We Got the Beat:
Atrial Fibrillation Guideline Update

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Learning Objectives

- Apply recommendations from the new 2019 atrial fibrillation guidelines to patient care decisions.
- Recommend the most appropriate pharmacotherapy for patients with atrial fibrillation complicating acute coronary syndrome.

Pre-Assessment Question 1

58 year old female with history of controlled hypertension.

Which treatment do you recommend?

A. Aspirin 325 mg
B. Aspirin 81 mg and clopidogrel 75 mg
C. Warfarin target INR 2-3
D. Apixaban 5 mg BID

Pre-Assessment Question 2

67 year old male with history of T2 diabetes, HTN and bioprosthetic aortic valve.

Which treatment do you recommend?

A. Aspirin 325 mg
B. Aspirin 81 mg and prasugrel 10 mg
C. Warfarin target INR 2-3
D. Edoxaban 60 mg

Pre-Assessment Question 3

62 year old female with history of obesity, hyperlipidemia, HTN and mechanical mitral valve.

Which treatment do you recommend?

A. Aspirin 325 mg and prasugrel 10 mg
B. Warfarin target INR 2.5-3.5
C. Edoxaban 60 mg
D. Rivaroxaban 15 mg BID

Pre-Assessment Question 4

66 year old male with history, hyperlipidemia, HTN, s/p ACS and PCI with a single DES to his LAD 2 weeks ago.

Which treatment do you recommend?

A. Aspirin 81 mg, ticagrelor 90 mg BID
B. Aspirin 81 mg, clopidogrel 75 mg, warfarin target INR 2-3
C. Aspirin 81 mg, apixaban 5 mg BID
D. Clopidogrel 75 mg, rivaroxaban 15 mg

Pre-Assessment Question 5

46 year old female with no past medical history, goes into paroxysmal AF during a hysterectomy operation.

Which treatment do you recommend?

A. Nothing
B. Aspirin 81 mg
C. Aspirin 81 mg, clopidogrel 75
D. Warfarin target INR 2-3
E. Dabigatran 150 mg BID

Before We Start, Let's Look Back …

Recommendations for prevention of thromboembolism in non-valvular AF	Class	Level
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences.	I	C
Antithrombotic therapy selection based on risk of thromboembolism.	I	B
The **CHA_2DS_2-VASc score is recommended to assess stroke risk**.	I	B
Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis.	I	B
With prior stroke, TIA, or **CHA_2DS_2-VASc score of $\geq$ 2 OAC therapy is recommended**. Options include:		
Warfarin	I	A
Dabigatran, rivaroxaban, apixaban	I	B
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR.	I	C
With **non-valvular AF and a CHA_2DS_2-VASc score of 0**, it is reasonable to **omit antithrombotic therapy**.	IIa	B
With **CHA_2DS_2-VASc score $\geq$ 2** and **end-stage CKD (CrCl < 15 mL/min)** or on **hemodialysis**, it is reasonable to **prescribe warfarin** for oral anticoagulation.	IIa	B

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January CT, et al. *J Am Coll Cardiol*. 2014;64:2246-2280.

… Continuing to Look Back

Recommendations for prevention of thromboembolism in non-valvular AF	Class	Level
With **non-valvular AF and a CHA_2DS_2-VASc score of 1**, **no antithrombotic therapy** or treatment with an **oral anticoagulant or aspirin** may be considered.	IIb	C
With **moderate-to-severe CKD and CHA_2DS_2-VASc scores of $\geq$ 2, reduced doses of direct thrombin or factor Xa inhibitors** may be considered.	IIb	C
Following **coronary revascularization** in patients **with CHA_2DS_2-VASc score of $\geq$ 2**, it may be **reasonable to use clopidogrel concurrently with oral anticoagulants**, but **without aspirin**.	IIb	B
Direct thrombin, **dabigatran**, and factor Xa inhibitor, **rivaroxaban**, are **not recommended with AF and end-stage CKD or on hemodialysis** because of the lack of evidence from clinical trials regarding the balance of risks and benefits.	III	C
Direct thrombin inhibitor, **dabigatran**, **should not be used with a mechanical heart valve**.	III	B

January CT, et al. *J Am Coll Cardiol*. 2014;64:2246-2280.

Stroke Risk Assessment

	Risk factor	Score
C	Congestive heart failure/LV dysfunction	+1
H	Hypertension	+1
A_2	Age ≥75y	+2
D	Diabetes mellitus	+1
S_2	Stroke/TIA/TE	+2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	+1
A	Age 65-74y	+1
Sc	Sex category (i.e., female gender)	+1
	Maximum Score	9

CHA_2DS_2-VASc Score	Stroke Rate During 1 yr
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

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Lip GY, et al. *Chest*. 2010;137:263-272.
Lip GY, et al. *Stroke*. 2010;41:2731-2738.

Bleeding Risk Assessment

Letter	Clinical Characteristic	Definition	Points
H	Hypertension	Uncontrolled, SBP > 160 mm Hg	1
A	Abnormal renal or hepatic function	Renal: dialysis, transplant, SCr ≥ 2.6 mg/dL Hepatic: cirrhosis, bilirubin > 2 x ULN, LFTs > 3 x ULN	1 or 2
S	Stroke	H/o stroke, particularly lacunar	1
B	Bleeding	H/o bleeding or anemia	1
L	Labile INRs	Time in therapeutic range < 60%	1
E	Elderly	Age > 65 years	1
D	Drugs or alcohol	Drugs: concomitant antiplatelets (ASA, clopidogrel) or NSAIDs ETOH: ≥ 8 drinks per week	1 or 2

Pisters R, et al. *CHEST.* 2010;138:1093-1100.
Lip GY, et al. *J Am Coll Cardiol*. 2011;57(2):173-180.

HAS-BLED Score and Bleeding Risk

Score	Number of Patients	Number of Bleeds	Bleeds/100 Patient-Years
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0
7, 8, 9	0	0	0
	3071	48	1.56

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Pisters R, et al. *CHEST.* 2010;138:1093-1100.

Areas Addressed - Focused Update

- **Selecting an anticoagulant regimen – balancing risks and benefits**
- **Interruption and bridging anticoagulation**
- Percutaneous approach to occlude the LAA
- Cardiac surgery – LAA occlusion/excision
- **Prevention of thromboembolism**
- Ablation in HF
- **AF complicating ACS**
- Device detection of AF and atrial flutter
- Weight reduction in patients with AF

January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

Selecting an Anticoagulant Regimen

Recommendations – Balancing Risks and Benefits	COR	LOE
In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the **CHA_2DS_2-VASc score is recommended** for assessment of stroke risk.	I	B
For patients with AF and an elevated **CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women**, **oral anticoagulants are recommende***d*. Options include:		
Warfarin	I	A
Dabigatran, rivaroxaban, apixaban	I	B
Edoxaban	I	B-R
NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are **recommended over warfarin in NOAC-eligible patients** with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).	I	A
For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a **CHA_2DS_2-VASc score of 1 in men and 2 in women**, prescribing an **oral anticoagulant** to reduce thromboembolic stroke risk **may be considered**	IIb	C-LD
For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a **CHA_2DS_2-VASc score of 0 in men or 1 in women**, it is **reasonable to omit anticoagulant therapy**.	IIa	B

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January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

What's In a Name?

- Nonvalvular AF vs. Valvular AF
  - Source of confusion amongst clinicians
  - Variance among AF clinical trials of NOACs
  - Differing between North American and European AF guidelines
  - NVAF seems to imply the absence of valvular heart disease

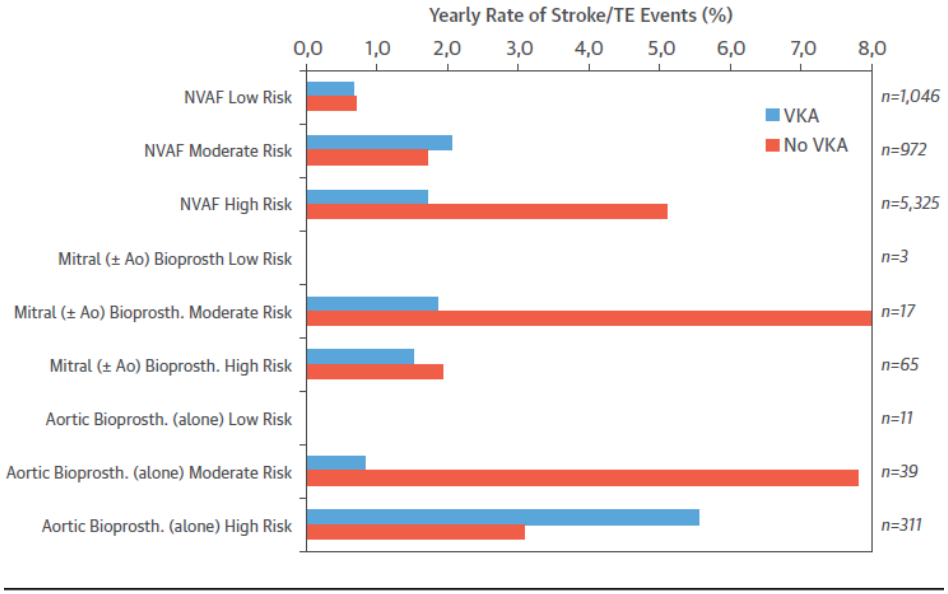
~~Nonvalvular AF~~

- ~20% of patients enrolled in NOAC trials had valvular defects
  - Mild mitral stenosis
  - Mitral regurgitation
  - Aortic stenosis
  - Aortic regurgitation
  - Tricuspid regurgitation
- Some trials enrolled patients s/p valve corrective procedures
  - Valve repair
  - Valvuloplasty
  - Bioprosthetic valves
- "Valvular AF" patients are excluded from NOAC therapy
  - Moderate-to-severe mitral stenosis
  - Mechanical heart valve

Granger CB, et al. *N Egl J Med*. 2011;365:981-992.
Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.
January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

Bio-Valve Patients - Utility of CHA_2DS_2-VASc

- Evaluate predictive value of CHA_2DS_2-VASc score in bio-valve pts
- Single-center, retrospective
- Included NVAF and bio-valve pts
- Reviewed and organized by CHA_2DS_2-VASc score and TE events
- Findings:
  - CHA_2DS_2-VASc score and age were independent predictors of TE risk
  - Low CHA_2DS_2-VASc score was associated with low TE risk +/- bio-valve



Low risk: CHA_2DS_2-VASc 0 in males, 1 in females; moderate: 1 in males, 2 in females; high: >1 in males, >2 in females. Ao = aortic; AF = atrial fibrillation; NVAF = nonvalvular atrial fibrillation; VKA = vitamin K antagonist.

Philippart R, et al. *J Am Coll Cardiol*. 2016;67:343-344.

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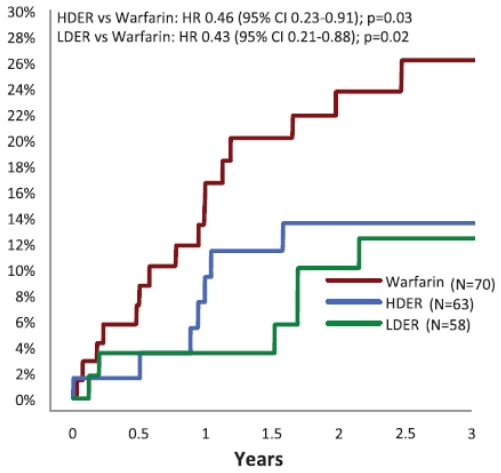
Bio-Valve Patients - Efficacy of NOACs

ENGAGE AF-TIMI 48

- 191 of 21,105 pts enrolled in main trial had bio-valve
- TTR for VKA was 68.9%
- Net clinical outcome: stroke/SEE, major bleeding, death



ARISTOTLE

- 18,201 pts enrolled: 104 had bio-valve and 52 had valve repair

	Apix (n=87)	VKA (n=69)	p-value
Stroke/SE	2.77 (4)	1.64 (2)	0.53
Major bleed	5.87 (7)	6.44 (7)	0.82
Death	4.61 (7)	4.79 (6)	0.98
Net	11.9 (16)	11.29 (13)	0.9

Carnicelli AP, et al. *Circulation*. 2017;135:1273-1275.
Pokorney SD, et al. *Clin Cardiol*. 2019 March 24 (Epub ahead of print).

Interruption and Bridging Anticoagulation

Recommendations	COR	LOE
Bridging therapy with UFH or LMWH **is recommended for patients with AF and a mechanical heart valve** undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding.	I	C
For **patients with AF without mechanical heart valves** who require interruption or warfarin for procedures, decisions about **bridging therapy** (UFH and LMWH) should **balance the risks of stroke and bleeding** an the duration of time a patient will not be anticoagulated.	I	B-R
Idarucizumab is recommended for the **reversal of dabigatran** in the event of life-threatening bleeding or an procedure.	I	B-NR
Andexanet alfa can be useful for the **reversal of rivaroxaban and apixaban** in the event of life-threatening or uncontrolled bleeding.	IIa	B-NR

January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

Prevention of Thromboembolism

Recommendations	COR	LOE
For patients with **AF or atrial flutter of 48 hours' duration or longer, or** when the duration of AF is **unknown, anticoagulation** with warfarin, a factor Xa inhibitor, or direct thrombin inhibitor **is recommended for at least 3 weeks before and at least 4 weeks after cardioversion, regardless of the CHA_2DS_2-VASc score** or the method used to restore sinus rhythm.	I	B-R
For patients with **AF or atrial flutter of less than 48 hours' duration** with a **CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women**, administration of **anticoagulation** (UFH, a factor Xa inhibitor, a direct thrombin inhibitor) **is reasonable as soon as possible** before cardioversion, followed by **long-term anticoagulation therapy**.	IIa	B
For patients with **AF or atrial flutter of less than 48 hours' duration** with a **CHA_2DS_2-VASc score of 0 in men or 1 in women**, administration of **anticoagulation** (UFH, a factor Xa inhibitor, a direct thrombin inhibitor), **versus no anticoagulant therapy, may be considered** before cardioversion, **without the need for postcardioversion oral anticoagulation**.	IIb	B-NR

January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

AF Complicating ACS

Recommendations	COR	LOE
For **patients with ACS and AF** at increased risk of systemic thromboembolism (based on **CHA_2DS_2-VASc risk score of 2 or greater**), **anticoagulation is recommended** unless the bleeding risk exceeds the expected benefit.	I	B-R
If **triple therapy** (oral anticoagulant, aspirin, and $P2Y_{12}$ inhibitor) is prescribed for patients with AF at increased risk of stroke who have **undergone PCI with stenting for ACS**, it is reasonable to **choose clopidogrel in preference to prasugrel**.	IIa	B-NR
In **patients with AF** at increased risk of stroke **who have undergone PCI with stenting for ACS**, **double therapy with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist is reasonable** to reduce the risk of bleeding as compared with triple therapy.	IIa	B-R
In **patients with AF** at increased risk of stroke **who have undergone PCI with stenting for ACS**, **double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and low-dose rivaroxaban (15 mg daily) is reasonable** to reduce the risk of bleeding as compared with triple therapy.	IIa	B-R
In **patients with AF** at increased risk of stroke **who have undergone PCI with stenting for ACS, double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable** to reduce the risk of bleeding as compared with triple therapy.	IIa	B-R
If triple therapy is prescribed **for patients with AF** who are at increased risk of stroke and **who have undergone PCI with stenting for ACS**, a **transition to double therapy at 4 to 6 weeks** may be considered.	IIb	B-R

January CT, et al. *J Am Coll Cardiol*. 2019 January 21 (Epub ahead of print).

WOEST Trial

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

- Open-label, multicenter, randomized controlled trial that enrolled 573 adults receiving OAC and undergoing PCI
- Assigned to either clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy)
- Primary endpoint: any bleeding episode within 1 year of PCI
- Secondary endpoint: composite of death, MI, stroke, TVR, and stent thrombosis

Dewilde WJM, et al. *Lancet*. 2013;381:1107-1115.

WOEST Trial - Primary Endpoint

	Double therapy (n=297)	Triple Therapy (n=284)	Hazard ratio (95% CI)	p-value
Any bleeding event	54 (19.4%)	126 (44.4%)	0.36 (0.26-0.5)	<0.0001
TIMI major	9 (3.2%)	16 (5.6%)	0.56 (0.25-1.27)	0.159
TIMI major/minor	39 (14%)	89 (31.3%)	0.4 (0.27-0.58)	<0.0001
GUSTO severe	4 (1.4%)	10 (3.5%)	0.4 (0.12-1.27)	0.119
GUSTO severe/mod	15 (5.4%)	35 (12.3%)	0.42 (0.23-0.76)	0.003
BARC 3	18 (6.5%)	36 (12.7%)	0.49 (0.28-0.86)	0.011
BARC 2+3	40 (14.3%)	90 (31.7%)	0.4 (0.28-0.58)	<0.0001
Any transfusion	11 (3.9%)	27 (9.5%)	0.39 (0.17-0.84)	0.011

Dewilde WJM, et al. *Lancet*. 2013;381:1107-1115.

WOEST Trial - Secondary Endpoints

	Double therapy (n=297)	Triple Therapy (n=284)	Hazard ratio (95% CI)	p-value
Composite	31 (11.1%)	50 (17.6%)	0.6 (0.38-0.94)	0.025
Death, all-cause	7 (2.5%)	18 (6.3%)	0.39 (0.16-0.93)	0.027
Death, cardiac	3 (1.1%)	7 (2.5%)	0.43 (0.11-1.66)	0.207
MI	9 (3.2%)	13 (4.6%)	0.69 (0.29-1.6)	0.382
TVR	20 (7.2%)	19 (6.7%)	1.05 (0.56-1.97)	0.876
Stroke, ischemic	2 (0.7%)	8 (2.8%)	0.25 (0.05-1.17)	0.056
Stroke, hemorrhagic	1 (0.4%)	0	NA	0.321
Stent thrombosis	4 (1.4%)	9 (3.2%)	0.44 (0.14-1.44)	0.165

Dewilde WJM, et al. *Lancet*. 2013;381:1107-1115.

PIONEER AF-PCI Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

- Open-label, multicenter, controlled trial of 2124 patients with nonvalvular AF who had undergone PCI with stenting
- Patients randomized in a 1:1:1 ratio
  - Rivaroxaban 15 mg daily + $P2Y_{12}$ inhibitor for 12 months (**group 1**)
  - Rivaroxaban 2.5 mg BID + DAPT for 1, 6, or 12 months (**group 2**)
  - VKA + DAPT for 1, 6, or 12 months (**group 3**)
- Primary safety endpoint: clinically significant bleeding
- Secondary efficacy endpoints: MACE, stent thrombosis

Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.

PIONEER AF-PCI - Primary Endpoint

	Group 1 (n=696)	Group 2 (n=706)	Group 3 (n=697)	Group 1 vs. Group 3	Group 2 vs. Group 3
Clinically significant bleeding	109 (16.8%)	117 (18%)	167 (26.7%)	$p < 0.001$	$p < 0.001$
Major	14 (2.1%)	12 (1.9%)	20 (3.3%)	$p = 0.23$	$p = 0.11$
Minor	7 (1.1%)	7 (1.1%)	13 (2.2%)	$p = 0.14$	$p = 0.13$
Required medical attention	93 (14.6%)	102 (15.8%)	139 (22.6%)	$p < 0.001$	$p = 0.002$

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Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.

PIONEER AF-PCI - Secondary Endpoints

	Group 1 (n=694)	Group 2 (n=704)	Group 3 (n=657)	Group 1 vs. Group 3	Group 2 vs. Group 3
MACE	41 (6.5%)	36 (5.6%)	36 (6%)	p = 0.75	p = 0.76
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	p = 0.52	p = 0.66
MI	19 (3%)	17 (2.7%)	21 (3.5%)	p = 0.62	p = 0.37
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	p = 0.89	p = 0.53
Stent thrombosis	5 (0.8%)	6 (0.9%)	4 (0.7%)	p = 0.79	p = 0.57

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Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.

RE-DUAL PCI Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

- Open-label, multicenter, controlled trial of 2725 patients with AF who had undergone PCI
- Patients were randomized one of the following:
  - Dabigatran 150 mg BID + $P2Y_{12}$ inhibitor and no ASA (150-mg dual-therapy group)
  - Dabigatran 110 mg BID + $P2Y_{12}$ inhibitor and no ASA (110-mg dual-therapy group)
  - VKA + DAPT (triple-therapy group)
- Primary safety endpoint: major or clinically significant bleeding
- Composite efficacy endpoints: thromboembolic events, death, unplanned TVR

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Cannon CP, et al. *N Engl J Med*. 2017;377:1513-1524.

RE-DUAL PCI - Primary Endpoint

	150-mg group (n=763)	Triple therapy (n=764)		110-mg group (n=981)	Triple therapy (n=981)	
Major / clinically relevant	154 (20.2%)	196 (25.7%)	p = 0.002	151 (15.4%)	264 (26.9%)	p < 0.001
ISTH major	43 (5.6%)	64 (8.4%)	p = 0.02	49 (5%)	90 (9.2%)	p < 0.001
Total bleeding	254 (33.3%)	316 (41.1%)	p < 0.001	266 (27.1%)	421 (42.9%)	p < 0.001
ICH	1 (0.1%)	8 (1%)	p = 0.047	3 (0.3%)	10 (1%)	p = 0.06

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Cannon CP, et al. *N Engl J Med*. 2017;377:1513-1524.

RE-DUAL PCI - Secondary Endpoints

	150-mg group (n=763)	Triple therapy (n=764)		110-mg group (n=981)	Triple therapy (n=981)	
Composite	90 (11.8%)	98 (12.8%)	p = 0.44	149 (15.2%)	131 (13.4%)	p = 0.3
Death	30 (3.9%)	35 (4.6%)	p = 0.44	55 (5.6%)	48 (4.9%)	p = 0.56
MI	26 (3.4%)	22 (2.9%)	p = 0.61	44 (4.5%)	29 (3%)	p = 0.09
Stroke	9 (1.2%)	8 (1%)	p = 0.85	17 (1.7%)	13 (1.3%)	p = 0.48
Stent thrombosis	7 (0.9%)	7 (0.9%)	p = 0.98	15 (1.5%)	8 (0.8%)	p = 0.15

Cannon CP, et al. *N Engl J Med*. 2017;377:1513-1524.

AUGUSTUS Trial

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

- Multicenter, two-by-two factorial, randomized evaluation of patients with AF who had an ACS or had undergone PCI and were on a $P2Y_{12}$ inhibitor
- Two randomization factors:
  - Apixaban 5 mg BID or VKA (open-label)
  - Aspirin 81 mg daily or placebo (double-blind)
- Primary endpoint: major or clinically relevant bleeding
- Secondary endpoints: composites of death, hospitalization, ischemic events

Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).

AUGUSTUS - Apixaban vs. VKA

Outcome	Apixaban	Vitamin K Antagonist	Hazard Ratio (95% CI)	P Value for Superiority
Anticoagulation-regimen comparison				
ISTH major or clinically relevant nonmajor bleeding†				
No. of patients with event/total no. (%)	241/2290 (10.5)	332/2259 (14.7)	—	—
Event rate per 100 patient-yr	24.7	35.8	0.69 (0.58–0.81)	<0.001
Death or hospitalization				
No. of patients with event/total no. (%)	541/2306 (23.5)	632/2308 (27.4)	—	—
Event rate per 100 patient-yr	57.2	69.2	0.83 (0.74–0.93)	0.002
Death or ischemic event‡				
No. of patients with event/total no. (%)	154/2306 (6.7)	163/2308 (7.1)	—	—
Event rate per 100 patient-yr	14.3	15.3	0.93 (0.75–1.16)	NS

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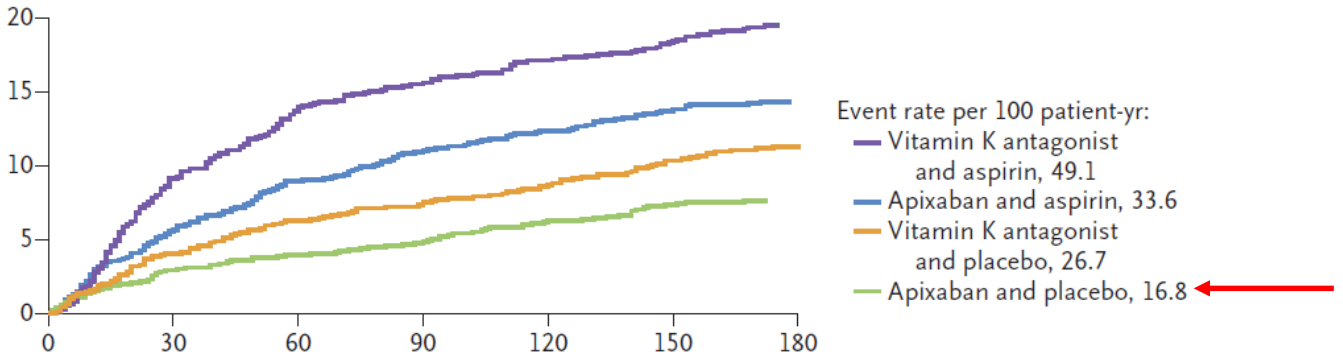
Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).

AUGUSTUS - Aspirin vs. Placebo

Antiplatelet-regimen comparison	Aspirin	Placebo		
ISTH major or clinically relevant nonmajor bleeding				
No. of patients with event/total no. (%)	367/2277 (16.1)	204/2279 (9.0)	—	—
Event rate per 100 patient-yr	40.5	21.0	1.89 (1.59–2.24)	<0.001
Death or hospitalization§				
No. of patients with event/total no. (%)	604/2307 (26.2)	569/2307 (24.7)	—	—
Event rate per 100 patient-yr	65.7	60.6	1.08 (0.96–1.21)	NS
Death or ischemic event				
No. of patients with event/total no. (%)	149/2307 (6.5)	168/2307 (7.3)	—	—
Event rate per 100 patient-yr	13.9	15.7	0.89 (0.71–1.11)	NT

Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).

AUGUSTUS - Intervention Combination Comparison



	Apixaban and ASA N=1145	Apixaban and Placebo N=1143	VKA and ASA N=1123	VKA and Placebo N=1126
ISTH major or CRNM bleeding	158/1145 (13.8%)	84/1143 (7.3%)	210/1123 (18.7%)	123/1126 (10.9%)
Event rate per 100 patient-years	33.6	16.8	49.1	26.7
ISTH major bleeding	48/1145 (4.2%)	23/1143 (2.0%)	62/1123 (5.5%)	44/1126 (3.9%)
Event rate per 100 patient-years	9.7	4.5	13.3	9.2
ISTH CRNM bleeding	118/1145 (10.3%)	62/1143 (5.4%)	158/1123 (14.1%)	88/1126 (7.8%)
Event rate per 100 patient-years	24.9	12.3	36.4	19.0

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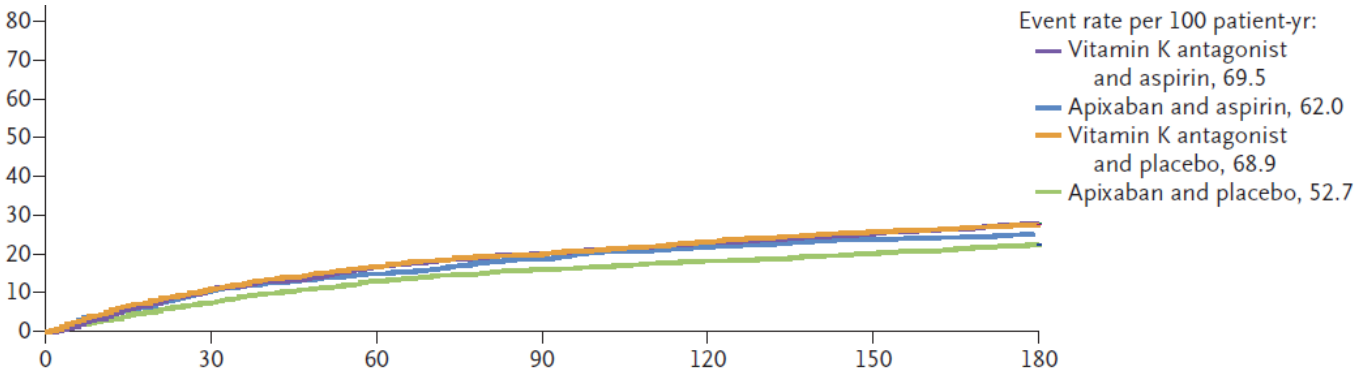
Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).

AUGUSTUS - Intervention Combination Comparison



	Apixaban and ASA N=1153	Apixaban and Placebo N=1153	VKA and ASA N=1154	VKA and Placebo N=1154
All-cause death or hospitalization	287/1153 (24.9%)	254/1153 (22.0%)	317/1154 (27.5%)	315/1154 (27.3%)
Event rate per 100 patient-years	62.0	52.7	69.5	68.9
Hospitalization	278/1153 (24.1%)	240/1153 (20.8%)	307/1154 (26.6%)	300/1154 (26.0%)
Event rate per 100 patient-years	60.0	49.8	67.3	65.6
Death	38/1153 (3.3%)	39/1153 (3.4%)	34/1154 (2.9%)	40/1154 (3.5%)
Event rate per 100 patient-years	6.9	7.1	6.2	7.3
All-cause death or ischemic events	71/1153 (6.2%)	72/1153 (6.2%)	66/1154 (5.7%)	84/1154 (7.3%)
Event rate per 100 patient-years	13.2	13.3	12.3	15.7

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Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).

Does $P2Y_{12}$ Inhibitor Selection Matter?

- Triple Therapy:
  - Consensus is to use clopidogrel for most patients
- Double Therapy:
  - Clopidogrel most used in AF/ACS trials:
    - PIONEER AF-PCI – 94.4% clopidogrel, 4.3% ticagrelor, 1.3% prasugrel
    - RE-DUAL PCI – 88% clopidogrel, 12% ticagrelor (no prasugrel)
    - AUGUSTUS – 92.7% clopidogrel, 6.2% ticagrelor, 1.1% prasugrel
  - RE-DUAL PCI clopidogrel vs. ticagrelor analysis:
    - ISTH Major/CRNM bleeding 26.3% with ticagrelor and 20.1% with clopidogrel (HR 1.35, 95% CI 1.05-1.72)
    - Death/TE/unplanned revasc 18.7% with ticagrelor and 12.9% with clopidogrel (HR 1.34, 95% CI 1.00-1.82)

Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.
Cannon CP, et al. *N Engl J Med*. 2017;377:1513-1524.
Lopes RD, et al. *N Engl J Med*. 2019 March 17 (Epub ahead of print).
Oldgren J, et al. *Eur Heart J*. 2019 January 23 (Epub ahead of print).

Summary

- Balance risks and benefits
  - CHA_2DS_2-VASc & HAS-BLED
- NOACs are recommended over VKA
- Anticoagulants > Antiplatelets
- Valvular conditions where VKA is required
- Double therapy > Triple therapy
- Need more RCTs (combinations, durations, etc.)

Post-Assessment Question 1

58 year old female with history of controlled hypertension.

Which treatment do you recommend?

A. Aspirin 325 mg
B. Aspirin 81 mg and clopidogrel 75 mg
C. Warfarin target INR 2-3
D. Apixaban 5 mg BID

Post-Assessment Question 2

67 year old male with history of T2 diabetes, HTN and bioprosthetic aortic valve.

Which treatment do you recommend?

A. Aspirin 325 mg
B. Aspirin 81 mg and prasugrel 10 mg
C. Warfarin target INR 2-3
D. Edoxaban 60 mg

Post-Assessment Question 3

62 year old female with history of obesity, hyperlipidemia, HTN and mechanical mitral valve.

Which treatment do you recommend?

A. Aspirin 325 mg and prasugrel 10 mg
B. Warfarin target INR 2.5-3.5
C. Edoxaban 60 mg
D. Rivaroxaban 15 mg BID

Post-Assessment Question 4

66 year old male with history, hyperlipidemia, HTN, s/p ACS and PCI with a single DES to his LAD 2 weeks ago.

Which treatment do you recommend?

A. Aspirin 81 mg, ticagrelor 90 mg BID
B. Aspirin 81 mg, clopidogrel 75 mg, warfarin target INR 2-3
C. Aspirin 81 mg, apixaban 5 mg BID
D. Clopidogrel 75 mg, rivaroxaban 15 mg

Post-Assessment Question 5

46 year old female with no past medical history, goes into paroxysmal AF during a hysterectomy operation.

Which treatment do you recommend?

A. Nothing
B. Aspirin 81 mg
C. Aspirin 81 mg, clopidogrel 75
D. Warfarin target INR 2-3
E. Dabigatran 150 mg BID

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(Don't You) Forget About Warfarin

Direct Oral Anticoagulant Use in Special Populations

Join my PollEverywhere by texting BUNNELL123 to 22333

Kristen Bunnell, PharmD, BCCCP

May 21, 2019

GMCCP Spring CE Event

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Objectives

- Compare and contrast anticoagulation-related recommendations in the 2018 American College of Chest Physicians guidelines and 2019 American Heart Association, American College of Cardiology, and Heart Rhythm Society update to previous guidelines for the management of atrial fibrillation.
- Describe the evidence for safety and efficacy of direct oral anticoagulants (DOACs) in the setting of renal dysfunction or pregnancy.

Presentation Outline

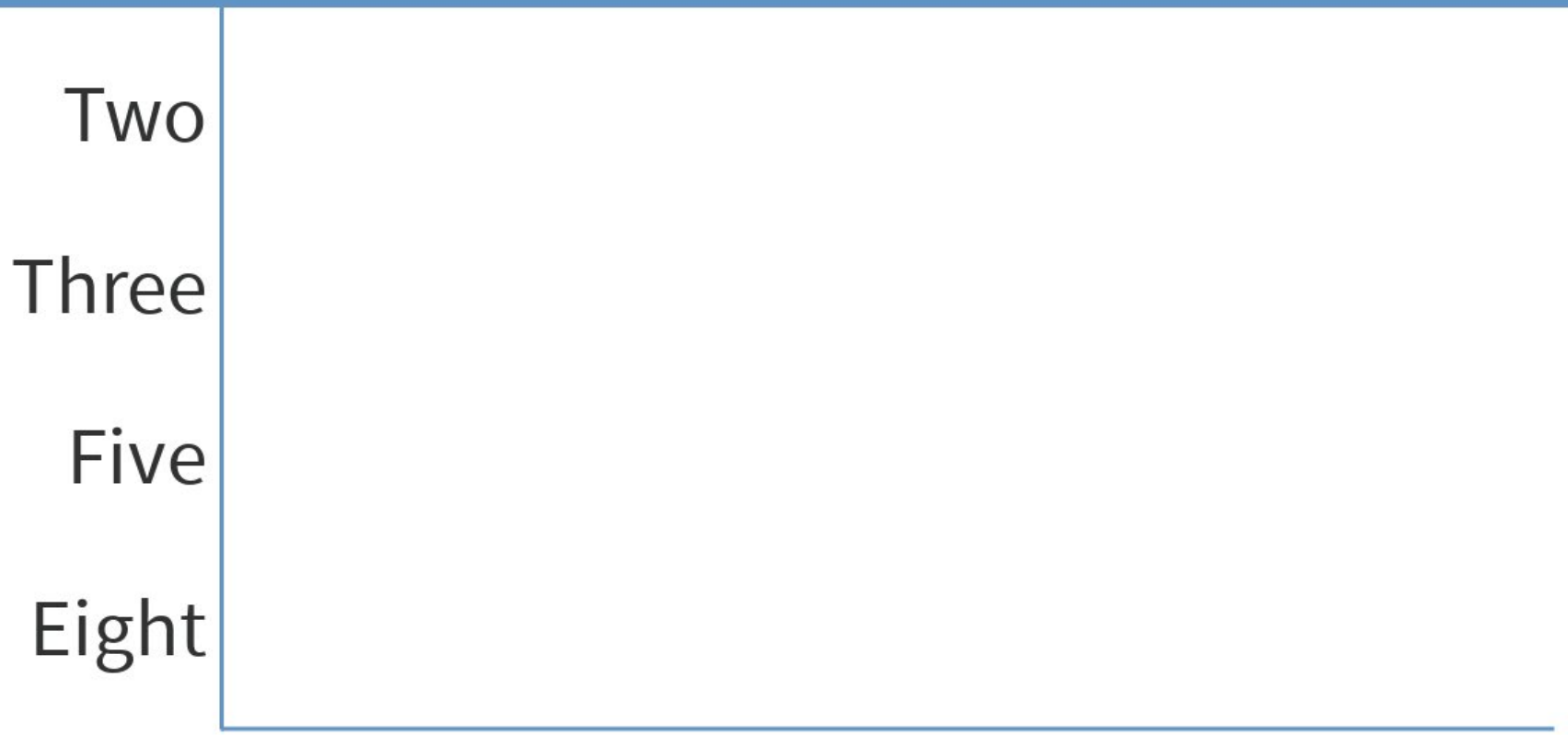
- Epidemiology of stroke in atrial fibrillation
- Anticoagulation guideline update
- DOAC use in renal dysfunction
- DOAC use in pregnant women
- Conclusions

Poll Everywhere

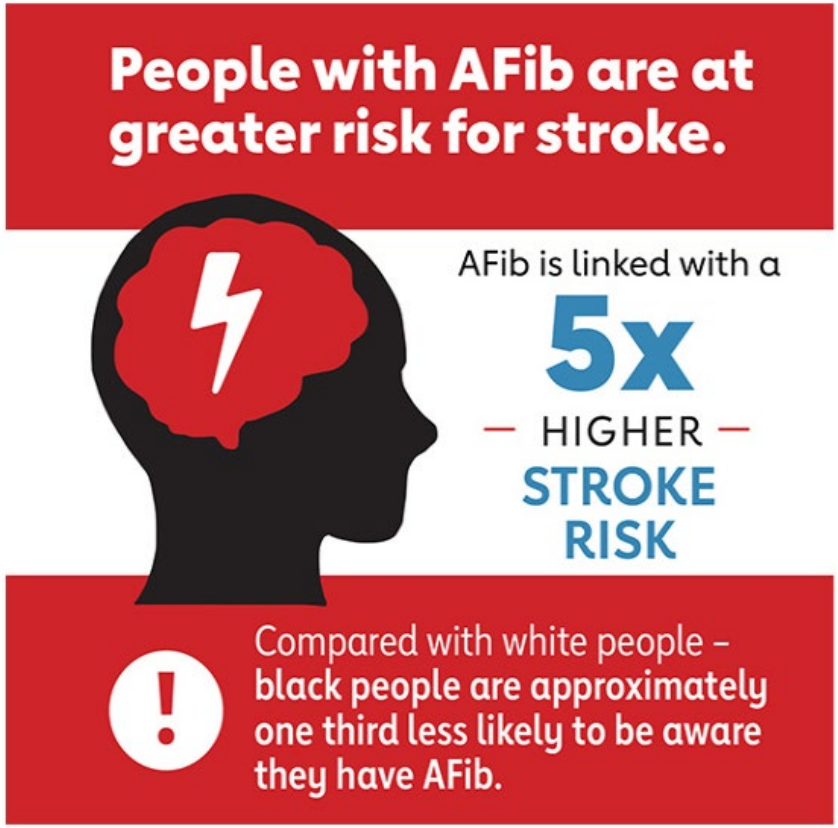
Atrial fibrillation increases a person's risk of stroke by ___ times compared to a person without atrial fibrillation.

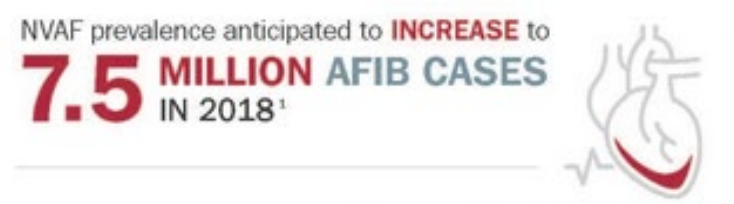
a. Two
b. Three
c. Five
d. Eight

Atrial fibrillation increases a person's risk of stroke by ___ times compared to a person without atrial fibrillation.



Epidemiology of stroke in atrial fibrillation (AF)





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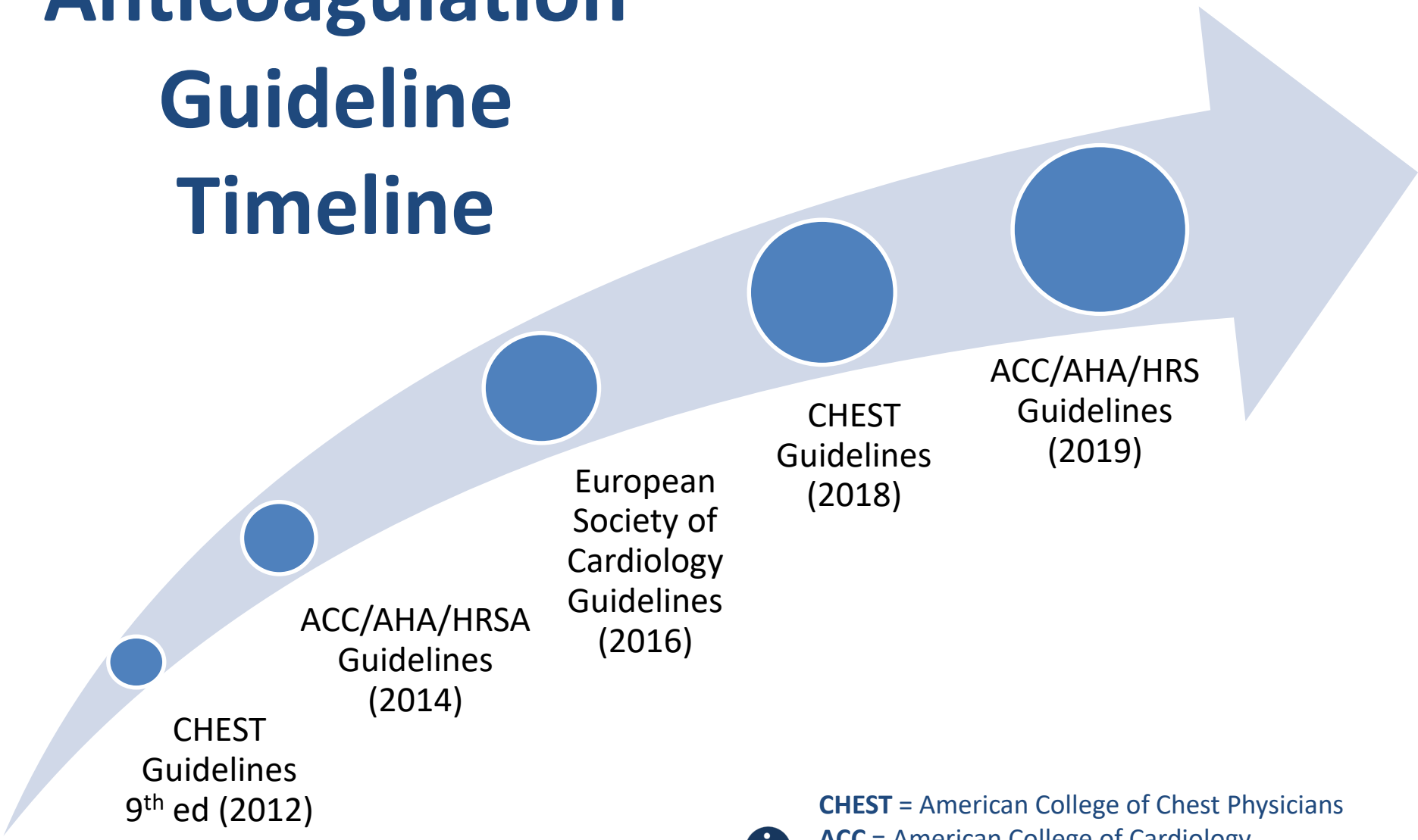
Images from: The American Heart Association www.heart.org &
Preventive Cardiovascular Nurses Association https://pcna.net

Anticoagulation Guideline Timeline



CHEST = American College of Chest Physicians
ACC = American College of Cardiology
AHA = American Heart Association
HRS = Heart Rhythm Society

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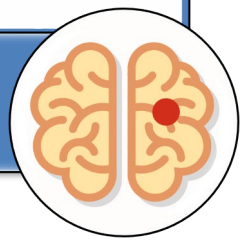
Scoring Tools for Assessing the Risk of Stroke & Bleeding in AF

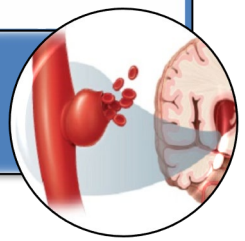
- $CHADS_2$
- CHA_2DS_2- VASc

STROKE



- HAS-BLED
- ATRIA
- $HEMORR_2HAGES$

BLEEDING



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Scoring Tools for Assessing the Risk of Stroke & Bleeding in AF

- $CHADS_2$
- **CHA_2DS_2- VASc**

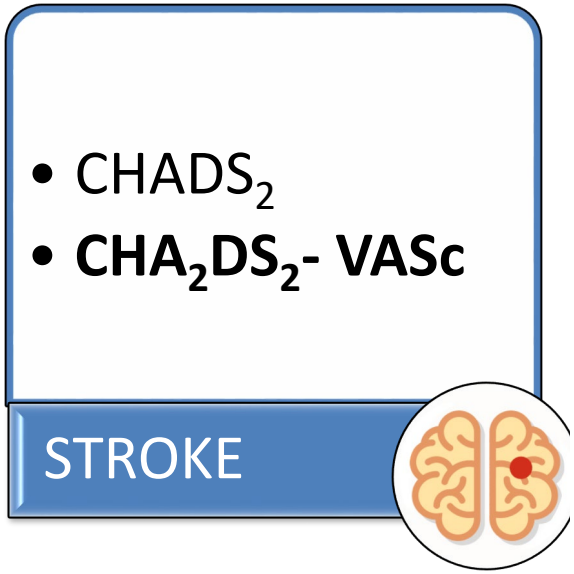

Figure 2

CHA_2DS_2-VASc Stroke Risk Scoring

Letter	Clinical Characteristic	Points
C	Congestive heart failure / LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
V	Vascular disease	1
A	Age 65 – 74	1
Sc	Sex category (i.e. female sex)	1
	Maximum CHA_2DS_2-VASc score	9

	CHA_2DS_2-VASc Score		Annual Adjusted Stroke Rate
LOW RISK 0 POINTS	0	=	0%
INTERMEDIATE RISK 2 POINTS	1	=	1.3%
	2	=	2.2%
	3	=	3.2%
	4	=	4.0%
HIGH RISK 2 OR MORE POINTS	5	=	6.7%
	6	=	9.8%
	7	=	9.6%
	8	=	6.7%
	9	=	15.2%

LV = left ventricular; TIA = transient ischemic attack; TE = thromboembolism; vascular disease = prior myocardial infarction, peripheral artery disease, or aortic plaque

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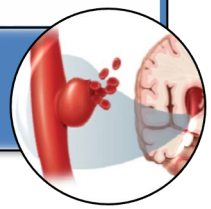
Image from: Atrial Fibrillation pocket guide. https://www.agingresearch.org

Scoring Tools for Assessing the Risk of Stroke & Bleeding in AF

- **HAS-BLED**
- ATRIA
- HEMORR$_2$HAGES

BLEEDING



Criteria		Poss. Point
Hypertension Uncontrolled hypertension (systolic BP > 160 mmHg)	Yes / No	+1
Abnormal renal or liver function **Renal:** Chronic dialysis, renal transplant, serum creatinine ≥ 2.3 mg/dL (200 µmol/L) **Liver:** Cirrhosis, bilirubin > 2x UNL with AST/ALT/AP > 3x UNL	None	+1 or +2
Stroke	Yes / No	+1
Bleeding Bleeding history or predisposition (anemia)	Yes / No	+1
Labile INR Therapeutic time in range < 60%	Yes / No	+1
Elderly Greater than 65 years old	Yes / No	+1
Drugs or alcohol **Drugs** - other antiplatelet agents or NSAIDs **Alcohol** - more than 8 drinks per week	None	+1 or +2

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Image from: Kane S. www.clincalc.com

CHEST Guidelines 2012 vs 2018

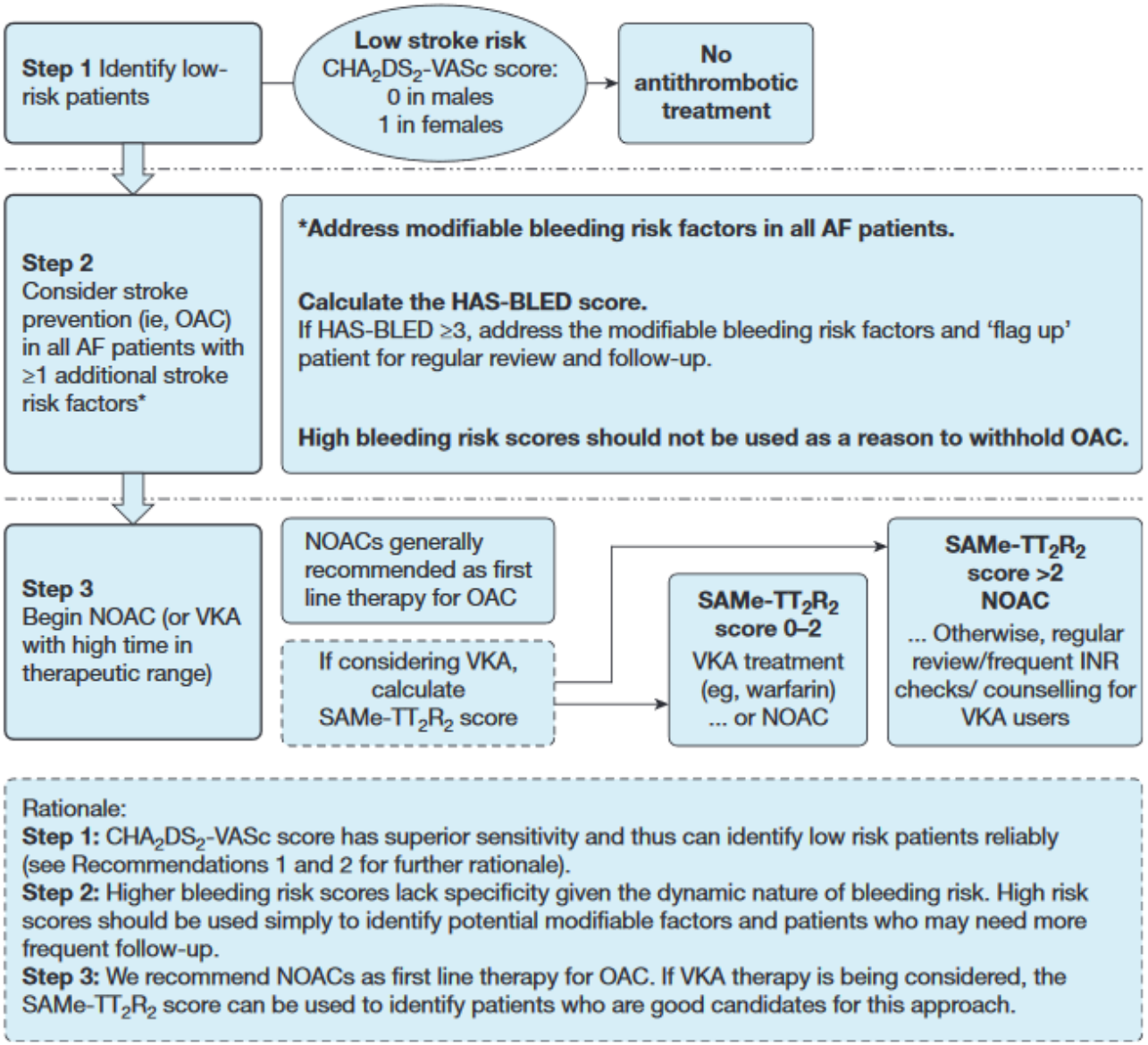
Parameter	2012	2018
Scoring Tool	$CHADS_2$	CHA_2DS_2VASc
Recommendations for lowest risk of stroke	$CHADS_2$= 1 Recommend OAC	CHA_2DS_2VASc= 1 ♂ or 2 ♀ Recommend OAC
Role of DOACs	Dabigatran over warfarin (weak/moderate)	DOACs over warfarin (strong/moderate)
Bleeding stratification	No specific recommendation	Recommend HAS-BLED: a score ≥ 3 warrants more frequent follow-up
Role of antiplatelets	ASA for $CHADS_2$= 0 (option if patient prefers antithrombotic) ASA + clopidogrel for intermediate-high risk patients who choose not to take OAC	No monotherapy, regardless of stroke risk

Grading= (recommendation strength/evidence strength)

ℹ OAC= oral anticoagulant

Lip GYH, et al. *CHEST* 2018;154(5):1121-1201.
You JJ, et al. *CHEST* 2012;141(2)(Suppl):e531S-e575S.

CHEST Guideline Algorithm 2018



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

ACC/AHA Guidelines 2014 vs 2019

Parameter	2014	2019
Scoring Tool	CHA_2DS_2VASc	CHA_2DS_2VASc
Recommendations for lowest risk of stroke	CHA_2DS_2VASc= 1 No OAC or OAC or ASA	CHA_2DS_2VASc= 1  or 2  Consider OAC (weak/limited data)
Role of DOACs	DOACS (LOE moderate) or warfarin (LOE high)	DOACs over warfarin (strong\high)
Bleeding stratification	No specific recommendation	No specific recommendation
Role of antiplatelets	Can consider monotherapy for low risk patients	No specific recommendation (except for ACS patients)

Grading= (recommendation strength/evidence strength)

LOE= level of evidence

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January CT, et al. *JACC 20*14;64(21):e1-76.
January CT, et al. *JACC* 2019; doi: https://doi.org/10.1016/j.jacc.2019.01.011

Guideline Comparison- Major Differences- OLD NEWS

CHEST (ACCP) Guidelines 2012	ACC/AHA/HRS Guidelines 2014	European Society of Cardiology Guidelines 2016
• $CHADS_2$ • Recommend aspirin in low risk group • Suggest DOACs over warfarin (B)	• CHA_2DS_2-VASc • Warfarin has a higher level of evidence (A) than DOACs (B) • Recommend aspirin as an alternative for intermediate risk	• CHA_2DS_2-VASc (but do not consider female sex to be an independent risk factor) • Recommend DOACs over warfarin • Do not recommend aspirin in any scenario • Recommend calculating HAS-BLED score, but states that benefits of anticoagulation outweigh risks at almost any HAS-BLED score

CHEST 2012;141(2):(Suppl):e531S-e575S.
January CT, et al. *JACC 2014*;64(21):e1-76.
Kirchhof P, et al. *European Heart Journal* 2016;37:2893-2962.

Guideline Comparison- Major Differences

	CHEST (ACCP) Guidelines 2018	ACC/AHA/HRS Guidelines 2019	European Society of Cardiology 2016
SCORING TOOL	• CHA_2DS_2-VASc- do not consider female sex to be an independent risk factor	• CHA_2DS_2-VASc- do not consider female sex to be an independent risk factor	• CHA_2DS_2-VASc- do not consider female sex to be an independent risk factor
OAC THRESHOLD	• Recommend OAC for CHA_2DS_2-VASc ≥ 1 (men) and ≥ 2 (women)	• Recommend OAC for CHA_2DS_2-VASc ≥ 2 (men) and ≥ 3 (women) [consider for ≥ 1 (men), ≥ 2 (women)]	• Recommend OAC for CHA_2DS_2-VASc ≥ 2 (men) and ≥ 3 (women) [consider for ≥ 1 (men), ≥ 2 (women)]
DOACs?	• DOACs over warfarin	• DOACs over warfarin	• DOACs over warfarin
ASPIRIN	• Do not recommend antiplatelet alone in any scenario	• No recommendations about aspirin or HAS-BLED	• Do not recommend aspirin in any scenario
BLEEDING	• HAS-BLED score should guide patients who need closer monitoring and more frequent follow-up		• Recommend calculating HAS-BLED score

Kirchhof P, et al. *European Heart Journal* 2016;37:2893-2962.
Lip GYH, et al. *CHEST* 2018;doi: 10.1016/j.chest.2018.07.040
January CT, et al. *JACC* 2019; doi: https://doi.org/10.1016/j.jacc.2019.01.011

OAC= oral anticoagulant

Poll Everywhere

The most recent CHEST and ACC/AHA guidelines for anticoagulation of patients with nonvalvular atrial fibrillation recommend that when oral anticoagulation is warranted for patients without severe renal dysfunction:

a. Direct oral anticoagulants (DOACs) and warfarin are equally recommended
b. DOACs are recommended over warfarin
c. Warfarin is recommended over the DOACs
d. Warfarin is recommended after a therapeutic failure on DOACs

The most recent CHEST and ACC/AHA guidelines for anticoagulation of patients with nonvalvular atrial fibrillation recommend that when oral anticoagulation is warranted for patients without severe renal dysfunction:

Direct oral anticoaglants (DOACs) and warfarin are equally recommended

DOACs are recommended over warfarin

Warfarin is recommended over the DOACs

Warfarin is recommended after a therapeutic failure on DOACs

DOAC Use in Renal Dysfunction

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DOAC Pharmacokinetics

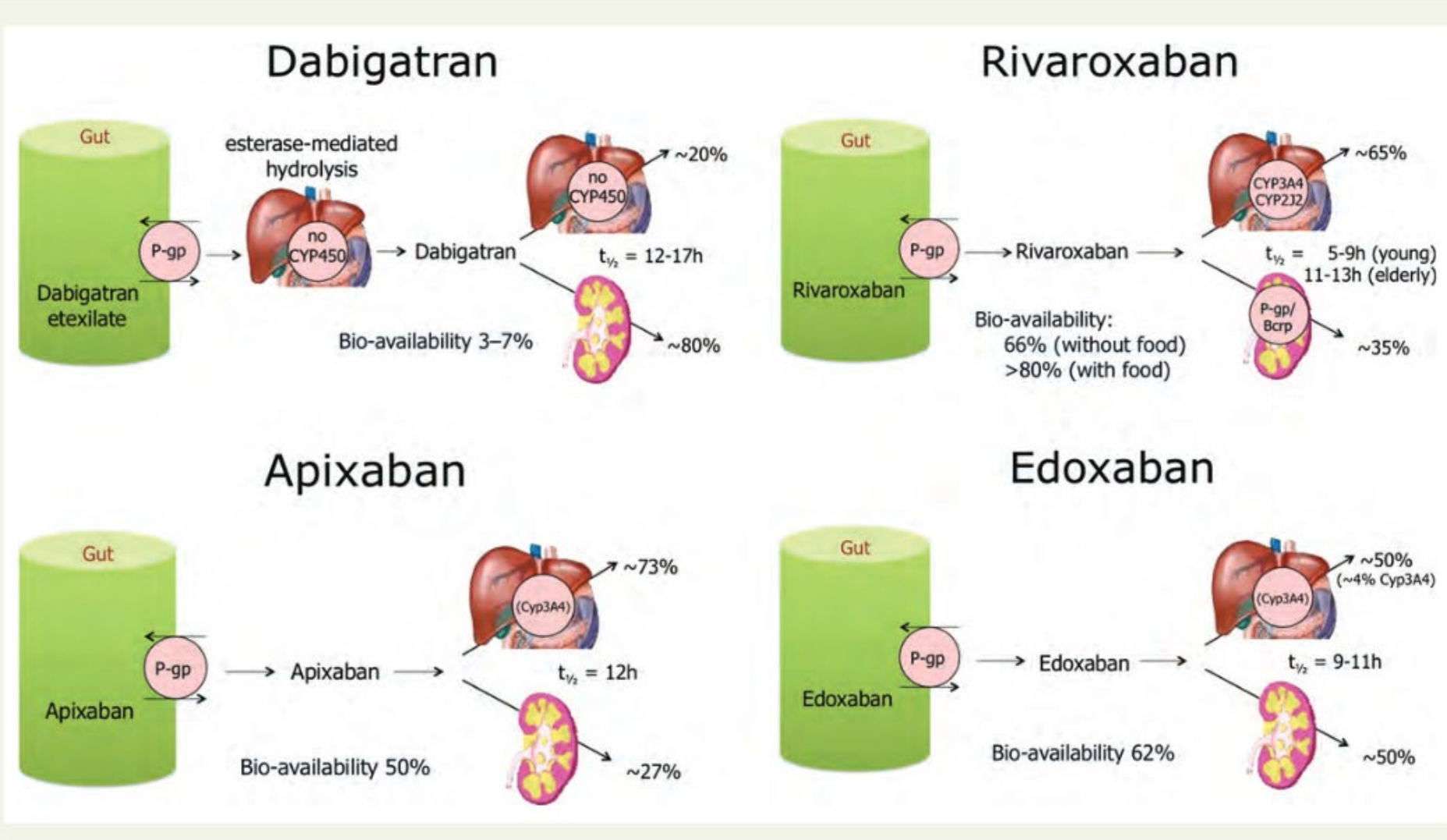


Image from: Heidbuchel H, et al. *Europace* 2013; 15:625-651

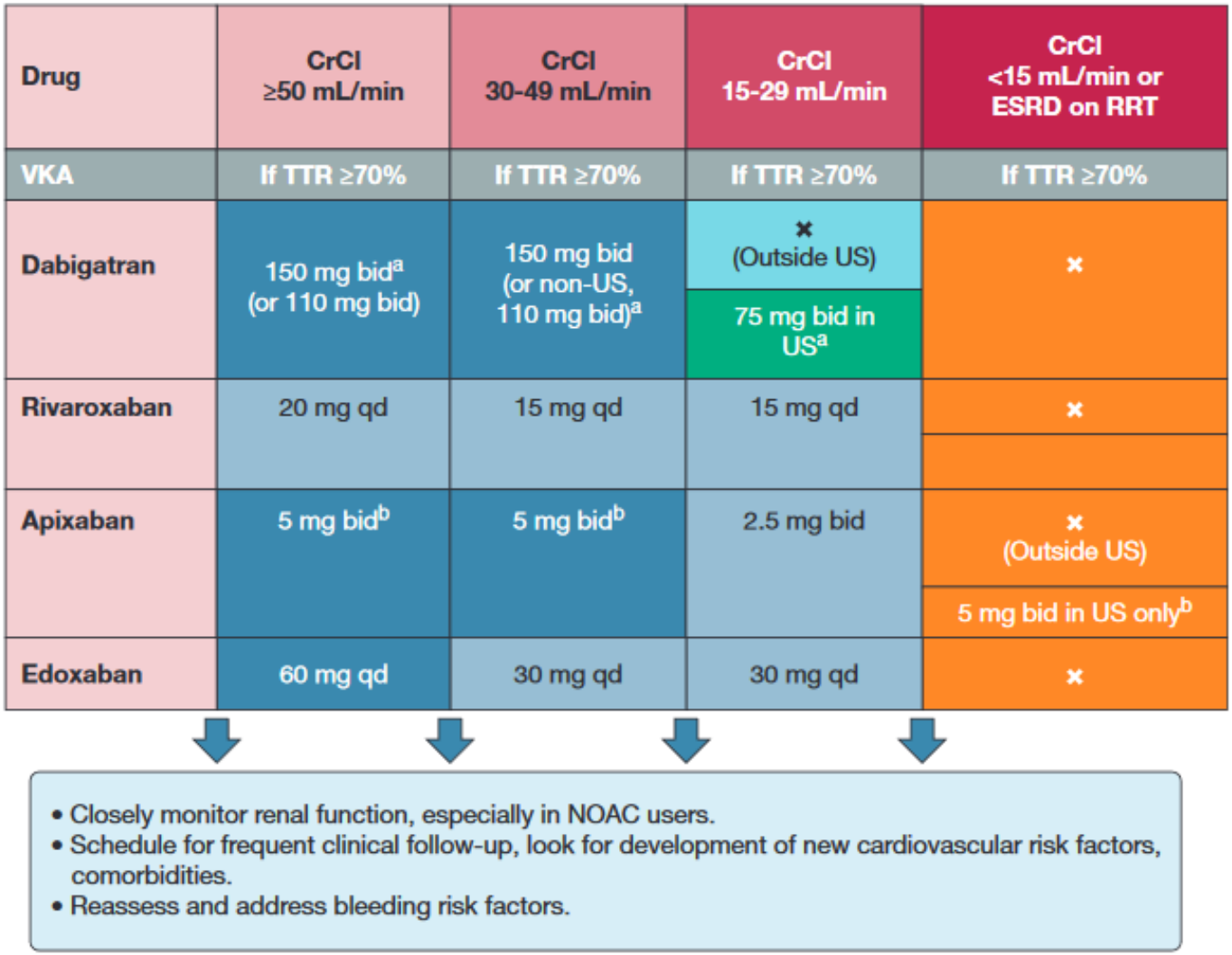
Guideline Statements: Renal

- **CHEST Guidelines (2018)**
  - **Mild CKD** (CrCl 60-89 mL/min)- DOACs over warfarin (weak/very low)
  - **Moderate CKD** (CrCl 30-59 mL/min)- DOACS (label-adjusted) or warfarin (weak/ very low)
  - **Severe non-dialysis** (CrCl 15-30 mL/min)- DOACS (label-adjusted) or warfarin (ungraded)
    - Rivaroxaban 15 mg PO daily
    - Apixaban 2.5 mg PO BID
    - Edoxaban 30 mg PO daily
    - Dabigatran 75 mg PO BID
  - **End-stage renal disease** (CrCl < 15 mL/min, dialysis) – warfarin (ungraded)

Grading= (recommendation strength/evidence strength)

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

CHEST Guideline Algorithm 2018



b. Use 2.5 mg BID if 2 of 3 of the following are present: age > 80 years, weight < 60 kg, or serum creatinine > 1.5 mg/dL

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

Guideline Statements: Renal

- **ACC/AHA Guidelines (2019)**
  - **Moderate-to-severe** (CrCl 15-30 mL/min or < 50 mL/min for rivaroxaban or edoxaban)- reduced doses of DOACs may be considered (weak/moderate randomized)
  - **End-stage renal disease** (CrCl < 15 mL/min, dialysis) – warfarin or apixaban for oral anticoagulation (weak/moderate non-randomized)
    - Dabigatran, rivaroxaban, edoxaban not recommended

Grading= (recommendation strength/evidence strength)

January CT, et al. *JACC* 2019; doi: https://doi.org/10.1016/j.jacc.2019.01.011

"Use of warfarin or apixaban might be reasonable in dialysis-dependent patients with AF, but further study is warranted"

ACC/AHA Guideline 2019

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January CT, et al. *JACC* 2019; doi: https://doi.org/10.1016/j.jacc.2019.01.011

DOACs in Renal Dysfunction

Drug	Manufacturer Recommendations	Clinical Trial Data
Dabigatran	AF: reduce 50% in CrCl 15-30 mL/min VTE: avoid CrCl < 30 mL/min	Excluded CrCl < 30 mL/min
Rivaroxaban	AF: reduce to 15 mg in CrCl 15-50 mL/min VTE: avoid CrCl < 30 mL/min	Excluded CrCl < 30 mL/min
Apixaban	AF: reduce 50% if 2 of the 3: Age ≥ 80 years, weight ≤ 60 kg, SCr ≥ 1.5 AF/VTE: no dose adjustment for ESRD	Excluded CrCl < 25 mL/min OR SCr > 2.5
Edoxaban	AF & VTE: reduce 50% in CrCl 15-50 mL/min	Excluded CrCl < 30 mL/min
Betrixaban	VTE: reduce 50% in CrCl 15-30 mL/mn	Excluded CrCl < 30 mL/min

AF = atrial fibrillation
VTE = venous thromboembolism
CrCl= creatinine clearance calculated with Cockcroft-Gault

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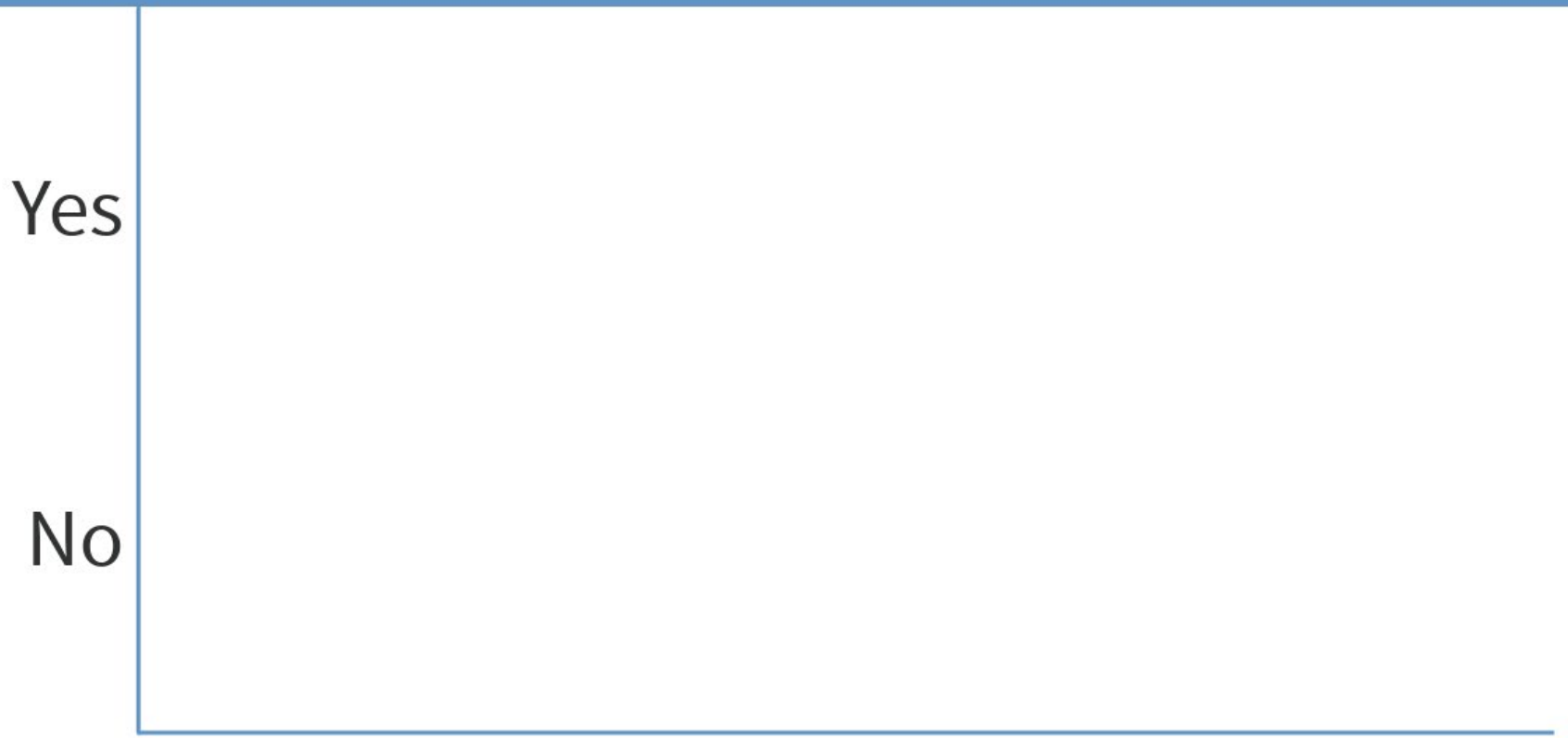
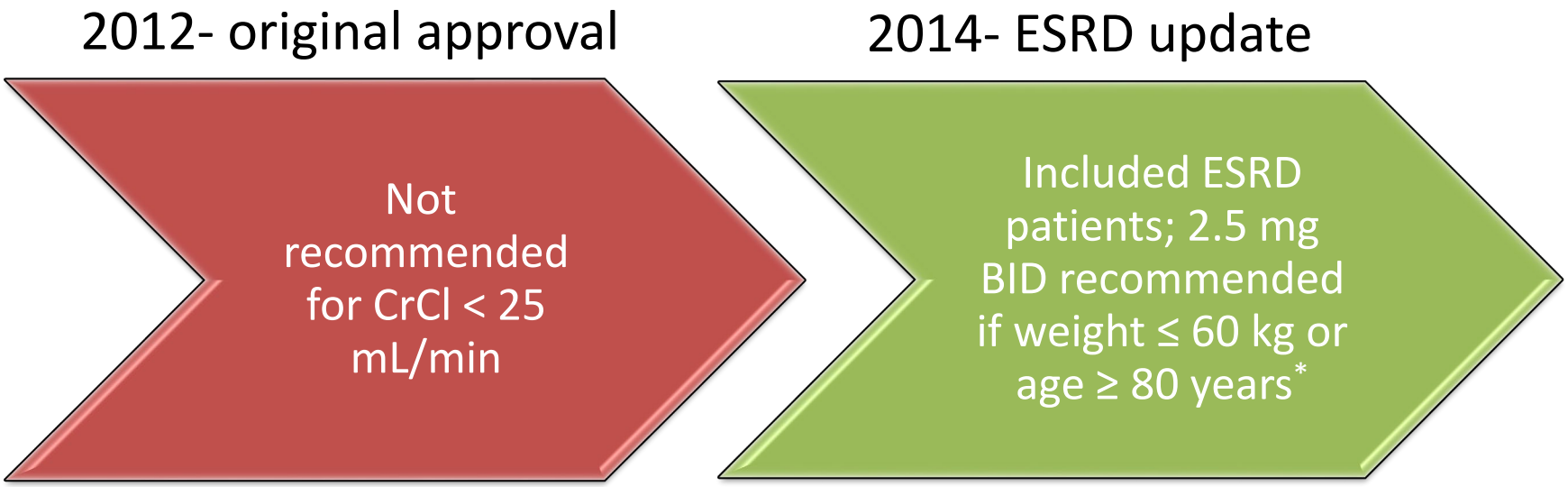
Slide recreated from 'DOAC in Renal Impairment- Manufacturer vs Data'- presentation by Sheley J, PharmD

Do prescribers at your institution prescribe apixaban for patients with end-stage renal disease (ESRD) who require dialysis?



A History of Apixaban Labeling in ESRD



* Based on pharmacokinetics data

Apixaban PK in ESRD: the data

Basis of the labelling change

- Open-label, parallel group single dose study in 8 subjects with ESRD on hemodialysis compared to 8 subjects with normal renal function
- Subjects received 5 mg doses

✓ Hemodialysis does not significantly remove apixaban

✓ $AUC_{0-\infty}$ was 36% higher in ESRD patients compared to those without renal dysfunction

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Wang X, et al. *J Clin Pharmacology* 2016;56:628-636.

Apixaban PK in ESRD: steady state data

- 7 ESRD patients with urine output < 200 mL/day
- Single dose and steady state pharmacokinetics
- Crossover study:
  - 2.5 mg PO BID x 8 days
  - 5 mg PO BID x 8 days
- Rich pharmacokinetic sampling on days 1 and 8

✓ Hemodialysis does not significantly remove apixaban

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Mavrakanas TA, et al. *J Am Soc Nephrol* 2017;(28):2241-2248.

Apixaban PK in ESRD: steady state data

Parameter	Steady-State 2.5 mg PO BID on Day 8	Steady-State 5 mg PO BID on Day 8	Reference (normal renal function)
AUC_{0-24} (ng-h/mL)	2019.7	6053.2	2100- 3370
C_{max} (ng/mL)	131.5	307.0	129- 171
Half-life (h)	7.5	17.4	8-15

Mavrakanas TA, et al. *J Am Soc Nephrol* 2017;(28):2241-2248.
Frost C, et al. *Br J Clin Pharmacol* 2013;76(5):776-786.

Dosage Adjustments Based Solely on Pharmacokinetic Data

Is this as crazy as it sounds?

FDA Guidance for Industry

- For drugs that are extensively renally eliminated, recommend a “full-design” pharmacokinetics study that includes subjects with mild-severe impairment
- A single-dose study is considered sufficient
- “Specific dosing recommendations are generally developed on the results of the stand-alone study that characterizes the relationship between creatinine clearance or eGFR and relevant PK parameters.”

FDA Briefing Document, Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, May 2019

Dosage Adjustments Based Solely on Pharmacokinetic Data

Has this ever backfired?

- Phase III trials comparing ceftazidime-avibactam (CAZ-AVI) + metronidazole to meropenem (RECLAIM I and II)
  - Clinical cure rates were lower in the CAZ-AVI group in patients with moderate renal impairment receiving 1.25 g q12h
- Phase III trial comparing ceftolozane-tazobactam (TOL-TAZ) to meropenem (ASPECT)
  - Clinical cure rates were lower in the TOL-TAZ group in patients with moderate renal impairment receiving

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Biddell MR. *Pharmacotherapy* 2018;38(12):1205-1215.

Apixaban in ESRD: the clinical data

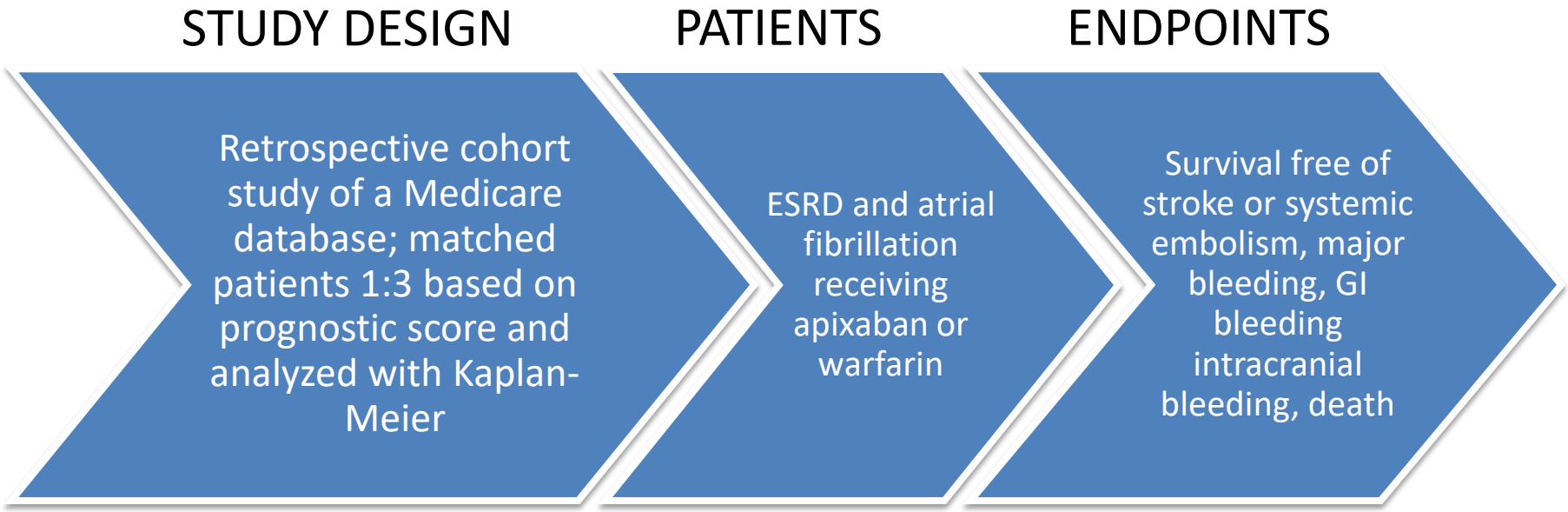
Circulation

ORIGINAL RESEARCH ARTICLE

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

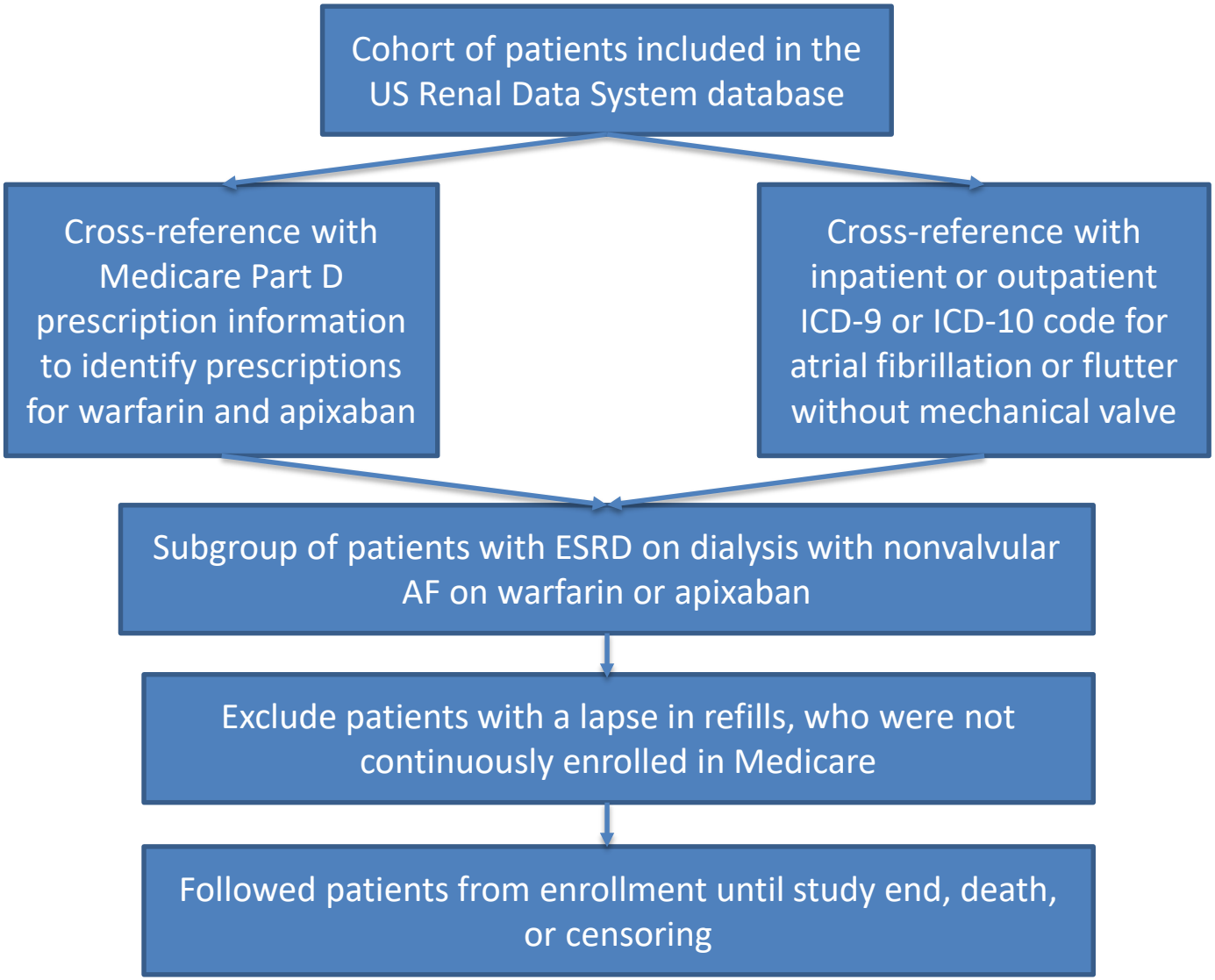
Siontis K, et al. *Circulation* 2018;138:1519-1529.

Siontis (2018)- Apixaban in ESRD



Siontis K, et al. *Circulation* 2018;138:1519-1529.

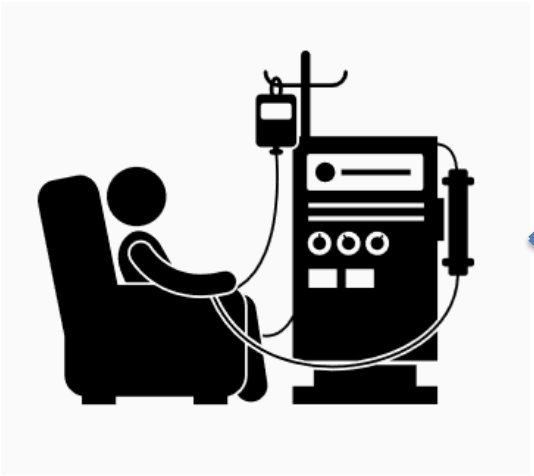
Siontis (2018)- Methods



Siontis K, et al. *Circulation* 2018;138:1519-1529.

Siontis (2018)- Results

High rates of censoring because of prescription expiration or > 30 day gap between prescriptions in both groups (> 50%)



Typical patient was 68 year old on intermittent hemodialysis for more than 3 years; CHA_2DS_2VASc score of 5

7,053 patients on warfarin

2,351 patients on apixaban

- 44% 5 mg BID
- 56% 2.5 mg BID

Siontis K, et al. *Circulation* 2018;138:1519-1529.

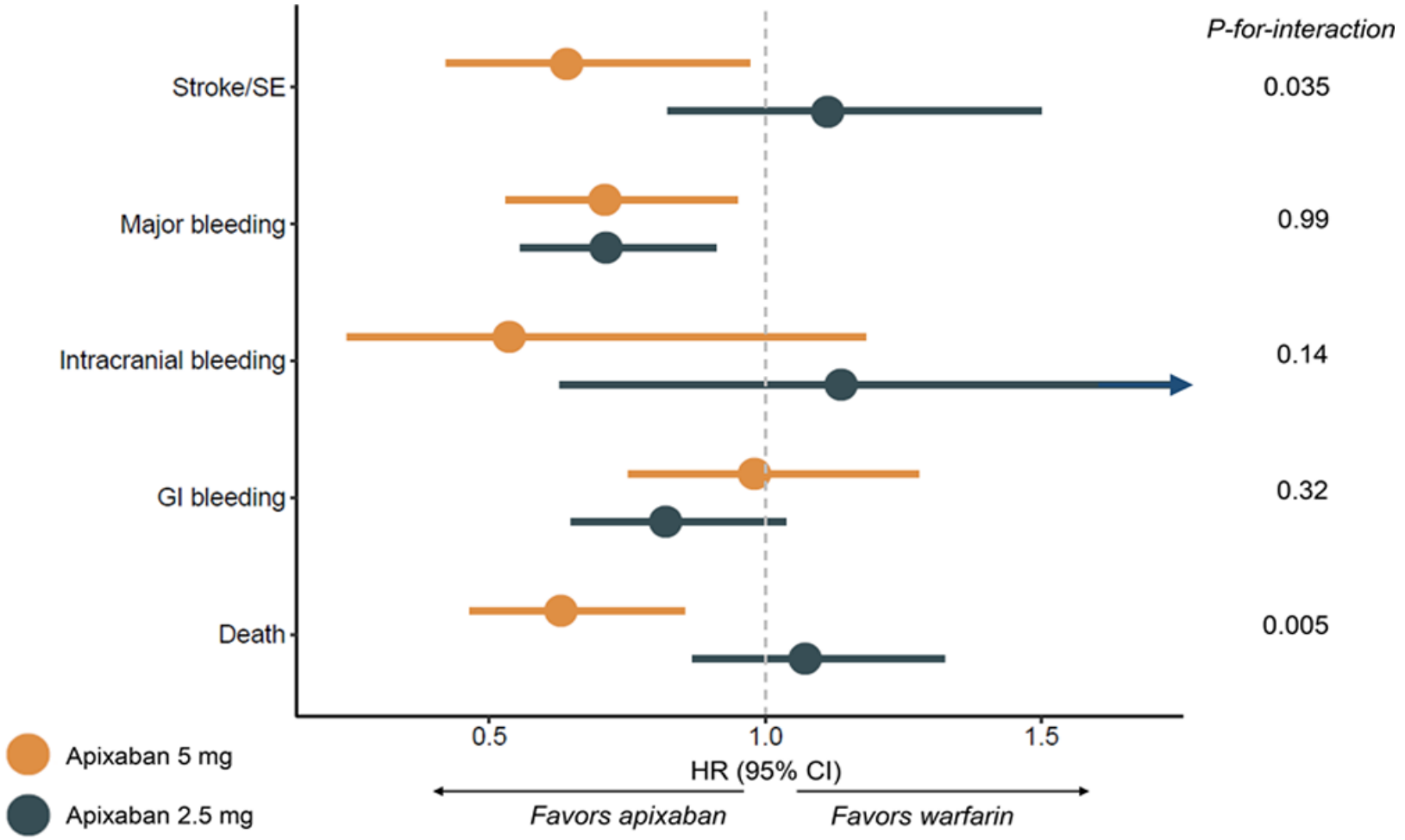
Siontis (2018)- Results

Outcome	Overall	Apixaban	Warfarin	Hazard Ratio (95% CI)	*P* Value
Stroke/systemic embolism					
No. of patients	9404	2351	7053	0.88 (0.69–1.12)	0.29
No. of events	454	81	373		
Event rate per 100 PY	11.9	12.4	11.8		
Major bleeding					
No. of patients	9404	2351	7053	0.72 (0.59–0.87)	<0.001
No. of events	844	129	715		
Event rate per 100 PY	22.3	19.7	22.9		
Gastrointestinal bleeding					
No. of patients	9404	2351	7053	0.86 (0.72–1.02)	0.09
No. of events	865	155	710		
Event rate per 100 PY	23.4	23.8	23.4		
Intracranial bleeding					
No. of patients	9400	2350	7050	0.79 (0.49–1.26)	0.32
No. of events	132	21	111		
Event rate per 100 PY	3.4	3.1	3.5		
Death					
No. of patients	9404	2351	7053	0.85 (0.71–1.01)	0.06
No. of events	912	159	753		
Event rate per 100 PY	24.7	23.7	24.9		

HR indicates hazard ratio; and PY, patient-years. Association estimates are derived from univariable Cox regression analyses with drug exposure (apixaban or warfarin) as the only predictor variable. Hazard ratio <1 favors apixaban.

Siontis K, et al. *Circulation* 2018;138:1519-1529.

Siontis (2018)- Results



Siontis K, et al. *Circulation* 2018;138:1519-1529.

Siontis (2018) Considerations

- ✓ Unable to collect information about aspirin use
- ✓ Unable to determine time in the therapeutic range for warfarin
- ✓ Unable to assess adherence
- ✓ Reliant on claims data and ICD-9 and ICD-10 codes for endpoints

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Siontis K, et al. *Circulation* 2018;138:1519-1529.

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Safety and effectiveness of apixaban compared to warfarin in dialysis patients

Daniel Reed MD[1] | Surabhi Palkimas PharmD[2]
Sumner Abraham MD[3] | Tri [illegible]

Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment

Brooke E. Stanton,[1*] Naomi S. Barasch,[1] and Katie B. Tellor,[2]
[1]Missouri Baptist Medical [illegible] St. Louis, Missouri; [2]Department of Pharmacy Practice, St. Louis College of [illegible] St. Louis, Missouri

Safety Outcomes of Apixaban Compared With Warfarin in Patients With End-Stage Renal Disease

Stefanie C. Sarratt, PharmD, BCPS[1], Ross Nesbit, MD[2], and Robert Moye, PharmD, AEMT[2]

ACCP Global Pharmacy Conference 2018

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Apixaban in ESRD: the clinical data

Study	Design	Endpoints	Results
Stanton (2017)	Retrospective, matched cohort study of hospitalized patients with CrCl < 25 mL/min or ESRD on apixaban (n= 73) or warfarin (n= 73) *Majority on 2.5 mg q12h apixaban*	• Major bleeding • Documented ischemic stroke • Recurrent thromboembolism	• Major bleeding: 9.6% apixaban vs 17.8% warfarin (NS) • No difference in stroke/recurrent VTE
Sarratt (2017)	Retrospective single-center cohort study of hospitalized ESRD patients receiving apixaban (n= 40) or warfarin (n= 120) *Majority on 2.5 mg PO q12h apixaban*	• Major bleeding • Nonmajor/minor bleeding	• No statistically significant differences in major bleeding or clinically relevant nonmajor bleeding
Steuber (2017)	Retrospective multicenter cohort study of hospitalized ESRD patients on apixaban (n= 114); logistic regression to determine significant predictors of bleeding	• Major bleeding • Nonmajor bleeding	• Bleeding events: 15% (6% major bleeding)
Reed (2018)	Retrospective single-center cohort study of ESRD patients on apixaban (n= 74) or warfarin (n= 50) *Majority on 5 mg q12h apixaban*	• Bleeding rate • Non-major bleeding • Recurrent VTE • Stroke	• Bleeding event: 18.9% apixaban vs 42% (22% major) warfarin (p= 0.01) • Recurrent VTE: 4.4% apixaban vs 28.6% warfarin

Stanton BE, et al. *Pharmacotherapy* 2017;37(4):412-419.
Sarratt SC, et al. *Ann,Pharmacother* 2017;51(6):445-450.
Steuber TD, et al. *Ann Pharmacother* 2017;51(11):954-960.
Reid D, et al. *Res Pract Thromb Haemost* 2018;2(2):291-298.

Poll Everywhere

The current body of evidence for apixaban safety and efficacy in patients with end-stage renal disease requiring hemodialysis consists of pharmacokinetic modelling and:

a. Case reports
b. Expert physician recommendations
c. Retrospective cohort studies
d. Randomized controlled trials

The current body of evidence for apixaban safety and efficacy in patients with end-stage renal disease requiring hemodialysis consists of pharmacokinetic modelling and:

Case reports

Expert physician recommendations

Retrospective cohort studies

Randomized controlled trials

Ongoing Studies with Apixaban

- **RENAL-AF**
  - Apixaban vs warfarin in ESRD patients (n= 762)
- **AXADIA**
  - Apixaban vs phenprocoumon in ESRD patients (n= 222)
- **AVKDIAL**
  - Warfarin vs no OAC in ESRD patients (n= 855)

DOAC Use in Pregnancy

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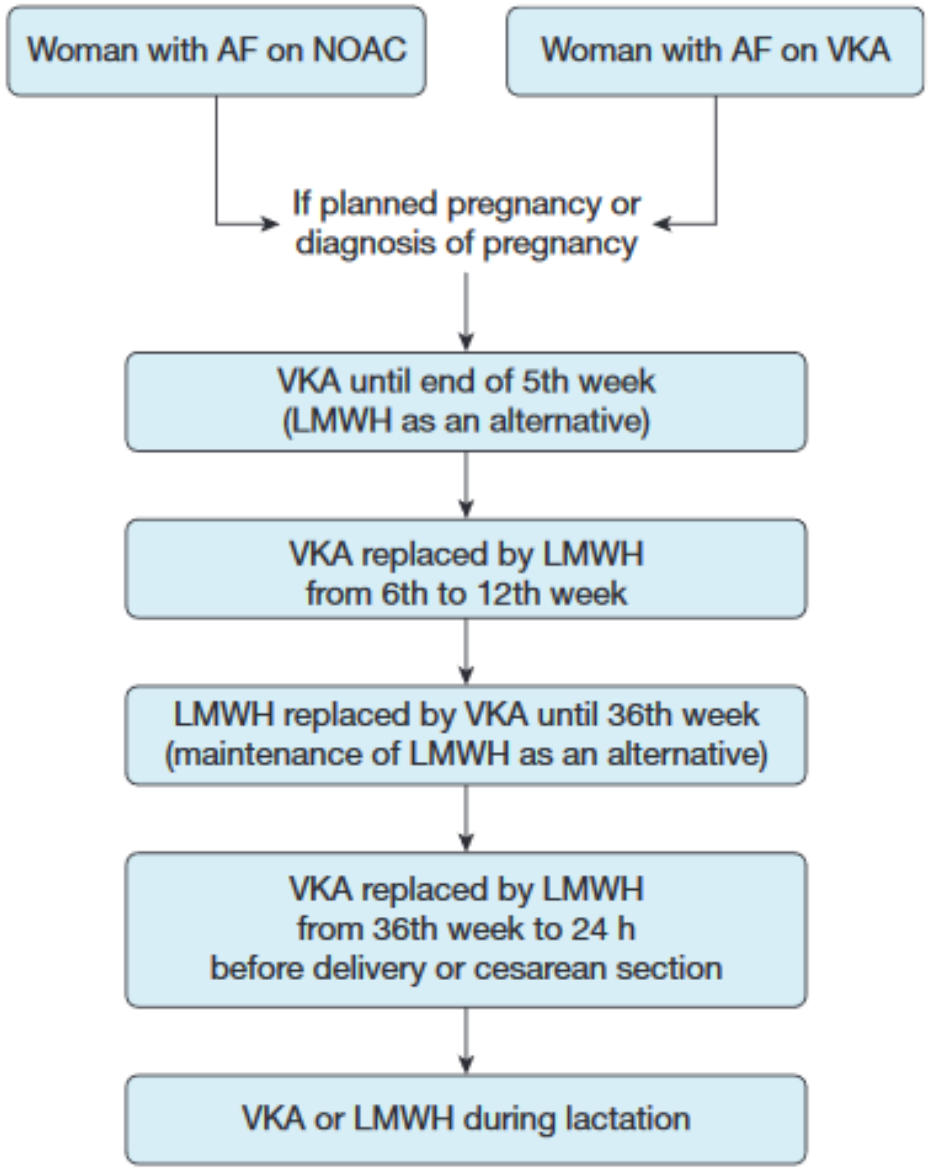
Guideline Statements: Pregnancy

- **CHEST Guidelines 2018**
  - Suggest discontinuation of both VKA (between 6-12 weeks gestation) and DOACs, and use twice daily LMWH (Ungraded)
  - Suggest warfarin over DOACs for women who are attempting to conceive (Ungraded)

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

CHEST Guideline Algorithm 2018



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

DOAC Pharmacokinetics Relevant to Pregnancy

EFFICACY

- Clearance of DOACs with significant renal elimination[+] may increase 2/2 increased GFR in pregnancy
- Elevated fibrinogen levels in pregnancy

SAFETY

- DOACs have a low molecular weight and are expected to cross the placenta

+ renal elimination dabigatran > edoxaban > rivaroxaban > apixaban

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Cohen H, et al. *J Thromb Hamost 2016;14:1673-6.*
Lameijer H, et al. *Thrombosis Research* 2018;169:123-127.

Food and Drug Administration (FDA) & European Medicines Agency (EMA) *Animal data*

DOAC	FDA Pregnancy Category	Fetal outcomes in animal studies
Apixaban	B	No increased risk
Rivaroxaban	C	At humanized plasma concentrations: irregular **ossification**, increased rate of malformations, placental changes, **post-implantation loss**
Edoxaban	C	At 20-60x humanized plasma concentrations: **increased fetal loss**, decreased fetal weight, gallbladder irregularities
Dabigatran	C	At 2.6-4.6x humanized plasma concentrations: **increased fetal loss**, irregular **ossification** of skull bones and vertebrae

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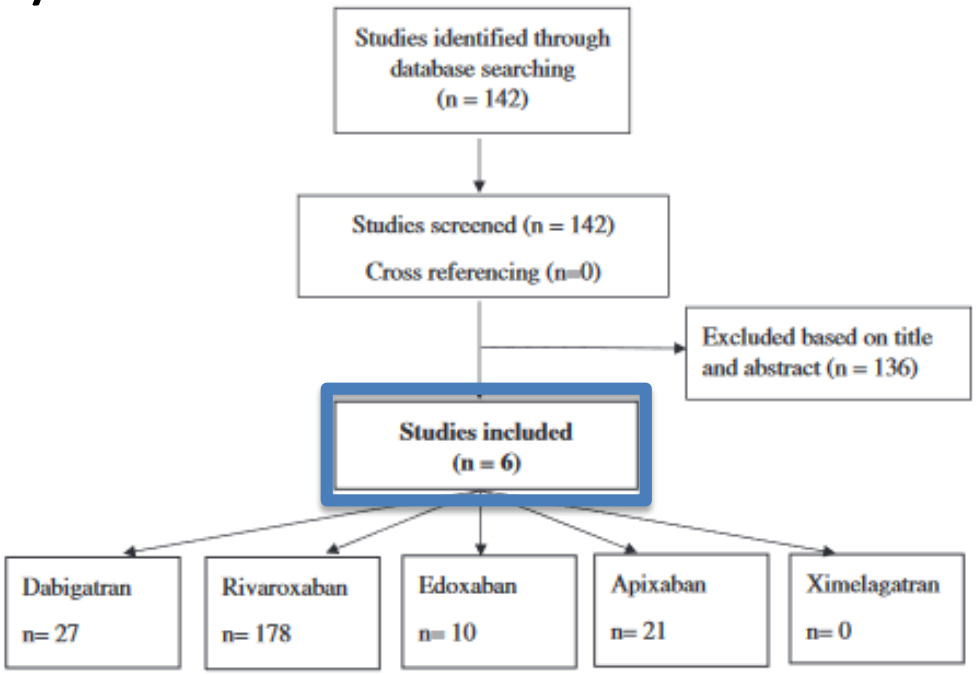
Lameijer H, et al. *Thrombosis Research* 2018;169:123-127.

DOACs in Pregnancy

A systematic literature review was performed by Lameijer and colleagues to identify all studies in the MedLine database describing DOAC use in pregnancy through July 2017



Lameijer H, et al. *Thrombosis Research* 2018;169:123-127.

Lameijer (2018)- DOACs in pregnancy

- Four of the six included studies were case reports with n= 1
- Essentially all data came from a database analysis by Beyer-Westendorf and colleagues in 2016
- 236 unique cases were identified
  - Rivaroxaban 75%
  - Dabigatran 11%
  - Apixaban 9%
  - Edoxaban 4%

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Lameijer H, et al. *Thrombosis Research* 2018;169:123-127.
Beyer-Westendorf J, et al. *Thromb Haemost* 2016;116:651-658.

Lameijer (2018)- DOACs in pregnancy

Duration of exposure

- Typically continued for less than 2 months during pregnancy+
- Maximum exposure 26 weeks

Miscarriage rate

- 28% elective
- 31% spontaneous

Fetal and neonatal abnormalities

All with rivaroxaban

- Possible causality: facial dimorphism, hip dysplasia, intra-uterine growth retardation, abnormal limbs

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+ Among cases where the data was available, n= 73 (31% of cases)

Poll Everywhere

Use of direct oral anticoagulants (DOACs) in the setting of pregnancy is not currently recommended by clinical practice guidelines because:

a. The risk of bleeding with DOACs is higher among pregnant women
b. The efficacy of DOACs may be compromised by pregnancy-related pharmacokinetic changes
c. DOACs are expected to cross the placenta and have been shown to be teratogenic in animal studies
d. Both B and C are correct

Use of the direct oral anticoagulants (DOACs) in the setting of pregnancy is not currently recommended by clinical practice guidelines because:

The risk of bleeding with DOACs is higher among pregnant women

The efficacy of DOACs may be compromised by pregnancy-related pharmacokinetic alterations

DOACs are expected to cross the placenta and have been shown to be teratogenic in some animal studies

Both B and C are correct

Conclusions

TL;DR: apixaban in ESRD (Siontis 2018)

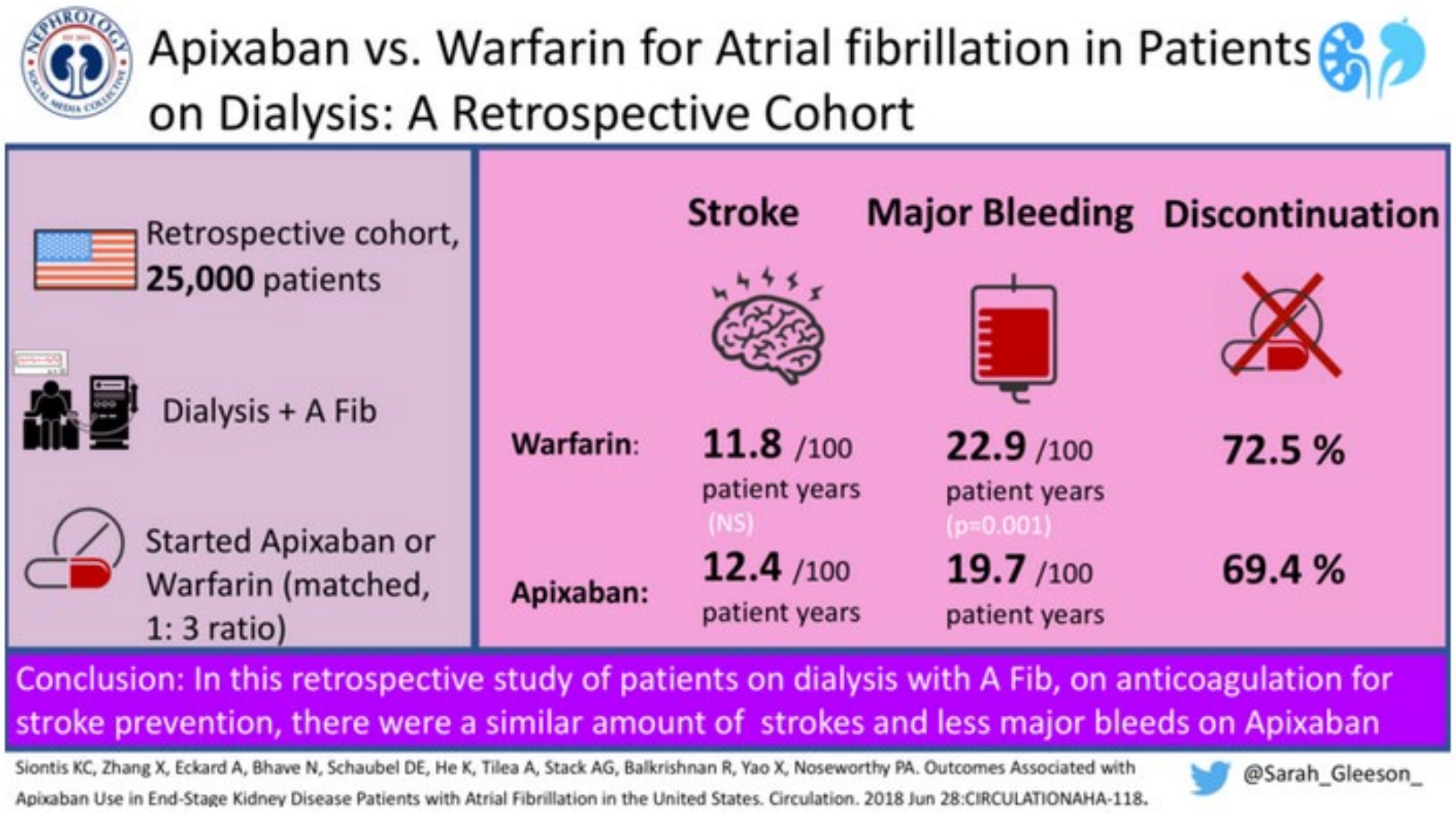

Image from: www.nephjc.com August 2018. Visual abstract created by Sarah Gleeson

Conclusions

- Optimal dosing of apixaban in ESRD patients is yet to be established
  - Greater efficacy in 5 mg BID subgroup in Siontis study
  - Steady state pharmacokinetics data suggests 2.5 mg BID results in more comparable exposure to healthy controls

Conclusions

- Current guidance is to avoid DOACs in pregnant women due to both efficacy and safety concerns
- Apixaban may be a promising alternative to warfarin given no increased fetal toxicity in animal studies, but more data is needed about potential human fetal harm

(Don't You) Forget About Warfarin

Direct Oral Anticoagulant Use in Special Populations

Join my PollEverywhere by texting BUNNELL123 to 22333

Kristen Bunnell, PharmD, BCCCP

May 21, 2019

GMCCP Spring CE Event

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Bad Blood: Update on Anticoagulation Reversal

Ben Jung, PharmD, MS, MPA
Anticoagulation Program Coordinator
Froedtert and the Medical College of Wisconsin

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Disclosures

The speaker has no actual or potential conflict of interest in relation to this presentation

Objectives

- Summarize reversal strategies for oral anticoagulation
- Provide recommendations for anticoagulation reversal in clinical settings

Need to Reverse?

- Stopping/holding agent
- Moderate to severe bleeding
- Bleeding related complications
- Hemodynamic instability
- Surgical procedure required to stop bleeding
- Urgent or emergent surgical procedure

Perfect Reversal Agent

- Easy to Mix
- Fast Administration
- Quick Onset
- Duration of Effect
- Complete Reversal
- Infusion Reactions
- Thrombotic Risk
- Drug Specific
- Cost (Average Wholesale Price)

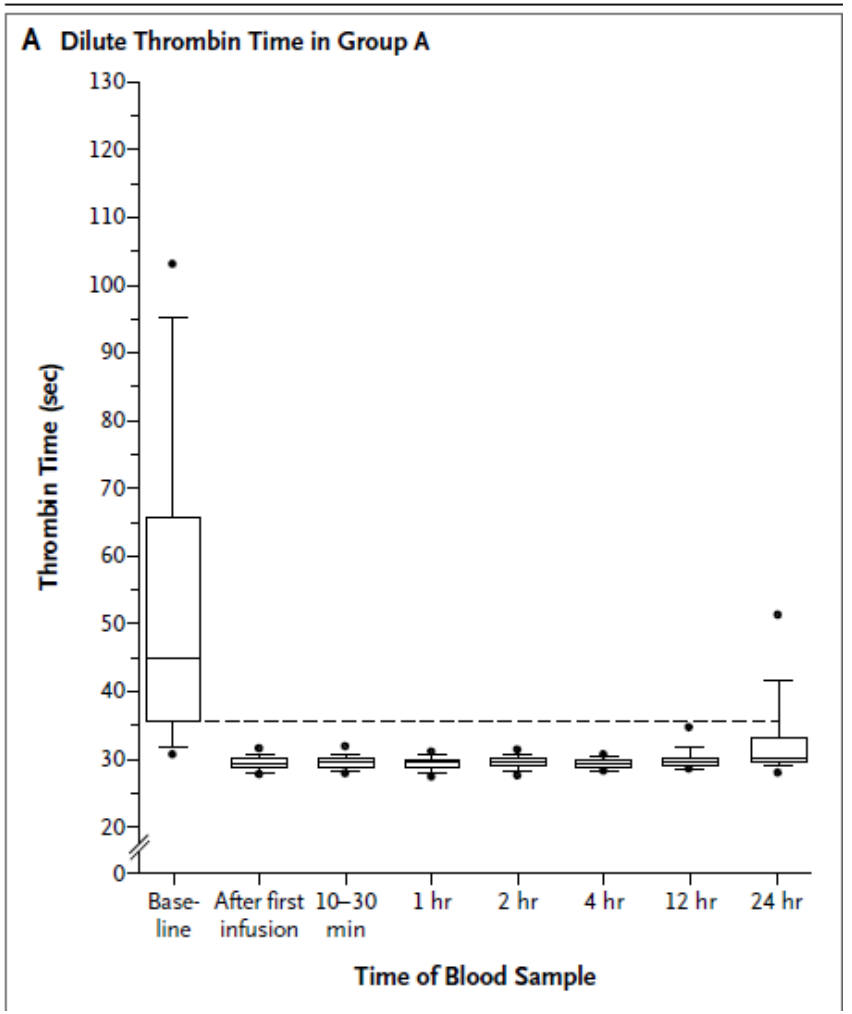
Dabigatran Reversal

- Half Life 12 to 17 hours
- Hemodialysis will remove drug
- Idarucizumab (Praxbind)
- Dosing is 5 grams given as two separate 2.5 gram doses each vial over 5 to 10 minutes

-Boehringer Ingelheim Pharmaceuticals. Pradaxa (dabigatran etexilate mesylate) capsules package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; April 2013.
-Boehringer Ingelheim. Idarucizumab (Praxbind) for injection [package insert]. Ridgefield, CT: Boehringer Ingelheim; October 2015.

Idarucizumab (PRAXBIND)

- Binds dabigatran with affinity ~350-fold greater than to thrombin
- Effect lasts up to 24 hours
- RE-VERSE AD phase III study
  - 90 patients reported
- Approved Oct 2015



Pollack, Chares V Jr., et al. Idarucizumab for Dabigatran Reversal N Engl J Med 2015;373:511-20.

Idarucizumab Reversal

• Easy to Mix	• Yes
• Fast Administration	• Yes
• Quick Onset	• Yes
• Duration of Effect	• At least 24 hours
• Complete Reversal	• Yes
• Infusion Reactions	• No
• Thrombotic Risk	• No
• Drug Specific	• Yes
• Cost	• ~$4500 per course

Warfarin Reversal

- Warfarin half life 20-60 hours
- Use of Vitamin K IV or Oral
- 4-PCC (KCENTRA) or Fresh Frozen Plasma (FFP)
- Monitor INR

-Bristol-Myers Squibb Company. Coumadin (warfarin sodium) tablets package insert. Princeton, NJ: Bristol-Myers Squibb Company; October 2011.

Question

Patients on warfarin with INRs of greater than 5 always need reversal?

a) True

b) False

Warfarin Reversal

INR 5 to 10 without bleeding- hold warfarin

INR >10 without bleeding- hold warfarin; Give 1 to 2.5 mg vitamin K orally if high risk

Major Life threating bleeding give 5 to 10 mg of IV vitamin K and Prothrombin complex concentrate (4-PCC) (KCENTRA)

-Ageno W, Gallus AS, Wittkowsky A, et al. American College of Chest Physicians. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012;141(2 Suppl):e44S-88S.
-Holbrook A, Schulman S, Witt DM, et al. American College of Chest Physicians. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012;141(2 Suppl):152S-184S.
-Douketis JD, Spyropoulos AC, Spencer, et al. American College of Chest Physicians. Perioperative management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012;141(2 Suppl):326S-350S.

Phytonadione- Vitamin K

- Reversal of warfarin
- IV route (given IV over at least 30 minutes)
  - Onset 1 to 2 hours
  - Peak 6 to 10 hours
- Oral route
  - Onset 6 to 10 hours
  - Peak 24 to 48 hours
- Recommend against subcut administration

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2018; September, 24 2013

Vitamin K Reversal- Warfarin

- Easy to Mix
- Fast Administration
- Quick Onset
- Duration of Effect
- Complete Reversal
- Infusion Reactions
- Thrombotic Risk
- Drug Specific
- Cost

- Yes
- Yes (IV 30-60 min)
- No
- Hours to days
- Yes
- Yes if IV push
- Increased?
- Yes, Production of new clotting factors
- ~$25-150

4-PCC (KCENTRA)

Pre-Treatment INR	2 to < 4	4-6	>6
Dose of 4-PCC units/kg (max)	25 (2500)	35 (3500)	50 (5000)

- Dosing based on weight and INR
- Onset with rapid INR decline in 10 minutes
- Duration 6-8 hours
- Infusion typically 10-30 minutes
- Vitamin K IV unless active clotting concerns
- Contains heparin cannot use in history of HIT

Kcentra (prothrombin complex concentrate human) [prescribing information]. Kankakee, IL: CSL Behring; October 2018.

Fixed Dosing 4-PCC Warfarin

- Off-Label Dosing
- Multiple studies primarly using 1000 units IV once (including ICH and trauma)
- Outcomes show effective lowering of INR
- Repeat INR testing is not required unless the patient experiences clinical changes in status related to bleeding

-Astrup G, Sarangarm P, Burnett A. Fixed dose 4-factor prothrombin complex concentrate for the emergent reversal of warfarin: a retrospective analysis. Journal of thrombosis and thrombolysis. 2018; 45: 300-5.
-Klein L, Peters J, Miner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. The American journal of emergency medicine. 2015; 33: 1213-8.

4-PCC Reversal- Warfarin

- Easy to Mix
- Fast Administration
- Quick Onset
- Duration of Effect
- Complete Reversal
- Infusion Reactions
- Thrombotic Risk
- Drug Specific
- Cost

- Yes
- Yes
- Yes
- Up to 12 hours
- No
- No
- Yes 5-7%
- No, studied in warfarin extensively
- ~$3000-14,000

Patient Case

Patient is a 67 yo male on warfarin for atrial fibrillation with INR of 1.8 who fell off a ladder and has subdural hematoma and needs an emergent evacuation

a) Reverse with Vitamin K 5 mg oral and 4-PCC
b) Reverse with Vitamin K 10 mg IV and 4-PCC
c) Reverse with Vitamin K 10 mg IV
d) Reverse with Vitamin K 10 mg IV and FFP

Patient Case

Patient is a 56 yo female on warfarin for an unprovoked DVT 3 months ago and presents with a painful abdominal hernia and is scheduled for surgery tomorrow afternoon, INR was 2.4 at presentation with a recheck of 2.5 the next morning, no Vitamin K was given, should this patient receive 4-PCC

a) Yes

b) No

Oral Factor Xa Inhibitors Reversal

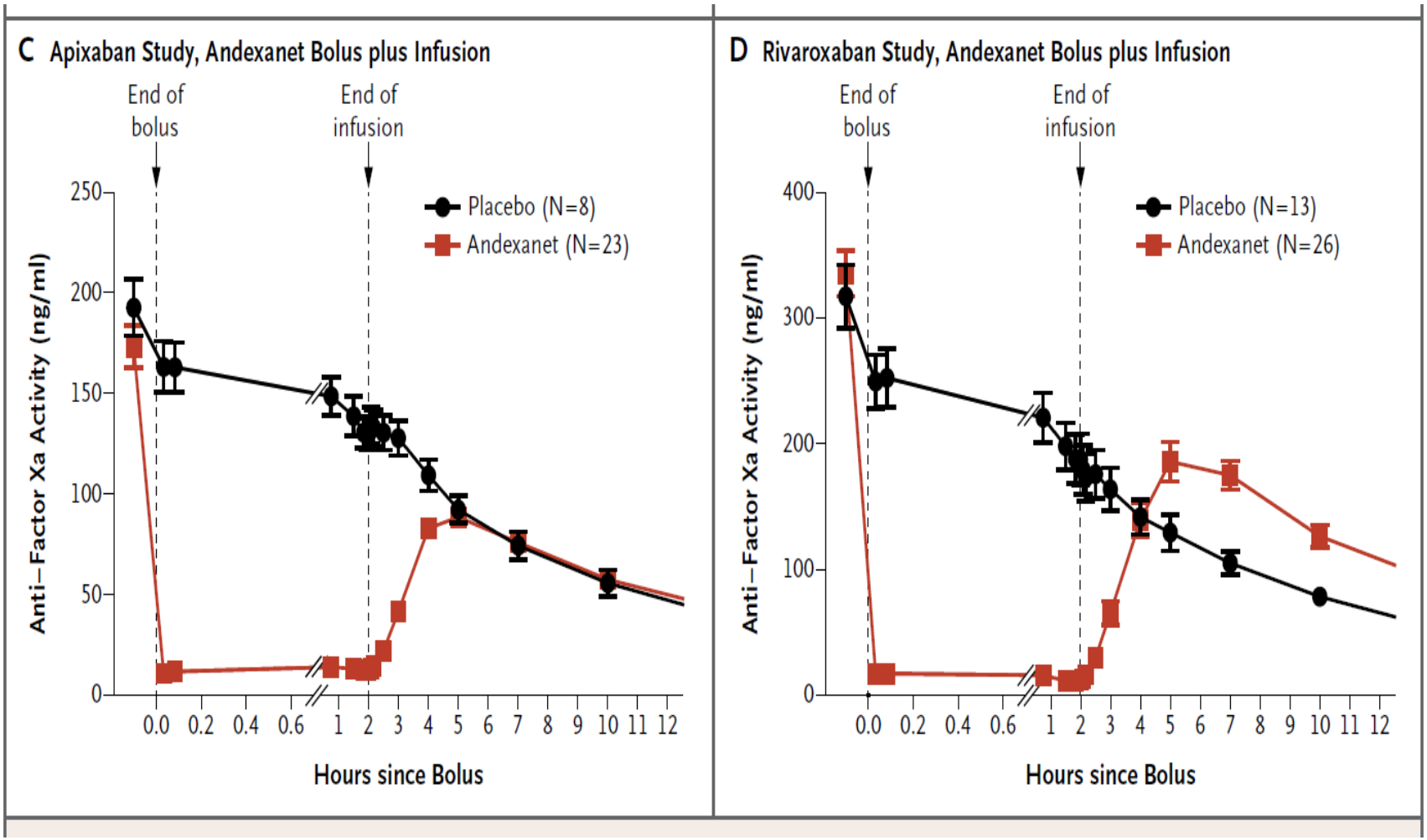
- Apixaban half life 12 hours
- Rivaroxaban half life 5 to 9 hours
- Edoxaban half life 10 to 14 hours
- Newly approved reversal agent Andexanet Alfa
- No reliable monitoring, Anti-Xa activity can show drug presence
- Alternative (Off-label) 4-PCC 25 to 50 units/kg

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2018; September, 24 2013

Andexanet Alfa (ANDEXXA)

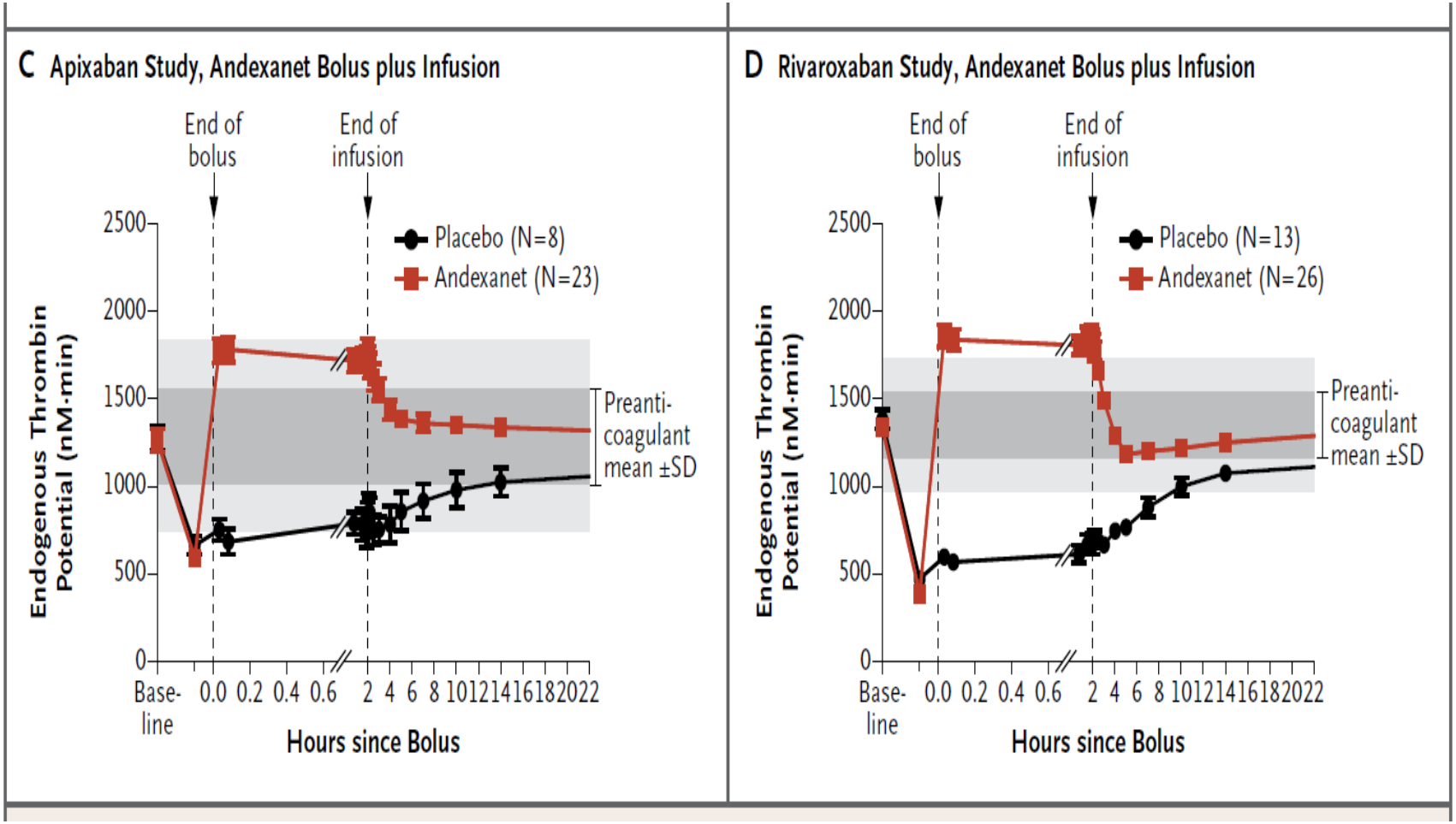
- Reversal of anticoagulation with apixaban or rivaroxaban due to life threatening or uncontrolled bleeding.
- Andexanet Alfa exhibits its procoagulant effects by binding and sequestering apixaban and rivaroxaban, which are FXa inhibitors.
- It also inhibits the activity of tissue factor pathway inhibitor (TFPI), this inhibition leads to increased levels of thrombin.

Anti-Xa Activity ANNEXA-A and R



Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-2424.

Thrombin Generation ANNEXA-A and R



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Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413-2424.

ANNEXA-4 Study Inclusion

- Age greater than 18
- Dose of medication within 18 hours (apixaban, rivaroxaban, edoxaban or enoxaparin)
- Acute Bleeding defined as potentially life threating bleeding with signs/symptoms hemodynamic compromise, acute overt bleeding with hemoglobin drop of at least 2 g/dL or within a critical organ

Connolly SJ, Crowther M, Eikelboom JW, et al; Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019;380:1326-35

ANNEXA-4 Exclusion Criteria

- Scheduled for Surgery within 12 hours
- ICH with GCS of less than 7
- Intra-cerebral hematoma > 60 mL
- Expected survival of less than 1 month
- Thrombotic event within 2 weeks
- Given within 7 days, warfarin, dabigatran, 4-PCC, whole blood, or plasma

Connolly SJ, Crowther M, Eikelboom JW, et al; Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019;380:1326-35

ANNEX-4 Results

- 352 patients (128 rivaroxaban and 194 apixaban)
- Intracranial Bleed 64% and GI 26%
- 92% reduction in anti-factor Xa activity
- Good Or Excellent Hemostasis 82% at 12 hours
- Death 49 patients (14%)
- Thrombotic events 34 patients (10%)
- 8 (2%) patients had thrombotic events after anticoagulation restarted

Connolly SJ, Crowther M, Eikelboom JW, et al; Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019;380:1326-35

Andexanet Alfa Dosing

- Supplied as 200 mg vials
- Low dose- 880 mg needed (400 bolus, 480 infusion)
- High dose- 1760 mg (800 bolus, 960 infusion)

Table 2-3 Recommended Dosage for Andexanet Alfa

	Initial IV bolus	Follow-on infusion
Low dose	400 mg at target rate of 30 mg/min	4 mg/min for up to 120 minutes
High dose	800 mg at target rate of 30 mg/min	8 mg/min for up to 120 minutes

		Timing of FXa inhibitor last dose before andexanet alfa initiation	
	FXa inhibitor last dose	< 8 hours or unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg or unknown	High dose	
Apixaban	≤ 5 mg	Low dose	
	> 5 mg or unknown	High dose	

IV – intravenous

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Portola Pharmacetuicals. Andexxa (Andexanet alfa) for injection [Package Insert]. San Francisco, CA: Portola Pharmaceutical; May 2018.

Andexanet Alfa Ideal Reversal

• Easy to Mix	• No (30-40 minutes)
• Fast Administration	• No (2.5 hours)
• Quick Onset	• Yes
• Duration of Effect	• 4-6 hours
• Complete Reversal	• No (during infusion)
• Infusion Reactions	• No
• Thrombotic Risk	• Yes (10%)
• Drug Specific	• Yes
• Cost	• ~$30,000-60,000

Patient Case

Patient is 56 yo male with Gastrointestinal bleed on apixaban 5 mg po bid (last dose 36 hours ago), normal renal function, BP 95/64 mmHg, Hgb of 6.4 g/dL, not in acute distress, what anticoagulation reversal is needed?

a) Andexanet Alfa low dose

b) 4-PCC (Kcentra)

c) Fresh Frozen Plasma

d) None

Question

What type of bleeding patient is andexanet alfa most appropriate for based on restrictions?

a) Intracranial Hemorrhage
b) GI bleed
c) Multiple Trauma patient needing OR
d) Cardiothoracic Surgery

Future of Anticoagulation Reversal

- PER977 (ciraparantag), a water-soluble small-molecule nonspecific reversal agent for anti-Xa and anti-IIa agents
- Better defined role for andexanet alfa
- Comparison of andexanet alfa to 4-PCC
- Optimized dosing strategies for 4-PCC
- Better information about adjuvants medications

Conclusions

- Oral anticoagulation medications now have reversal medications
- Costs of anticoagulant reversal remain high with thrombotic risk present
- Education of frontline providers and restrictions needed
- More medications on the horizon and hopefully data showing best patients and approaches
- Patients remain at high risk for thrombotic events post bleeding events

Bad Blood: Update on Anticoagulation Reversal

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Anticoagulation Program Coordinator
Froedtert and the Medical College of Wisconsin

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Minding the Bleeding Heart: Update on Therapeutics in Anticoagulation and Cardiology

CE Code: _____

CE must be claimed by 7/20/19 at accp.com

Claiming CE

- Log in to ACCP (https://www.accp.com/) – you will have to register as a guest and create a free account if not an ACCP member
- Click on Education
- Click on CPE Center
- Click on Claim CPE for a Chapter Activity

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