

Initial Warfarin Dosing

[Goal INR (2-3)]

Day 4

INR	Dose
<1.5	10mg
1.5-1.9	5-7.5mg
2.0-3.0	0-5mg
>3.0	0mg

Day 5

INR	Dose
<1.5	10mg
1.5-1.9	5-10mg
2.0-3.0	0-5mg
>3.0	0mg

Day 6

INR	Dose
<1.5	7.5-12.5mg
1.5-1.9	5-10mg
2.0-3.0	0-7.5mg

Warfarin is bridged with a parenteral anticoagulant like enoxaparin

Ansell AM, et al. Vitamin K antagonists. Amer Coll of Chest Phys 2008;133(6) Suppl:160S-198S. USPHS Pawhuska Indian Clinic Anticc

Weekly Adjustments Once Stable

- Increase or decrease weekly dose by 5-15%
  - Depending on most recent INR
- Potentially hold 1-2 doses if high INR
- Monitor every 1-2 weeks during dosing changes, then every 2-4 weeks after that

Ansell AM, et al. Vitamin K antagonists. Amer Coll of Chest Phys 2008;133(6) Suppl:160S-198S. USPHS Pawhuska Indian Clinic Anticoagulation Service Protocol 2015.

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Warfarin Patient Interview R

- Before adjusting warfarin dose due to out of range INR, always assess:
  - ✓Drug-drug interactions
  - ✓Changes in diet
  - ✓Drug-disease state interactions
  - ✓Noncompliance
- Always provide patient education at each visit

USPHS Pawhuska Indian Clinic Anticoagulation Service Protocol 2015.

https://healthjade.com/vitamin-k/

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Desirable qualities in a new anticoagulant:

- As or more effective than warfarin
- As or more safe than warfarin
- Oral administration
- Fixed dosing (preferably once daily)
- Minimal food and drug interactions
- Predictable anticoagulant response (no monitoring)
- Rapid onset and offset
- Reversible

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Currently Available PO Anticoagulants

- Warfarin → Vitamin K Antagonist
- Dabigatran → Direct Thrombin Inhibitor
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

→ Direct Factor Xa Inhibitor

DOACs

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Abbreviations

- ~~NOAC~~ – new/novel oral anticoagulants
- ~~TSOAC~~ – target specific oral anticoagulants
- DOAC – direct oral anticoagulants

Barnes, GD, Ageno W, Ansel J, et al. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. Accepted article, doi: 10.1111/jth.12969

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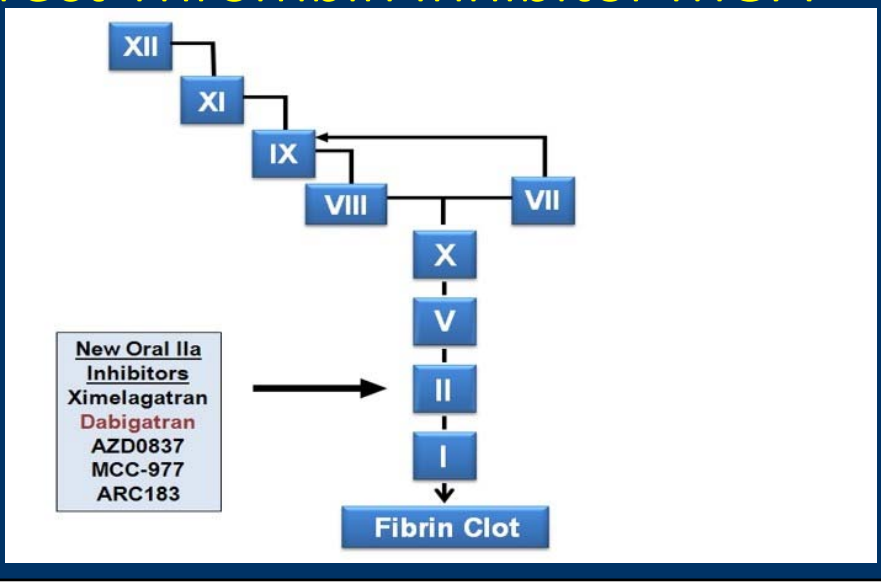
Direct Thrombin Inhibitor MOA



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Dabigatran

- Direct thrombin inhibitor
  - Inhibits thrombin-dependent conversion of fibrinogen to fibrin, blocks free and clot-bound fibrin from further clot formation, and decreases platelet aggregation

Medication	NVAF	VTE Prevention	VTE Treatment
Dabigatran	RE-LY	RE-NOVATE I & II RE-MODEL RE-MOBILIZE	RE-COVER I & II

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Dabigatran

- Bleeding Risk
  - RE-LY – Major bleeding (NS), GI bleeding ↑ with dabigatran (SS), ICH ↓ with dabigatran (SS)
  - RE-COVER I-II – Major bleeding (NS), GI bleeding ↑ with dabigatran (SS)
  - Side note: RE-ALIGN studied mech heart valves and was HALTED EARLY due to a (SS) increase in stroke and bleeding

Connelly SM. NEJM 2009;361:1139-51. Schulman S, et al. NEJM 2009;361:2342-52. Schulman S, et al. Circulation 2014;129:764-72. Eikelboom JW, et al. NEJM 2013;269:1206-14.

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Dabigatran

- Sig: Parenteral anticoagulation x 5d, then 150mg PO BID
  - Alternate: 75mg PO BID
    - CrCl 15-30 mL/min
    - Patients taking strong inducers or inhibitors (ketoconazole, dronedarone) with CrCl 30-50
- AE: bleed, GI (tartaric acid pellets), MI?
- Avoid in severe renal dysfunction CrCl <15, elderly >80yo
- No monitoring, but aPTT values >2.5x control may indicate over-anticoagulation

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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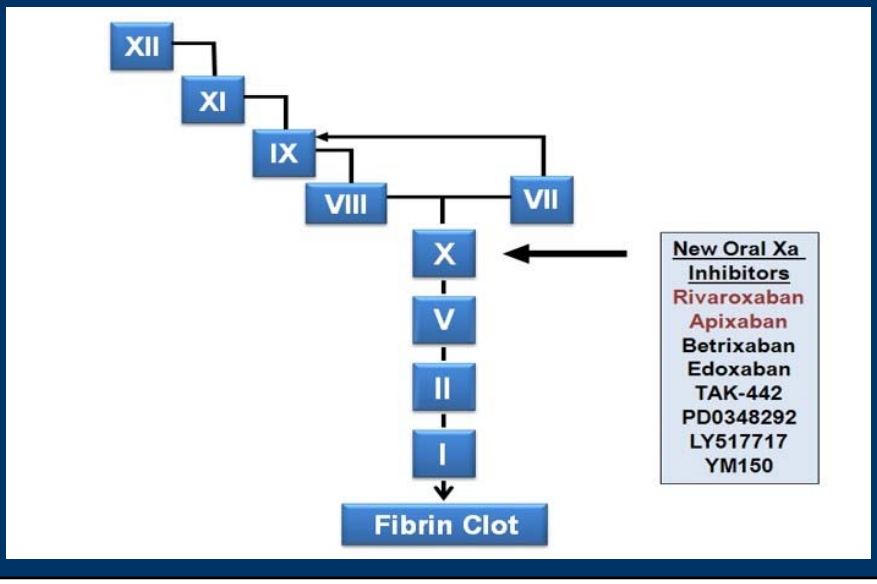
Factor Xa Inhibitors MOA



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Rivaroxaban

- 1st Factor Xa Inhibitor
  - Binds free and clot-bound factor Xa to provide its anticoagulant effect

Medication	NVAF	VTE Prevention	VTE Treatment
Rivaroxaban	ROCKET-AF	RECORD I, II, III, IV	EINSTEIN-DVT EINSTEIN-PE EINSTEIN-EXT

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Rivaroxaban

- Bleeding Risk
  - ROCKET-AF – major and minor bleed rates (NS)
  - RECORD 1-4 – NS major bleed risk in all studies (0.1-0.7%)
  - EINSTEIN DVT, EINSTEIN PE – NS major bleed risk (8.1-10.3%)
  - EINSTEIN EXT – bleeding risk ↑ with rivar ($p<0.001$)

Patel MR. NEJM 2011;35:883-91. EINSTEIN Investigators NEJM 2010;363:2499-510. EINSTEIN-PE Investigators NEJM 2012;366:1287-97.

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Rivaroxaban

- Afib sig: 20mg po q PM with food
- DVT/PE Tx sig: 15mg po BID with food x 21 days, then 20mg po q PM with food
  - If a dose is missed, take 2 at the same time
- Activated through P-glycoprotein and CYP3A4
  - Avoid CBZ, phenytoin, ketoconazole, ritonavir
  - Use caution if renally insufficient with amiodarone, diltiazem, erythromycin, azithromycin
- AE: GI, bleed, back pain

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Apixaban

- 2nd Factor Xa Inhibitor
  - Binds free and clot-bound factor Xa to provide its anticoagulant effect

Medication	NVAF	VTE Prevention	VTE Treatment
Apixaban	ARISTOTLE AVERROES	ADVANCE I, II, III	AMPLIFY AMPLIFY-EXT

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Apixaban

- Bleeding Risk
  - ARISTOTLE –major bleeding ↓ with apixaban (SS)
  - ADVANCE 1-3 – major bleeding (NS)
  - AMPLIFY – major bleeding ↓ with apixaban (SS)
  - AMPLIFY-EXT – major bleeding (NS) vs placebo

Granger CB. NEJM 2011;36:981-92. Agnelli G, et al. NEJM 2013;369:799-808.

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Apixaban

- Afib: 5mg po BID*
- PE/DVT Tx: 10mg po BID x 7d then 5mg po BID
- 2º Risk Reduction: 2.5mg po BID for 6 months

  *2.5mg po BID if pt has 2: ≥80yo, ≤60kg, ≥1.5mg/dl or has drug interactions
- Metabolized through CYP3A4, et al.
- AE: bleeding, nausea, anemia

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Edoxaban

- 3rd Factor Xa Inhibitor
  - Binds free and clot-bound factor Xa to provide its anticoagulant effect

Medication	NVAF	VTE Prevention	VTE Treatment
Edoxaban	ENGAGE-AF-TIMI-48	STARS E-3 STARS J-5 STARS J-4	HOKUSAI-VTE

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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Edoxaban

- Bleeding Risk
  - ENGAGE-AF TIMI 48 – Bleeding ↓ in edoxaban group (SS)
  - HOKUSAI-VTE – Major bleeding (NS), less non-major bleeding with edoxaban (SS)

Giugliano RP, et al. N Engl J Med 2013;369:2093-104. The Hokusai-VTE Investigators. NEJM 2013;369:1406-15.

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Edoxaban

- Afib: 60mg po daily
- Use 30mg po daily if:
  - Pt weighs ≤60kg
  - CrCl 15-50 mL/min
  - Verapamil, quinidine, azith, clarith, eryth, itraconazole, ketoconazole
- DVT/PE tx: Parenteral anticoagulant x 5-10d, then 60mg daily

- Do not use if CrCl >95mL/min
- Caution with LPs – spinal/epidural hematomas = paralysis
- Cancer patient conundrum

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

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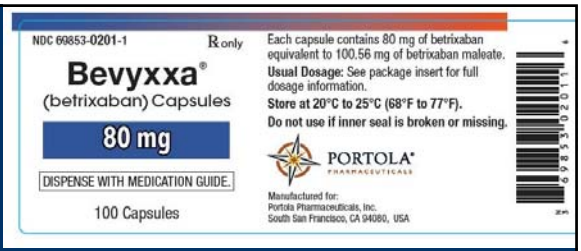
Betrixaban



- 4th Factor Xa Inhibitor
  - Inhibits fibrin clot formation via direct and selective inhibition of factor Xa

Medication	NVAF	VTE Prevention	VTE Treatment
Betrixaban	EXPLORE-Xa	APEX EXPERT	

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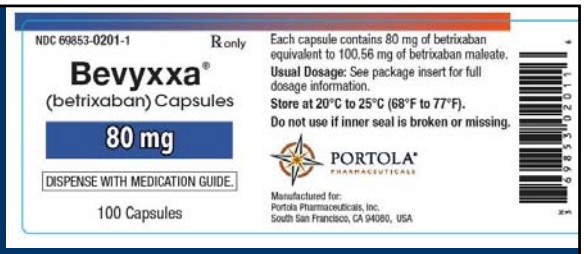
Betrixaban



- Bleeding Risk:
  - APEX: major bleeding (NS in either dosage arm vs enoxaparin)

Gibson CM, Halaby R, Korjian S, et al. The safety and efficacy of full- versus reduced-dose betrixaban in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention With Extended-Duration Betrixaban (APEX) trial. *Am Heart J.* 2017;185:93-100.

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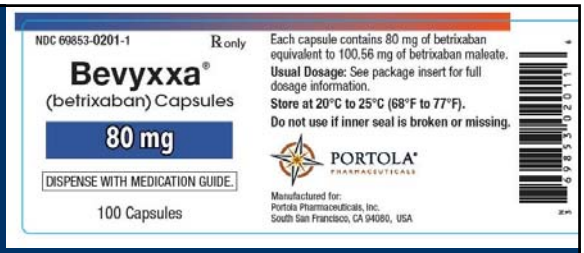
Betrixaban



- VTE Prophylaxis
  - 160mg (single dose) on day 1, then 80mg daily for 35-42 days
  - Dose adjust:
    - Reduce dose by 50% with p-glycoprotein inhibitors (amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil)
    - CrCl 15-29 ml/min
  - Avoid in severe renal impairment and hepatic impairment
  - AE: hypertension, epistaxis, constipation, hypokalemia, UTI

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; April 26, 2018.

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DOAC Characteristics

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015.

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Brand Name	Coumadin®	Pradaxa®	Xarelto®	Eliquis®	Lixiana, Savaysa (US)	Bevyxxa
Target	II, VII, IX, X	Thrombin	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Daily Dosing	Individualize	150mg BID *75mg BID*	20mg Q day *15mg Q day*	5mg BID *2.5mg BID*	60mg Q day *30mg Q day*	*160mg x 1* *80mg Q day*
Bioavailability	100%	6%	100% (w/ food) ~66% (no food)	80%	62%	34%
Peak (Tmax)	72-96 hrs	1-3 hrs	1-3 hrs	1-3 hrs	1-2 hrs	3-4 hrs
Affects INR?	Yes	No	No	Yes	Yes	?????????
Renal Clearance	N/A	80%	33%	25%	50%	11%
Renal Dosing?	Yes	Yes	Yes	No?	Yes	Yes
Interactions	2C9, 3A4, 1A2	P-gp	CYP3A4, P-gp	CYP3A4, P-gp	P-gp	P-gp
$T^{1/2}$ (normal GFR)	~ 40 hrs	13.8 hrs	8.3 hrs	15.1 hrs	9-11 hrs	19-27 hrs

Adapted with permission from Dr. Ryan Schupbach, PharmD, BCPS, CACP, NCPS.

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; May 1, 2015. [35]

Choices…

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Major AFib Guideline Recommendations

	AHA/ACC/HRS*	AHA/ASA	ACCP	ESC*
Year issued	2014	2012, 2014 updates address $CHADS_2 \geq 2$	2012	2012
Low Risk ($CHADS_2 = 0$)	None	ASA or None	None, ASA alt	None
Mod Risk ($CHADS_2 = 1$)	No therapy, ASA, or oral anticoagulation	ASA 81-325mg/day or oral anticoag. (warf, dabig, apix)	Oral anticoagulant (dabig > warfarin) preferred. ASA+clopidogrel alternative.	Oral anticoagulant (dabig, apix, or rivarox > warf)
High Risk ($CHADS_2 \geq 2$)	Oral anticoagulation (warf or DOAC)	Oral anticoagulation (warf, apix, dabig preferred. Rivarox is "reasonable.")	Oral anticoagulation (dabig > warf)	Oral anticoagulation (dabig, apix, rivarox > warf)

* Treatment recommendations based off CHADS2-VASc

Parker MH. Stroke prevention in atrial fibrillation. In: Dong BJ, Elliott DP, eds. Ambulatory Care Self-Assessment Program, 2014 Book 2. Cardiology Care. Lenexa, KS: American College of Clinical Pharmacy, 2014:156.

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VTE Guidelines

- Proximal DVT/PE
  - No cancer: dabig, rivar, apix, or edox > VKA > LMWH
  - Cancer: LMWH over VKA, dabig, rivar, apix, edox
- Extended therapy (no scheduled stop date) rec'd for
  - First VTE, unprovoked, with low/mod bleed risk
  - Second VTE, unprovoked, with low/mod bleed risk
  - VTE + cancer

Kearon C, et al. Antithrombotic therapy for VTE disease. Chest 2016;149(2):315-352.

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Warfarin

- Inexpensive drug cost ($4 at Wal-Mart)
- Frequent monitoring (more copays for visits)
- Individualized dosing
- Drug-drug/drug-disease interactions

https://www.allern.com/2016/12/trick-warfarin-tablet-strength-identification/

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DOACs vs. Warfarin: Comparison Table

Effect	RE-LY (Dabigatran 150mg)	ROCKET-AF (Rivaroxaban 20mg QD[ITT])	ARISTOTLE (Apixaban 5mg BID)	ENGAGE-AF (Edoxaban 60mg QD)
Reduction in Stroke / SE	Superior	Non-Inferior	Superior	Non-Inferior
Reduction in Ischemic stroke	↓	↔	↔	↔
Major Bleeding	↔	↔	↓	↓
ICH	↓	↓	↓	↓
GI Bleeding	↑	↑	↔	↑
Mortality	↔	↔	↓	↔

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Connelly SM. NEJM 2009;361:1139-51 Patel MR. NEJM 2011;35:883-91. Granger CB. NEJM 2011; 36:981-92 Giugliano RP. NEJM 2013;369:2093-104. Slide used with permission from Dr. R. Schupbach

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellolio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

- Mayo Group, 2016

- Effectiveness
  - Stroke and systemic embolism
- Safety
  - Major bleeding

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- Effectiveness

	Apixaban	Dabigatran	Rivaroxaban
Stroke and Systemic Embolism	↓	↔	↔
Hemorrhagic Stroke	↓	↔	↔
Ischemic Stroke	↔	↔	↔

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- Safety

	Apixaban	Dabigatran	Rivaroxaban
Major Bleeding	↓	↓	↔
GIB	↓	↔	↑
ICH	↓	↓	↓

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Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population

Alpesh Amin[a], Allison Keshishian[b], Jeffrey Trocio[c], Oluwaseyi Dina[c], Hannah Le[d], Lisa Rosenblatt[d], Xianchen Liu[c], Jack Mardekian[c], Qisu Zhang[b], Onur Baser[e,f,g] and Lien Vo[d]

- Medicare database query from January 2013-December 2014
  - "Real world" anticoagulation study
- Primary outcomes: Stroke/SE and Major Bleeding

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- Efficacy

	Apixaban	Dabigatran	Rivaroxaban
Stroke and Systemic Embolism	↓	↔	↓
Hemorrhagic Stroke	↓	↓	↔
Ischemic Stroke	↓	↔	↓
Syst. Embolism	↔	↔	↓

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- Safety

	Apixaban	Dabigatran	Rivaroxaban
Major Bleeding	↓	↓	↑
GIB	↓	↔	↑
ICH	↓	↓	↓
Other	↓	↓	↑

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Pointers towards which DOAC to choose

Specific patient characteristics

High risk of bleeding, e.g. HAS-BLED ≥ 3	Consider agent / dose with the lowest incidence of bleeding	Dabigatran 110, Apixaban, Edoxaban
Previous GI bleeding or high-risk	Consider agent with the lowest reported incidence of GI bleed	Apixaban
High risk of ischemic stroke, low bleeding risk	Consider agent / dose with the best reduction of ischemic stroke	Dabigatran 150
Previous stroke (secondary prevention)	Consider best investigated agent or greatest reduction of 2º stroke	Rivaroxaban, Apixaban
CAD, previous MI or high-risk for ACS/MI	Consider agent with a positive effect in ACS	Rivaroxaban
Renal impairment	Consider agent least dependent on renal function	Apixaban, Rivaroxaban
GI upset / disorders	effects	Rivaroxaban
Patient preference	Consider once daily formulation	Rivaroxaban

Slide courtesy of Dr. Renato Lopes, MD; Duke University, Cardiology

DOACs in Obese Patients

1. Standard dosing of DOACs in patients with BMI ≤ 40 kg/m2 and weight ≤ 120 kg

2. Do not use in a BMI >40 kg/m2 or weight >120 kg
   - Limited clinical data, PK/PD evidence suggests decreased drug exposures, reduced peak concentrations, shorter half-lives

3. If DOACs are used for patients who fall in statement 2, checking drug-specific peak/trough levels.

Martin K, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14(6):1308-1313.

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Payment Considerations:

	APIXABAN	RIVAROXABAN
Cash Price	~$447.00	~ $448.00
Free 30 Day Starter Supply coupon available	Yes	Yes
For those commercially insured, with coupon card:	$10 for 30 day supply	$0 for 30 days supply
Citizenship Status	Social security number required to be eligible	Eligible regardless of citizenship status

Bristol-Myers Squibb Company. Pfizer. Eliquis. https://www.eliquis-bmscustomerconnect.com/#/hb. Accessed March 2018. Janssen Pharmaceuticals, Inc. 2018. Xarelto tablets. https://www.xarelto-us.com. Updated January 2018. Accessed March 2018. Pan X, et al. ESC 2014, Barcelona, Spain. Oral poster presentation, ESC 2014.

Meds Summary

- Dosing: daily (rivaroxaban) vs. BID (apixaban)
- Don't give a DOAC if a patient has cancer-related thromboses
- Avoid DOACs in BMI >40 and weight >120 kg
- GI bleed may be more likely when taking rivaroxaban (ROCKET-AF, Yao et al, Amin et al) and dabigatran (RE-LY)
- Free 1 month coupons for rivaroxaban and apixaban
  - Copay reduction cards for additional months
- Undocumented patients can sign up for assistance with rivaroxaban but not apixaban

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Oral Anticoagulant Reversal Strategies



Consider Half Lives

- Normal dosing and excretion
  - Greater than 5 half-lives since last dose means there is very little to no drug in the body

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
$T^{1/2}$ (normal GFR)	~ 40 hrs	13.8 hrs	8.3 hrs	15.1 hrs	9-11 hrs	19-27 hrs
5 half-lives =	8.3 days	2.8 days	1.7 days*	3.1 days	2.2 days	5.6 days

* Food may prolong half-life of rivaroxaban

American College of Emergency Physicians. Reversal of non-vitamin K antagonist oral anticoagulants (NOACs) in the presence of major life-threatening bleeding. ACEP Policy Statement. June 2017. Accessed at https://www.acep.org/clinical---practice-management/reversal-of-non-vitamin-k-antagonist-oral-anticoagulants-(noacs)-in-the-presence-of-major-life-threatening-bleeding/ on 27 Apr 2018.
Lexi-complete. Accessed online at http://www.uptodate.com on 27 Apr 2018.

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Reversal of Oral Anticoagulants in the ED

Oral Anticoagulant	Antidote
VKA Warfarin	Vitamin K
Direct Thrombin Inhibitor Dabigatran	Idarucizumab
Direct Factor Xa Inhibitors Rivaroxaban, Apixaban, Edoxaban, Betrixaban	NONE*

*andexanet alfa, ciparantag

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Reversal of Warfarin

Supratherapeutic INR	Action
INR above ther range <4.5 (no bleeding)	Lower or hold next warfarin dose and monitor
INR 4.5-10 (no bleeding)	Hold next 1-2 warfarin doses and monitor
INR >10 (no bleeding)	Give Vitamin K po 2.5-5mg. INR will reduce in 24-48 h. Monitor. Resume warfarin at adjusted dose when INR is in range.
Minor bleeding at any INR	Hold warfarin, may administer Vit K po 2.5-5mg, monitor. Resume warfarin at adjusted dose when INR in range.
Major bleeding at any INR	PCC and IV Vitamin K 5-10mg

Ansell AM, et al. Vitamin K antagonists. Amer Coll of Chest Phys 2008;133(6) Suppl:160S-198S.

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Vitamin K – Phytonadione (Mephyton)

- PO
  - Non-urgently elevated INR
  - Non-urgent procedure of minimal bleeding
- IV
  - Major bleeding suspected
  - IM not recommended due to hematoma risk
  - Give slowly – over 20 min – to avoid allergic rxns
- Monitor
  - PT/INR – PO (6-12h), IV (1-2h)

Pharmacotherapy 2013;33(11):1199-213.

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FFP – Fresh Frozen Plasma

- Contains all factors inhibited by warfarin (II, VII, IX, X)
- Need 1-2 liters to replete clotting factors successfully
  - Caution in patients who may not tolerate high volumes or rapid fluid shifts (e.g. heart failure)
- Potential allergic reactions
- Cheap

Pharmacotherapy 2013;33(11):1199-213.

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Prothrombin Complex Concentrate (PCC)

- 4 Factor (Kcentra) or 3 Factor (Bebulin, Profilnine)
  - 4 Factor PCC is gold standard
  - 3 Factor PCC may require higher doses, vitamin K, FFP, rFVIIa may be needed to achieve adequate coagulation
- Lower infusion volumes than FFP, more costly, less complications
- Recommended by ACCP over FFP

Pharmacotherapy 2013;33(11):1199-213. Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; April 26, 2018.

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Dosing of 4 Factor PCC

Use Actual Body Weight

- Bleeding due to warfarin:
  - Pretreatment INR 2 to <4: 25 units/kg (max 2500 units)
  - Pretreatment INR 4 to 6: 35 units/kg (max 3500 units)
  - Pretreatment INR >6: OR 50 units/kg (max 5000 units)
  - FIXED DOSE: 25 units/kg
- Bleeding due to DOAC:
  - 50 units/kg x 1 dose
  - An additional 25 units/kg x 1 dose may be given if clinically necessary

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Reversal of Dabigatran (Pradaxa)

- Hold dabigatran
- Supportive measures (fluid, FFP)
- Adequate diuresis
- Consider hemodialysis
- Consider oral activated charcoal (2 hour window)
- Consider reversal agent (PCC)
- Consider idarucizumab

Pharmacotherapy 2013;33(11):1199-213.

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Hemodialysis?

- Only works for dabigatran
  - 80% excreted by kidneys as unchanged drug
- Why not direct Xa inhibitors?
  - Rivaroxaban – 36% excreted
  - Apixaban – 27% excreted
  - Edoxaban – 50% excreted
  - Betrixaban – 11% excreted

Lexi-Comp Online ™. Lexi-Drugs ™. Reversal of Oral Anticoagulants. Accessed online on April 25, 2018.

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Idarucizumab (Praxbind)

- Antidote for dabigatran (Pradaxa)
- Humanized monoclonal antibody fragment (Fab) that binds to dabigatran and metabolites with an affinity ~250 times greater than that of thrombin
  - Time to neutralization = minutes
- Dosing (adult): IV – 5 grams (administered as two 2.5g bolus doses no more than 15 minutes apart)
  - Watch aPTT for re-elevation / bleeding

Lexi-Comp Online ™. Lexi-Drugs Online ™, Hudson, Ohio: Lexi-Comp, Inc.; 2015; April 26, 2018.

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Idarucizumab – Interim Analysis

- REVERSE-AD:
  - n=90
  - Test results normalized in 88-98% of the patients within minutes
    - Time to cessation of bleeding = 11.4 hours
  - 18 deaths (20%) + 5 thrombotic events + 21 serious Aes
- REVERSE-AD (full cohort analysis)
  - n=503
    - Time to cessation of bleeding = 2.5 hours
      - Lots of group A (uncontrolled bleeding) was excluded

Pollack CV, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373(6):511-20.
Pollack CV, et al. Idarucizumab for dabigatran reversal – full cohort analysis. N Engl J Med 2017;377(5):431-441.

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Reversal of Direct Xa Inhibitors

- Hold Xa inhibitor
- Supportive measures (fluid, blood product replacement)
- Consider oral-activated charcoal (2 hour window)
- Consider reversal agent (PCC)

*Hemodialysis not an option – drugs highly protein bound

Pharmacotherapy 2013;33(11):1199-213.

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On the Horizon…

- Andexanet alfa
  - Reversal agent for factor Xa inhibitors
  - Portola Pharmaceuticals
  - ANNEXA-A and ANNEXA-R n=145 (age 50-75)
    - Reversal in minutes, short-lived (t ½ ~1h)
  - ANNEXA-4 n=47 (mean age 77y)

Connolly SJ, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131.
Siegal DM, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015;373(25):2413-24.

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On the Horizon…

- Ciparantag (aka PER977, Aripazine ™)
  - Reversal agent for factor Xa inhibitors, dabigatran, UFH, LMWH, fondaparinux
  - Animal model success
  - Edoxaban healthy volunteer success
  - Bleeding patient success IS TO BE DETERMINED…

Ansell JE, et al.. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med 2014;371:2141–2142

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Summary

- Weigh risks versus benefits of DOACs and warfarin when prescribing
  - DOACs much easier to prescribe for outpatient treatment because apixaban and rivaroxaban require no bridging
- Think of patient specific factors that will guide your selection of anticoagulants
  - Medication cost, daily dosing/compliance concerns
- Consider reversal strategies for the oral anticoagulant you selected
  - Half-lives matter, overdoses matter, cost matters
- Know your institution's anticoagulation reversal protocols

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Assessment Question

- Which of the following anticoagulants can be successfully removed by hemodialysis in an emergency situation?

A. apixaban
B. warfarin
C. dabigatran
D. rivaroxaban

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Assessment Question

2. Direct acting oral anticoagulants like rivaroxaban and apixaban should be held if the patient weighs over _____ kg.

A.80
B. 100
C. 120
D. 140

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Assessment Question

3. Based on the studies by Amin and Yao (et al), which DOAC causes statistically significantly higher rates of GI bleeding?

A. apixaban
B. warfarin
C. dabigatran
D. rivaroxaban

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Assessment Question

4. What is the dose of 4-factor PCC when treating a life-threatening bleed due to a DOAC?

A. 25 mg/kg
B. 35 mg/kg
C. 45 mg/kg
D. 50 mg/kg

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