Stop the Stroke, Prevent the Bleed in Patients with Atrial Fibrillation

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Disclosures

- No disclosures relevant to this presentation.

- Dr. Davis **does not intend** to discuss the use of any unapproved use of drugs or devices.
  - If an unapproved drug is listed on a slide it will be clearly noted as such.

Objective

Discuss key differences in the pharmacologic profiles of various oral chronic anticoagulation agents that influence treatment selection for individual patients with atrial fibrillation who are at risk of stroke.

Outline

- Review evidence-based scoring assessments to risk stratify adults with A Fib while considering stroke and bleeding risks.
- Compare/contrast pharmacologic profiles of the options for chronic oral anticoagulants that influence the selection of a specific agent for an individual patient with chronic atrial fibrillation.
- Discuss starting and target dosing options for oral anticoagulant therapy for adults with atrial fibrillation, including those with kidney or liver impairment and other patient-related factors.

Outline (continued)

- Review drug-drug interactions related to various chronic anticoagulation treatment options.
- Discuss patient teaching related to use of various chronic anticoagulation including monitoring drug levels as appropriate and possible drug-food interactions.
- Review indications and options for reversal of various chronic anticoagulation should situations arise.

The Burden of Atrial Fibrillation (AF)

- Relatively common cardiac dysrhythmia in adults
- Approximately 2.7–6.1 million adults in United States in 2010
  - –Expected to double (12.1 million) by year 2030
- Remaining life-time risk in 40-year-old adults ~1 in 4
- Most develop AF later in life
  - –Mean age for men is ~67 years
  - –Mean age for women is ~75 years

Benjamin EJ, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(4):e56-528.

Types of Atrial Fibrillation*

- Acute AF
  - Lasting <48 hours
- Lone AF
  - AF without coexisting risk factors that precede AF
- Paroxysmal AF
  - Recurrent AF; typically <7 days; spontaneously returns to sinus rhythm without intervention
- Persistent AF
  - Recurrent AF; typically >7 days; requires treatment (electrical or pharmacological) to revert to sinus rhythm
- Permanent AF

**Patients are categorized by the most frequent type with which they present.*[1]

Keep in mind that paroxysmal, persistent, and permanent AF all appear to increase the risk of ischemic stroke to a similar degree.[2]

1. Furie KL, et al. *Stroke*. 2012;43(12):3442-3453. 2. Mozaffarian D, et al. *Circulation*. 2015;131(4):e29-322.

Consequences of Atrial Fibrillation

- Increased risk of death
  - Odds ratio for men with AF 1.5
  - Odds ratio for women with AF 1.9
- Increased risk of stroke
  - 4- to 5-fold ↑ in likelihood of ischemic stroke
  - Stroke risk varies greatly depending on comorbidities, age, and whether they have had a stroke in the past
- Increased risk of other conditions
  - More likely to develop heart failure
  - More likely to develop cognitive decline

Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-322.

Major Treatment Goals for Treatment of AF

- Prevention of stroke and other thromboembolic events*
- Control the ventricular heart rate during episodes of AF
- In select patients, restore sinus rhythm

** The focus of this presentation.*

Recommendations for Prevention of Stroke and Thromboembolism

- Acute AF (<48 hours), associated w/ hemodynamic instability:
  - Immediate cardioversion
- Acute AF (<48 hours), stable:
  - Assess risk and underlying cause
- AF ≥48 hours, if urgent/emergent:
  - Heparin should be given unless contraindicated
  - aPTT should be 1.5-2 times upper limit of normal
- AF ≥48 hours, if nonemergent:
  - Risk stratify by calculating $CHADS_2$ or CHA_2DS_2VASc score
  - Consider bleeding risk and patient preferences
  - Anticoagulation as an outpatient

***Note: All patients with newly diagnosed AF need an assessment of their heart valves (to determine if they have valvular heart disease).**

AHA/ACC/HRS AF Guidelines

- **Nonvalvular AF is defined as** the **absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair**
- **CHA_2DS_2VASc** preferred over $CHADS_2$
- Increase use of AF ablation in nonvalvular AF
- Call for a greater understanding of rate vs rhythm control treatment strategies
- **Warfarin recommended** for patients with **AF and ESRD** or on dialysis with a CHA_2DS_2VASc score of ≥2
- Emphasis on individualizing treatment by patient/clinician
  - **Shared decision making** based on risk of stroke and bleeding and the patient's preferences and values
- Nearly concordant with ESC guidelines

ESRD = end stage renal disease, ECS= European Society of Cardiology

January CT, et al. *Circulation.* 2014;130(23):e199-267.

Risk Stratification for Stroke and Thromboembolism in Patients With Atrial Fibrillation

Stroke Risk Scoring Schemata

- $CHADS_2$ – traditionally used in US
- CHA_2DS_2VASc – use this now!

$CHADS_2$ vs CHA_2DS_2VASc

Risk Factor	$CHADS_2$ Score	CHA_2DS_2VASc Score
Congestive heart failure /**LV dysfunction***	1	1
Hypertension	1	1
Age ≥75	1	2
Diabetes mellitus	1	1
Stroke/TIA/ **thromboembolism***	2	2
Vascular disease (previous MI, PAD, aortic plaque)	-	1
Age 65-74	-	1
Female sex	-	1
Maximum score	**6**	**9**

*LV dysfunction and thromboembolism specific to CHA_2DS_2VASc; not included in original $CHADS_2$

LV = left ventricular, MI = myocardial infarction, PAD = peripheral artery disease

Odum LE, et al. *Pharmacotherapy.* 2012;32(3):285-296.

Risk Factor For Stroke in Afib

CHA_2DS_2-VASc	
Congestive Heart Failure	1
Hypertension	1
Age > 75	2
Diabetes	1
Stroke	2
Vascular Disease	1
Age > 65-74	1
Sex category (Female)	1

CHA_2DS_2-VASc Score	Adjusted Stroke Rate % per year
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	
9	15.2

Andrade J et al. Circ Res. 2014;114:1453-68.
Lip G et al. Chest 2010;137:263-72.

HAS-BLED Bleeding Risk Assessment

	Clinical Characteristic	Score
H	Hypertension (>160 mmHg systolic)	1
A	Abnormal kidney or liver function (Cr 2.26) (**1 each**)	1 or 2
S	Stroke	1
B	Bleeding history or predisposition	1
L	Labile INR (≤60%TTR)	1
E	Elderly age (≥65 years)	1
D	Drugs or alcohol (**1 each**)	1 or 2
	Maximum Score	9

Score ≥3 indicates high risk; caution and regular review of the patient is necessary.
Drugs = antiplatelet agents (ie, aspirin), NSAIDs

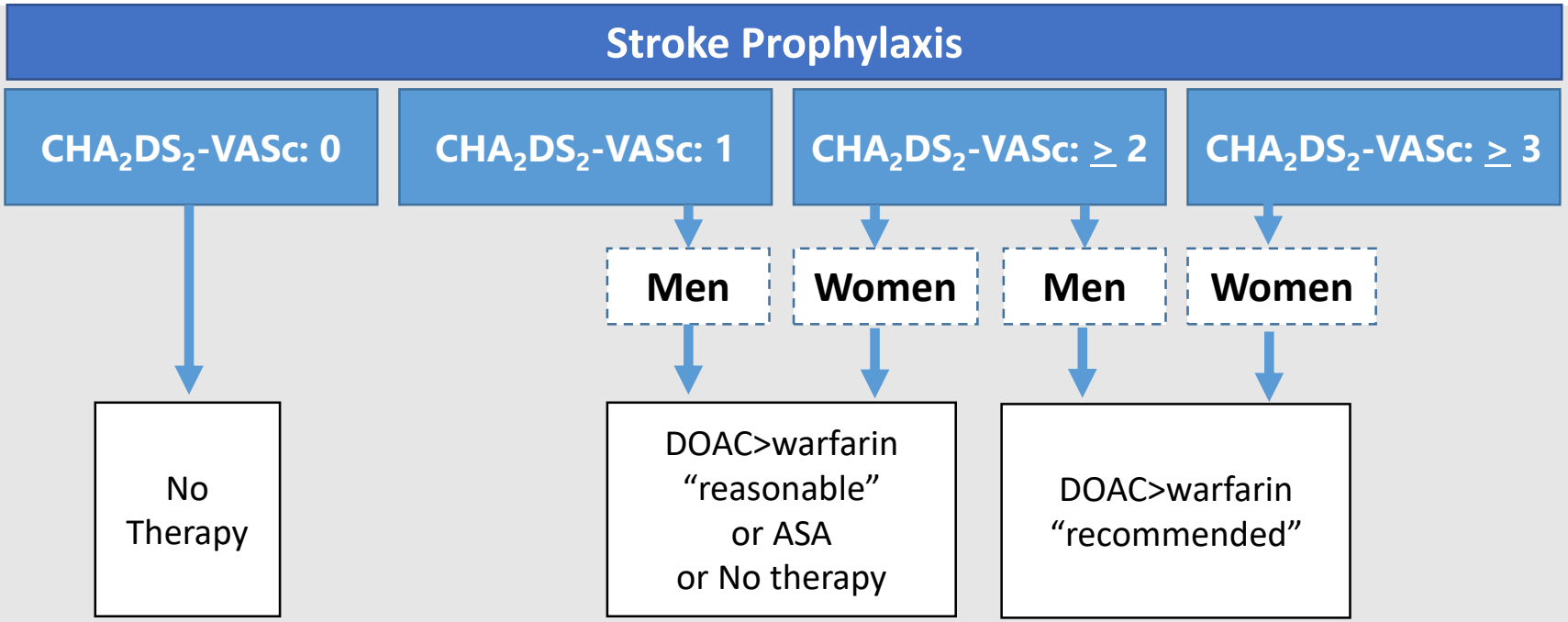
European Heart Rhythm Association, et al. *Eur Heart J*. 2010;31(19):2369-2429; Pisters R, et al. *Chest.* 2010;138(5):1093-1100.

Treatment Guidelines After Calculating Stroke Risk and Bleeding Risk

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons



January CT et al. Circulation 2019;140:e125-e151.

Atrial Fibrillation guidelines comparison

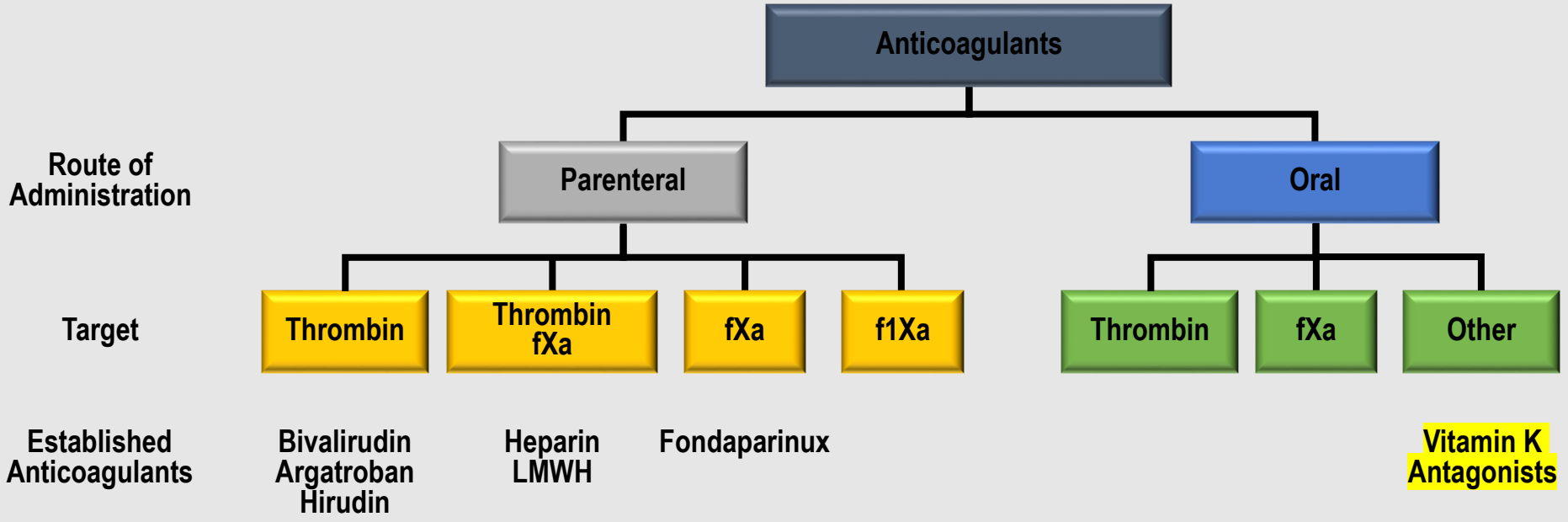
Old Guidelines		New Guidelines			Updated Guidelines
Risk Profile	Recommended Therapy	Risk Profile	Recommended Therapy		
	AHA/ACC/HRS 2008		**ESC 2012**	**AHA/ACC/HRS 2014**	**AHA/ACC/HRS 2019**
No risk factors $CHADS_2$=0	Nothing	**No risk factors CHA_2DS_2-VASc=0**	Nothing	Nothing	Nothing
$CHADS_2$=1	ASA or OAC	**CHA_2DS_2-VASc=1**	DOAC>VKA	Nothing or ASA or OAC	**Male = 1, Female =2** DOAC vs warfarin or ASA or nothing
$CHADS_2$ ≥2	OAC	**CHA_2DS_2-VASc ≥2**	DOAC>VKA	DOAC or VKA	**Male ≥2, Female ≥3** DOAC vs warfarin
Mechanical Valve	OAC	Mechanical Valve	**Warfarin: INR 2.0-3.0 for aortic Warfarin: INR 2.5-3.5 for mitral**		

VKA= Vitamin K antagonist
OAC = oral anticoagulant

ESC Guidelines: Eur Heart J 2012; 2623–2630.
January CT et al. AHA/ACC/HRS Guidelines 2014. J Am Coll Cardiol 2014; e1-e76.
January CT et al. Circulation 2019;140:e125-e151.

Options for Anticoagulation in Patients With Atrial Fibrillation

Classification of Established and New Anticoagulants*



*Others in development

*This information includes agents that have not been approved by the FDA.

We will focus on the ones in yellow highlight.

Eikelboom JW, Weitz JI. *Circulation.* 2010;121(13):1523-1532.

Warfarin

- **Mechanism of Action:** Vitamin K antagonist
- **Pharmacokinetics:**
  - Half-life: 20-60 hours
  - Time to peak effect: 72-96 hours
  - Bioavailability: 100%
  - Excretion: 1% excreted unchanged in the urine
- **Pros:**
  - Until recent years, the most efficacious treatment for stroke prevention in patients with AF
  - Relatively inexpensive
- **Cons:**
  - Clinician reluctance to prescribe (esp. older adults); patient reluctance to take; potential for bleeding
  - Difficulty in keeping INR in therapeutic range, variable dosing & need for dose adjustment, often need bridging when starting therapy, monitoring issues, drug-drug interactions, drug-food interactions, genetic variability in metabolism

Warfarin Treatment Is Challenging

A delicate balance of efficacy and safety

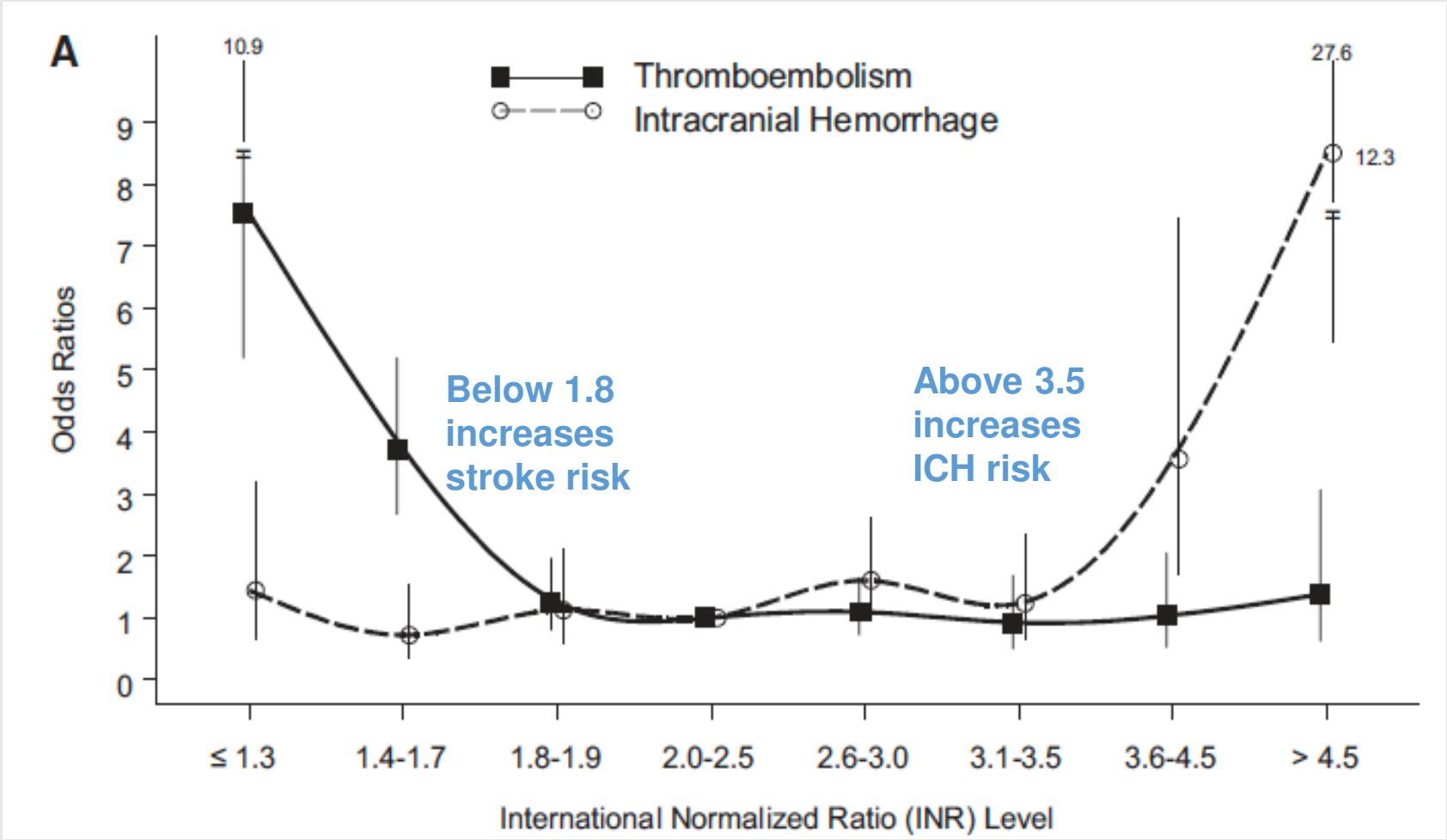
- Delayed onset of action
- Drug-food interactions
- Drug-drug interactions
- Dose response variability
- Drug nonadherence

- Slow reversal of anticoagulant effect
- Drug-drug interactions
- Comorbid conditions
- Dose response variability

Singer DE, et al. *Ann Intern Med.* 2009;151(5):297-305.
Crowther M, et al. *Ann Intern Med.* 2009;150(5):293-300.
Horton JD, et al. *Am Fam Physician.*1999;59(3):635-646.

Therapeutic Range for Warfarin

Balancing Safety and Efficacy



ICH = intracranial hemorrhage

Singer DE, et al. *Circ Cardiovasc Qual Outcomes.* 2009;2:297-304.

Underutilization of Stroke Prophylaxis

- Meta-analysis about utilization of warfarin therapy[1]
  - **Factors associated with higher use of warfarin:**
    - Male sex and those with prior stroke
  - **Factors associated with lower use of warfarin:**
    - Alcohol and drug abuse, noncompliance, warfarin contraindications, dementia, falls, gastrointestinal and/or intracranial hemorrhage, kidney impairment, advancing age
- One study found only ~45% of those with AF who ***should*** have been on warfarin ever got it;[2] lower percentage for older adults or those without insurance[2]
- **Risk stratification** of patients with chronic AF helps determine who should be on stroke prophylaxis

1. Mozaffarian D, et al. *Circulation*. 2015;131(4):e29-322; 2. Go AS, et al. *Ann Intern Med*. 1999;131(12):927-934.

Alternatives to Warfarin for Stroke Prevention in Patients With Nonvalvular AF

- Direct thrombin inhibitors
  - Dabigatran (Pradaxa®)
    - First alternative approved in 2010
- Direct factor Xa inhibitors
  - Rivaroxaban (Xarelto®)
    - FDA approved in September 2011
  - Apixaban (Eliquis®)
    - FDA approved in December 2012
  - Edoxaban (Savaysa®)
    - FDA approved in January 2015
  - Others in development
    - Betrixaban (not FDA approved for nonvalvular A Fib)

Prasad V, et al. *Cerebrovasc Dis.* 2012;33(3):199-208; Study of a New Anticoagulant Drug in Patients With Atrial Fibrillation. Accessed August 13, 2015: http://clinicaltrials.gov/ct2/show/NCT00431782?term=ATI-5923&rank=2

Direct Oral Anticoagulants (DOACs): Indications

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Class	**Direct Thrombin Inhibitor**	**Factor Xa Inhibitor**	**Factor Xa Inhibitor**	**Factor Xa Inhibitor**
Approval	2010	2011	2012	2015
Indications	• **Reduction of risk of stroke and systemic embolism in nonvalvular AF** • Treatment of DVT and PE • Reduction of recurrence of DVT and PE	• **Reduction of stroke and systemic embolism in nonvalvular AF** • Treatment of DVT and PE • Reduction of recurrence of DVT and PE • Prophylaxis of DVT following hip or knee replacement surgery	• **Reduction of stroke and systemic embolism in nonvalvular AF** • Treatment of DVT and PE • Reduction of recurrence of DVT and PE • Prophylaxis of DVT following hip or knee replacement surgery	• **To reduce the risk of stroke and systemic embolism in patients with nonvalvular AF** • Treatment of DVT and PE following 5-10 days of initial therapy with a parenteral anticoagulant

Dabigatran Prescribing Information, 2014; Rivaroxaban Prescribing Information, 2014; Apixaban Prescribing Information, 2014; Edoxaban Prescribing Information, 2015.

DVT = deep venous thrombosis, PE = pulmonary embolus

Approved DOACs: Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	**Thrombin (IIa)**	**Factor Xa**	**Factor Xa**	**Factor Xa**
Peak Effect (hrs)	0.5-2	2-4	3-4	1-2
Half-life (hrs)	12-17	5-9 (young); 11-13 (elderly)	8-15	19-11
Lab Monitoring	Not needed	Not needed	Not needed	Not needed
Administration	Twice daily	Once daily	Twice daily	Once daily
Bioavailability	3%-7%	66% (fasting) 100% (w/food)	50%*	62%
Renal excretion	80%	36%	27%	50%
Drug interactions	P-gp inducers± (rifampin)	Strong dual inhibitors & inducers of P-gp CYP3A4	Strong dual inhibitors & inducers of P-gp CYP3A4	P-gp inducers± (rifampin)
Protein binding	35%	95%	87%	40-59%

*from Averroes trial; ±P-gp inducer (rifampin); no clinically significant interactions with P-gp inhibitors except ketoconazole and verapamil; CYP = cytochrome P450

Apixaban Prescribing Information, 2014; Dabigatran Prescribing Information, 2014; DeLoughery TG. *Am J Hematol*. 2011;86(7):586-590; Rivaroxaban Prescribing Information, 2014; Samama MM, et al. *J Thromb Thrombolysis.* 2010;29(1):92-104; Prom R, Spinler SA. *Ann Pharmacother.* 2011;45(10):1262-1283; Weitz JI, et al. *Chest*. 2008;133(6 suppl):234S-256S; Edoxaban Prescribing Information, 2015; Giugliano RP, et al. *N Engl J Med.* 2013;369(22):2093-2104.

DOACs: Renal Dosing Instructions

	Normal Dosage	Dose Adjustments	Additional Comments
Dabigatran	150 mg twice daily CrCl >30 mL/min	75 mg twice daily CrCl 15-30 mL/min or CrCl 30-50 mL/min in those taking concomitant P-gp inhibitors, (such as dronedarone or systemic ketoconazole)	**Not recommended in pts with CrCl <15 mL/min or on dialysis** Avoid use in patients with CrCl 15-30 mL/min taking concomitant P-gp inhibitors
Rivaroxaban	20 mg once/day **with food** CrCl >50 mL/min	15 mg once daily **with food** CrCl 15-50 mL/min	**Not recommended in pts with CrCl <15 mL/min or on dialysis**
Apixaban	5 mg twice daily (including ESRD on HD ***(unless situations listed to the right)***	2.5 mg twice daily if **2 of 3 of the following** are present: •Age ≥80 yrs •Weight ≤60 kg •Serum creatinine ≥1.5 mg/dL •Strong dual inhibitors of CYP3A4 and P-gp	**5 mg twice daily for pts with ESRD on dialysis;** *2.5 mg if age ≥80 years or body weight ≤60 kg
Edoxaban	60 mg once/day CrCl >50 mL/min to CrCl ≤95 mL/min	30 mg once daily CrCl 15-50 mL/min	**Not for use in patients with CrCl <15 mL/min or CrCl >95 mL/min**

Rivaroxaban Prescribing Information, 2019; Apixaban Prescribing Information, 2019; Dabigatran Prescribing Information, 2018; Edoxaban Prescribing Information, 2019.

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Chew/crush	**Do not chew/crush!** (↑ active drug by 75%)	Applesauce PO/ in 50mL water via NGT (stable 4 h)	Applesauce PO/ in 60 mL water via NGT (stable 4 h)	Applesauce PO/ in 60-90 ml water via PO or NGT (use immediately)
Food	With or without	w/food (↑ active drug by 39%)	With or without	With or without
Age	↑ bleeding ≥ 75 yrs.	Half-life prolonged	≥ 80 yrs. dosing factor	No effect (per PI)
Weight	20% ↓ trough in pt. >100kg, no dose adj. rec.	TBW >120kg not assoc. w/ significant PK Δ's	20% ↓ peak conc. >120kg, no dose adj.	Exposure ↑ ~55 kg
Adv. effects	Dyspepsia (11%)	Epistaxis, hematuria	---	---
Warnings	• **Do not use** in mechanical valves or with moderate to severe mitral valve stenosis • **Do not use** antiphospholipid syndrome lupus anticoagulant; anticardiolipin, and anti-beta 2-glycoprotein I			

Dabigatran: Acidic environment required for absorption; Store in original package (moisture labile)

Upreti VJ Br et al. J Clin Pharmacol. 2013;76:908-16.
Kubitza D et al. J Clin Pharmacol. 2007;47:218-26.
Pradaxa(TM) [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2018.
Xarelto(TM) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2019.
Eliquis(TM) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2019.
Savaysa(TM) [package insert]. Parsippany, NJ: Daiichi Sankyo; 2019.

Outcomes of DOAC Trials

Clinical Trial	Therapy	All stroke or systemic embolism	Ischemic or unspecified stroke	Hemorrhagic stroke	Myocardial infarction	All-cause mortality	Vascular mortality
ARISTOTLE	Apixaban (n=9120)	1.27%	0.97%	0.24%	0.53%	3.52%	1.8%
	Warfarin (n=9081)	1.6%	1.05%	0.47%	0.61%	3.94%	2.02%
	HR (95% CI)	0.79 (0.66-0.95)	0.92 (0.74-1.13)	0.51 (0.35-0.75)	0.88 (0.66-1.17)	0.89 (0.8-0.998)	0.89 (0.76-1.04)
RE-LY	Dabigatran (n=6076)	1.11%	0.92%	0.1%	0.81%	3.64%	2.28%
	Warfarin (n=6022)	1.71%	1.2%	0.38%	0.64%	4.13%	2.69%
	HR (95% CI)	0.65 (0.52-0.81)	0.76 (0.6-0.98)	0.26 (0.14-0.49)	1.27 (0.94-1.17)	0.88 (0.77-1.00)	0.85 (0.72-0.99)
ROCKET AF	Rivaroxaban (n=7081)	2.1%	NR	0.26%	0.91%	1.87%	1.53%
	Warfarin (n=7090)	2.4%	NR	0.44%	1.12%	2.21%	1.71%
	HR (95% CI)	0.88 (0.75-1.03)	NR	0.59 (0.37-0.93)	0.81 (0.63-1.06)	0.85 (0.7-1.02)	0.89 (0.73-1.1)
ENGAGE AF-TIMI 48	Edoxaban (60 mg; n=7053)	1.18%	1.25%	0.26%	0.7%	3.99%	2.74%
	Warfarin (n=7036	1.5%	1.25%	0.47%	0.75%	4.35%	3.17%
	HR (95% CI)	0.79 (0.63-0.99)	1.00 (0.83-1.19)	0.54 (0.38-0.77)	0.94 (0.74-1.19)	0.92 (0.83-1.01)	0.86 (0.77-0.97)

Miller CS, et al. *Am J Cardiol.* 2012:110(3):453-460; Giugliano RP, et al. *N Engl J Med.* 2013;369(22):2093-2104.

Advantages of DOACs

- All are at least as effective as warfarin
- All have favorable bleeding profiles
- No routine INR testing needed
- Predictable pharmacokinetics and dynamics
- Once or twice fixed oral daily dosing
- Rapid onset and termination of action
- Fewer drug interactions to monitor than with warfarin
- Reduced intracranial bleeds for all 4 (vs warfarin)

Mega JL. *N Engl J Med.* 2011;365(11):1052-1054; del Zoppo GJ, Eliasziw M. *N Engl J Med.* 2011;365(10):952-953.

DOAC follow up and monitoring

- Kidney function (every 6 months)
- Liver function (every 6-12 months)
- Adherence
- Drug Interactions
  - substrate for P-glycoprotein, metabolized by CYP450 enzymes
- Coagulation assay (aPTT, PT) = Not useful
- Plasma drug concentrations = Limited use

Conway SE et al. Pharmacotherapy 2017;37:236-48.
Dixon DL. Amer College of Cardiology. March 21, 2017. Accessed online https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/03/21/13/48/clinical-monitoring-of-direct-acting-oral-anticoagulants.

Ongoing Care for Patients on DOACs

- Checklist to review with each patient at every visit
  - Instruct patients to bring medication to visit
  - Check pill counts (for adherence)
  - Any thromboembolic events
  - Any bleeding
  - Other side effects
  - What other meds (including pain meds or other over the counter meds)

Considerations for DOAC Selection

- Level of kidney impairment (if any)
- Age $\geq$ 80 years
- Overall bleeding risk
- GI upset/disorders
- Patient preference (twice daily versus once daily dosing)
- Concomitant CYP inhibition
- History of coronary artery disease, prior MI, or high risk for ACS/MI
- Likely to be adherent

DOAC cost

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Cost*	$417.97	$451.91	$448.13	$368.36
Co-pay card available	30-day trial $0 co-pay (max $2400)	30-day trial $10 co-pay (max $3400)	30-day trial $10 co-pay	N/A $4 co-pay

*30-day supply

Cost of warfarin: $4/month

www.goodrx.com, accessed Oct 6, 2019

Cost of DOACs

- Studies have demonstrated that the medical costs are reduced with DOACs as compared to warfarin
- Genotyping pts for warfarin sensitivity prior to prescribing treatment was more cost-effective

Amin A, et al. *J Med Econ.* 2015;18(6):399-409; Deitelzweig S, et al. *J Med Econ.* 2012;15(4):776-785; You JH. *Pharmacogenet Genomics.* 2014;24(1):6-14.

Who Should Not Get the Newer Agents

- Prosthetic heart valves
- Hemodynamically significant valve disease
- Severe renal failure (CrCl <15 mL/min)
  - Exception: apixaban in pts on stable hemodialysis
  - Warfarin is treatment of choice for ESRD
- Advanced liver disease (impaired baseline clotting function)
- Patients with upper GI problems
- Those who may miss doses frequently

January CT, et al. *Circulation.* 2014;130(23):e199-267.

Transitions

- **When transitioning from warfarin to a DOAC:**
  - Rivaroxaban may be started when INR is <3
  - Edoxaban may be started when INR ≤2.5
  - Apixaban or dabigatran can be administered when INR is <2
- **When bridging from a DOAC to warfarin:**
  - 2- to 3-day therapy overlap is recommended to avoid thromboembolic events, particularly in high-risk patients
- **When bridging from one DOAC to another DOAC:**
  - In general discontinue one; then start the other at the time of the next dose.
  - No info avail on dabigatran (so consider pt specific situation; kidney function & risk of bleeding or stroke)

Rivaroxaban Prescribing Information, 2014; Apixaban Prescribing Information, 2014; Dabigatran Prescribing Information, 2014; Edoxaban Prescribing Information, 2015; Camm AJ, et al. *Eur Heart J*. 2012;33(21):2719-2747; Kovacs RJ et al. J Am Coll Card, 2015: 65: 1340-60

Temporary Interruption of DOACs

- **In general**
  - If low bleeding risk
    - 24-36 hrs is when most of anticoag effect is gone
  - If high bleeding risk
    - 2-3 days is when most of anticoag effect is gone
- **If moderate to high risk bleeding**
  - Apixaban: stop agent at least 48 hrs prior to surgery
    - for low risk bleeding at least 24 hrs prior to surgery
  - Rivaroxaban & edoxaban
    - At least 24 hr prior to surgery
  - Dabigatran
    - If CrCl $\geq$ 50 mL/min at least 24-48 hrs prior to surgery
    - If CrCl < 50 mL/min 3-5 days prior to surgery

Rivaroxaban Prescribing Information, 2014; Apixaban Prescribing Information, 2014; Dabigatran Prescribing Information, 2014; Edoxaban Prescribing Information, 2015; Camm AJ, et al. *Eur Heart J*. 2012;33(21):2719-2747; Kovacs RJ et al. J Am Coll Card, 2015: 65: 1340-60

Education Topics for Oral Anticoagulation (1)

- Basics related to oral anticoagulation
  - Indication (why they are taking it)
  - Life long
  - Reversibility
- Adherence
  - Importance of not missing a dose (esp with DOACs)
  - What to do if missed a dose

Education Topics for Oral Anticoagulation (2)

- Risks and benefits
  - Common signs of clotting
  - Common signs of bleeding
    - Unusual bleeding from nose/gums, heavier than normal menstrual bleeding, red or brown urine, red or black colored stools, hemoptysis, vomiting blood or coffee ground emesis, unusual bruising, or discoloration of the skin
    - If patients experience bleeding notify their clinician immediately or seek medical attention right away
  - Need for birth control in women of child bearing age
- Preventative care to minimize risk of trauma or bleeding
- Substances to avoid
  - Alcohol, NSAIDS
  - Avoid aspirin unless prescribed

Education Topics for Oral Anticoagulation (3)

- Health care
  - General lab monitoring
  - Which providers to notify about anticoagulation
  - Carrying identification (med bracelet or necklace; wallet card)
- Administration of medication
  - Storage requirements
    - Dabigatran must be kept in original container; do not put in pillbox; do not discard desiccant.
  - Timing of dose (with or without food)
    - Dabigatran: swallow whole, do not break, crush, or open capsule. Take with a full glass of water.
    - Rivaroxaban: take with food (evening meal)

Management of Bleeding for the DOACs

General Assessment of Bleeding in Patients taking DOACs: 4 Steps

- Review
- Remove
- Repair
- Reverse

Kovacs RJ et al. J Am Coll Cardio. 2015; 65(13):1340-60.

Step 1: Review

- Stop anticoagulation (& antiplatelet therapy)
- Timing of the last dose*
  - Resolution of anticoagulation: dabigatran 2.5-3.5 days; rivaroxaban 1.5-3.5 days; apixaban 1-2 days; edoxaban 1.3-2 days
- Review medications
- Comorbid conditions
- Baseline labs*
- Source of bleeding
- Maintain organ perfusion
- Evaluate for transfusion

***Note: timing of last dose & kidney function are important factors**

Kovacs RJ et al. J Am Coll Cardio. 2015; 65(13):1340-60.

Step 2: Remove & Step 3: Repair

Step 2:

- Gastric lavage for recent ingestion
- Activated charcoal (within 2-6 hours of ingestion)
- Dialysis (dabigatran)
  - 49-57% cleared from plasma
  - Other DOACs are highly protein-bound so dialysis is unlikely to be effective

Step 3:

- Assess need for surgery
  - Surgical hemostasis
  - Endoscopic hemostasis (if GI bleed)

Kovacs RJ et al. J Am Coll Cardio. 2015; 65(13):1340-60.

Step 4: Reverse

Vitamin K antagonists

- Vitamin K
- Consider FFP for poor hemodynamic condition
- 4-factor prothrombin complex concentrate (PCC)
- Platelet transfusion (for those with thrombocytopenia or if pts received platelets)

Direct oral anticoagulants

- Consider 4-factor prothrombin complex concentrate (PCC) or activated PCC, or as last choice activated factor VIIa.
- Platelet transfusion (for those with thrombocytopenia or if pts received platelets)
- New reversal agents

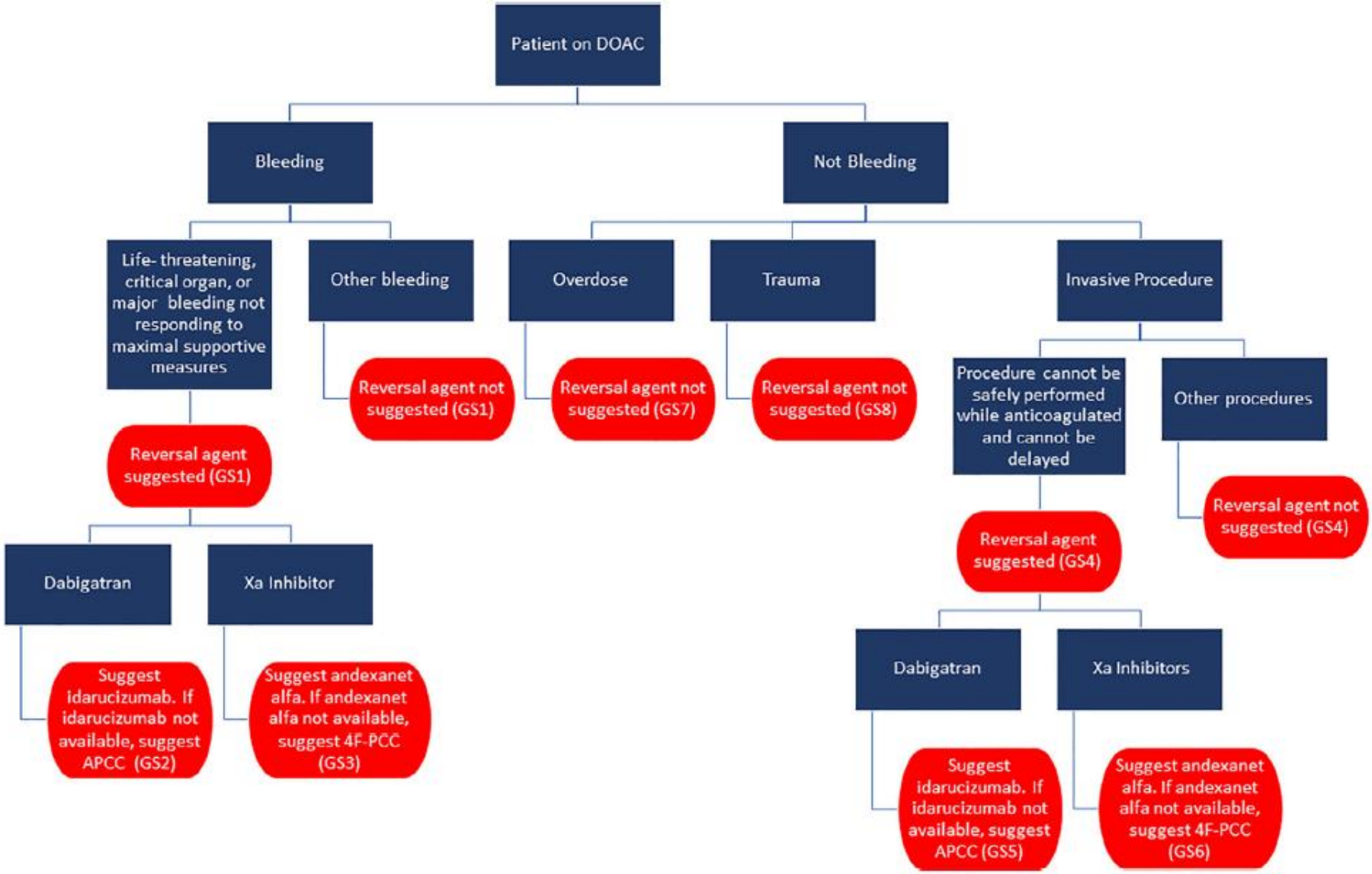
Kovacs RJ et al. J Am Coll Cardio. 2015; 65(13):1340-60.

Potential Reversal Therapies for DOACs

Potential Reversal Agent	DOAC
Idarucizumab (Praxbind®)	Dabigatran
Andexanet alfa (Andexxa®) *FDA approved for reversal of Factor Xa inhibitors (rivaroxaban & apixaban)	Specific antidote for 2 factor Xa inhibitors
4 Factor Prothrombin complex concentrate (4 F-PCC) (Kcentra®) **(Four factor inhibition: II, VII, IX, X)** *FDA approved for reversal of Vit K antagonists	Non-specific antidote. Use for Factor Xa inhibitors if andexanet is not avail
Activated Prothrombin complex concentrate (APCC) (Feiba®)*FDA approved for bleeding disorders	Non-specific antidote. Use for dabigatran reversal if Idaruizumab is not avail

Ansell JE, et al. *New Engl J Med.* 2014;371(22):2141-2142;
Cuker A et al. *Am J Hematol*. 2019;94:697–709;
Eerenberg ES, et al. *Circulation.* 2011;124(14):1573-1579;
Pollack CV, et al. *New Eng J Med*. 2015;373(6):511-520.

Summary of guidance on DOAC reversal



Cuker A et al. Am J of Hematol 2019; 94:697-709.

Idarucizumab (Praxbind®)

- **FDA approved (October 2015)**
- Target: direct thrombin inhibitors
  - Reverses dabigatran's anticoagulant effects
  - Does not reverse factor Xa inhibitors or LMWH/fondaparinux
- Mechanism of action:
  - Humanized monoclonal antibody fragment (Fab)
  - Binds to dabigatran
- Indication: use in pts taking dabigatran when reversal of the anticoagulation effects are needed for:
  - Emergency surgery/urgent procedures
  - Life-threatening or uncontrolled bleeding

Packet insert: Praxbind® 10/2015

Idarucizumab (continued)

- Dose: 5 gram IV is recommended
  - Avail in 2.5 g/50 mL vials (need 2 vials)
  - Administer within 1 hour of preparing the solution
  - Flush IV line with 0.9% sodium chloride
  - No dose adjustment for those with kidney impairment
- Speed of action:
  - For those w/serious bleeding: hemostasis restored at median 11.4 hrs
  - For those who underwent a procedure: 33/36 had normal intraoperative hemostasis reported
- Side effects:
  - Thromboembolic risk (**You are reversing the anticoagulation!**)
  - Hypersensitivity reaction (pyrexia, bronchospasm, hyperventilation, rash, pruritis)
  - Risk of serious adverse reaction in those with hereditary fructose intolerance due to sorbitol excipient
    - Reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure, death may occur.

Packet insert: Praxbind® 10/2015

Reversal Agents

	Andexanet Alpha (Andexxa®)	Idarucizumab (Praxabind®)	4F- PCC (Kcentra®)	APCC (FEIBA®)
Classification	Specific antidote	Specific antidote	Non-specific prohemostatic agent	Non-specific prohemostatic agent
Onset of action	2-5 min	< 5 min	Unknown in DOAC patients	Unknown in DOAC patients
Half-life	Pharmacodynamic 30-60m. Terminal 5-7 h	Pharmacodynamic 45m. Terminal 4-8 h	Dependent on $t_{1/2}$ of indiv Clotting Factors Elev. Lev CF persist 24 h	Dependent on $t_{1/2}$ of indiv Clotting Factors Elev. Lev CF persist 24 h
Elimination	Unknown	Renal	Hepatic	Hepatic
Dosage form	100 mg vial powder * 200 mg vial powder	5 g boxed kit- 2 2.5 g/50 ml vials	Potency based on F IX content	Potency based on amount of F VIII inhibitor bypassing activity in units
Cost	200 mg vial $5,500	5 g kit- $3,500-4,200	$.60 – 2.77 per unit	$1.64 per unit
Storage	Refrigerate ~Stickers to emphasize only used for Factor Xa inhibitor reversals	Refrigerate, in original carton, protect from light ~sticker	Does not require refrigeration Protect from light	Does not require refrigeration Protect from light

*to be phased out per US FDA

Cuker A et al. Am J of Hematol 2019; 94:697-709.
Almegren, M. Reversal of direct oral anticoagulants. Vascular Health and Risk Management 2017; 13:287–292.

	Andexanet Alpha (Andexxa®)	Idarucizumab (Praxabind®)	4F- PCC (Kcentra®)	APCC (FEIBA®)
Stability	-Shelf life- 24 mo -Reconstituted-8 hr at RT, 24 hr REFRIG -IV bag- 8 hrs RT	-Shelf- life 24 mo -Unopened vials-RT 48 hrs -RT, not protected from light- 6 hrs	-Shelf –life 36 mo -reconstituted use within 4 h	-Shelf – life 24 mo -reconstituted use within 3 hr -do not REFRID after reconstitution
Preparation	-200 mg with 20 ml Sterile water (20 mg/ml) - Withdraw using 60 ml syringe and transfer IV bag with 250 ml NaCl	-May be delivered at bedside -given as 2 consecutive 2.5 mg	-Maybe reconstituted at bedside -Multiple vials maybe pooled	-Maybe reconstituted at bedside -Multiple vials maybe pooled
Administration	-Separate infusion line -Bolus- IV 30 mg/min with filter -Infusion 4 mg/min -flush line	Separate line -administer 2 vials consecutively within 15 min -flush line	- Separate line -total dose infused within 15-30 min	-flush line with isotonic saline prior and post -separate line -total dose infused within 15-30 min

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Almegren, M. Reversal of direct oral anticoagulants. Vascular Health and Risk Management 2017; 13:287–292.

Reversal agents for DOAC - Major Bleeding

	Idarucizumab (Praxabind®)	Andexanet Alpha (Andexxa®)	4F- PCC (Kcentra®)	APCC (FEIBA®)
Dabigatran	5 g IV	n/a	n/a	50 units/kg
Rivoraxaban or Apixaban	n/a	See table	2000 units	n/a
Edoxaban or Betrixaban	n/a	High -dose	2000 units	n/a

TABLE 2 Dosing and administration of andexanet alfa according to the United States Food and Drug Administration package insert

Drug	Last Dose	Time from last dose: <8 h or unknown	Time from last dose: ≥8 h
Rivaroxaban	≤10 mg	Low dose[a]	Low dose[a]
	>10 mg or unknown	High dose[b]	
Apixaban	≤5 mg	Low dose[a]	
	>5 mg or unknown	High dose[b]	

[a]Initial 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.
[b]Initial 800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min.

Cuker A et al. Am J of Hematol 2019; 94:697-709.

Summary

Management of Atrial Fibrillation

- Changes to CHA_2DS_2VASc for men vs women
- Clarification of Valvular Afib

DOACs

- Four on the market now for use in non-valvular A Fib stroke prevention
- More in development
- Offer additional stroke prevention as compared to warfarin

Reversal

- FDA approved agents for both dabigatran and anti-Xa inhibitors
- Anticoagulation Forum *limits the use* of reversal agents to life threatening bleeding and surgical procedures that cannot be delayed.