Direct Oral Anticoagulants:
Beyond Atrial Fibrillation and Venous thrombosis

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MAYO CLINIC

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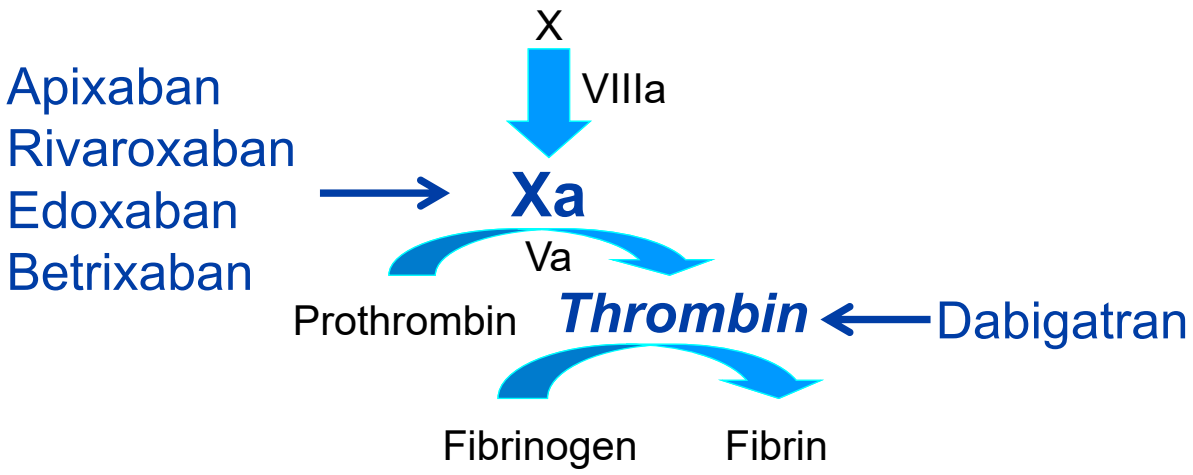
Disclosures

Bristol-Myers Squibb Research Grant
"Apixaban in Cancer Related VTE"

Oral Direct Factor Inhibitors

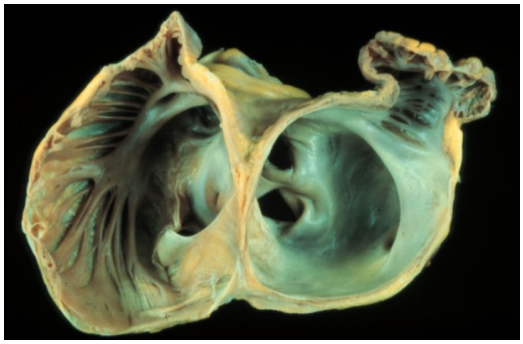


Oral Direct Factor Inhibitors

Advantages:

- No food interactions
- No monitoring
- No continuous dose adjustments

Oral Direct Factor Inhibitors



Atrial fibrillation

Venous Thromboembolism

- Excellent safety
- Good efficacy…..relative to warfarin

DOAC Update:

Learning Objectives

- To list the ***efficacy*** and ***safety*** of direct oral anticoagulants in ***stable arterial occlusive disease, cryptogenic stroke,*** and ***heart failure*** based on recently published RCTs.

- To review an algorhythm for ***DOAC reversal*** during urgent and emergent clinical scenarios

Case #1

58 y/o male

Two year history of bilateral calf pain with walking 100-150m. His pain is improved with standing. He has no rest pain or ulcers. These symptoms have not changed. He continues to smoke 1 pack per day ("for 50 years").

Exam BP Right 152/72 Left 110/68

Left Carotid and subclavian bruit

Pulse (R/L):		
	Fem	4/4
	Pop	0/0
	PT	0/0
	DP	0/0

Which of the following medications would improve his outcome?*

1. Apixaban 5 mg BID
2. Apixaban 2.5 mg BID with aspirin
3. Dabigatran 150 mg BID
4. Dabigatran 75 mg BID with aspirin
5. Rivaroxaban 20 mg daily
6. Rivaroxaban 2.5 mg BID with aspirin

If rivaroxaban 2.5 mg BID is added to aspirin, which outcomes would we anticipate to improve?*

1. Stroke
2. Venous thromboembolism
3. Need for major amputations
4. Cardiovascular Death
5. All of these events will be improved

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease
Compass Trial

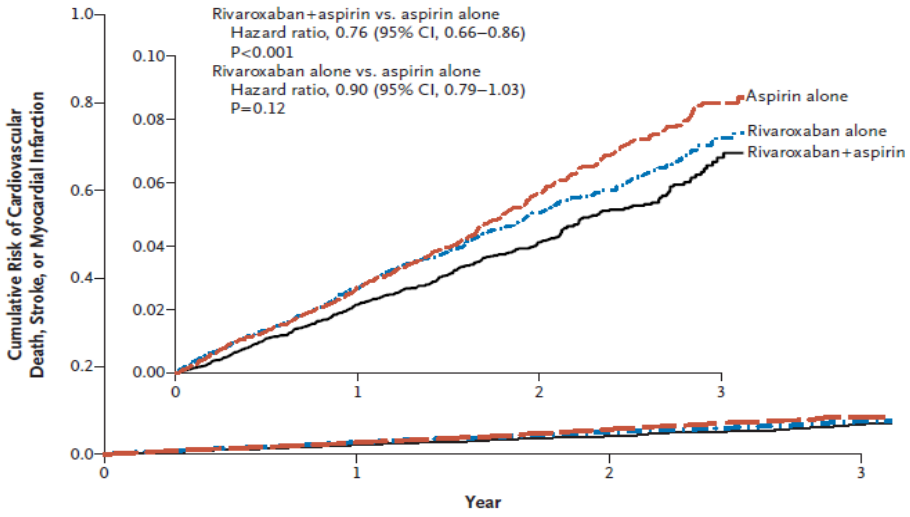
Patients: Stable cardiovascular disease (CAD, PAD or both)

27,395 patients →
- Rivaroxaban 2.5 mg BID plus ASA
- Rivaroxaban 5 mg BID
- ASA

Primary outcome: Death, Stroke or MI

N Engl J Med 2017; 377:1319

Compass Trial



Major Bleeding: R/A 3.1%
R 2.8%
A 1.9%

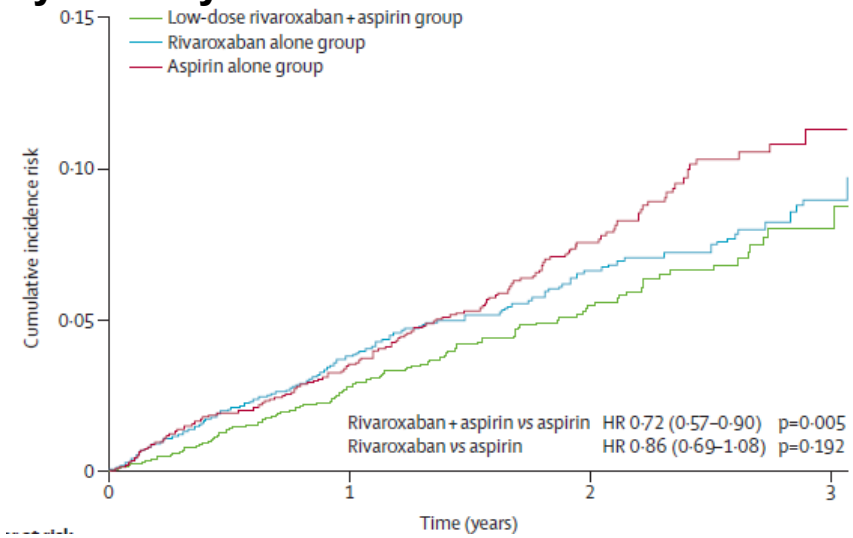
N Engl J Med 2017; 377:1319

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value
		number (percent)			
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001
Secondary outcomes‡					
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001
Other outcomes§					
Non-CV death	153 (1.7)	171 (1.9)	175 (1.9)	0.87 (0.70–1.08)	0.20
Death from CHD	86 (0.9)	128 (1.4)	117 (1.3)	0.73 (0.55–0.96)	0.03
Ischemic or uncertain type	68 (0.7)	91 (1.0)	132 (1.4)	0.51 (0.38–0.68)	<0.001
Hemorrhagic	15 (0.2)	27 (0.3)	10 (0.1)	1.49 (0.67–3.31)	0.33
Myocardial infarction	178 (1.9)	182 (2.0)	205 (2.2)	0.86 (0.70–1.05)	0.14
Heart failure	197 (2.2)	191 (2.1)	192 (2.1)	1.02 (0.84–1.24)	0.84
Hospitalization					
For CV causes	1303 (14.2)	1317 (14.4)	1394 (15.3)	0.92 (0.86–1.00)	0.04
For non-CV causes	1701 (18.6)	1649 (18.1)	1624 (17.8)	1.05 (0.98–1.13)	0.14

N Engl J Med 2017; 377:1319

Compass Trial: PAD Patients

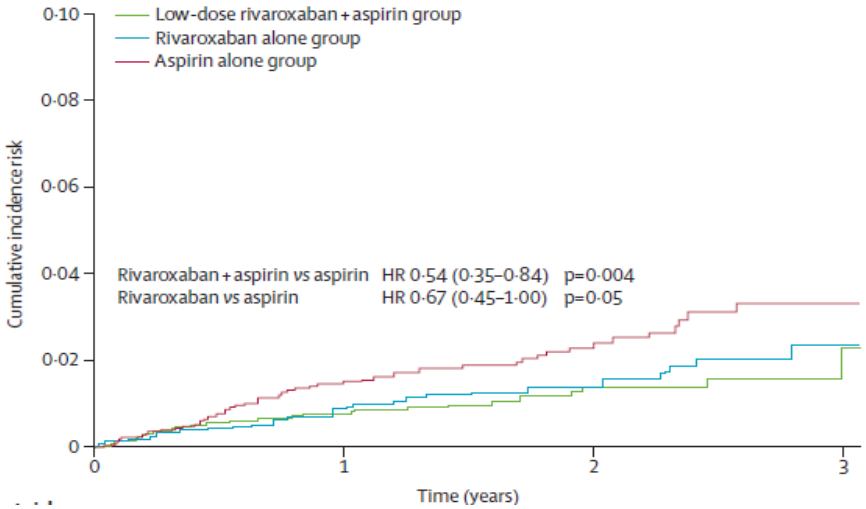
Primary efficacy outcome



Lancet 2018; 391: 219

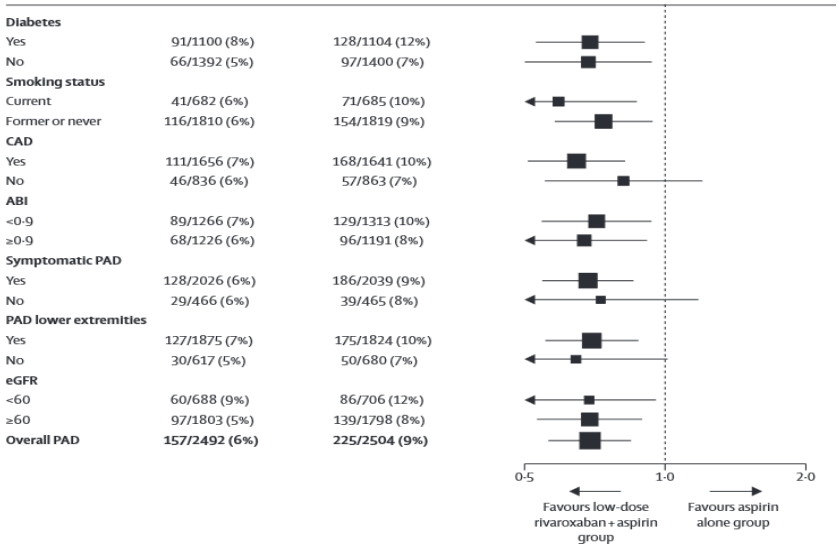
Compass Trial: PAD Patients

Major adverse limb events



Lancet 2018; 391: 219

Compass Trial: PAD Patients



Diabetes		
Yes	91/1100 (8%)	128/1104 (12%)
No	66/1392 (5%)	97/1400 (7%)
Smoking status		
Current	41/682 (6%)	71/685 (10%)
Former or never	116/1810 (6%)	154/1819 (9%)
CAD		
Yes	111/1656 (7%)	168/1641 (10%)
No	46/836 (6%)	57/863 (7%)
ABI		
<0·9	89/1266 (7%)	129/1313 (10%)
≥0·9	68/1226 (6%)	96/1191 (8%)
Symptomatic PAD		
Yes	128/2026 (6%)	186/2039 (9%)
No	29/466 (6%)	39/465 (8%)
PAD lower extremities		
Yes	127/1875 (7%)	175/1824 (10%)
No	30/617 (5%)	50/680 (7%)
eGFR		
<60	60/688 (9%)	86/706 (12%)
≥60	97/1803 (5%)	139/1798 (8%)
Overall PAD	**157/2492 (6%)**	**225/2504 (9%)**

Lancet 2018; 391: 219

Which of the following medications would improve his outcome?

1. Apixaban 5 mg BID
2. Apixaban 2.5 mg BID with aspirin
3. Dabigatran 150 mg BID
4. Dabigatran 75 mg BID with aspirin
5. Rivaroxaban 20 mg daily
6. Rivaroxaban 2.5 mg BID with aspirin

If rivaroxaban 2.5 mg BID is added to aspirin, which outcomes would we anticipate to improve?

1. Stroke
2. Venous thromboembolism
3. Need for major amputations
4. Cardiovascular Death
5. All of these events will be improved

COMPASS Trial: Bottom Line

- New treatment paradigm for patients with stable arterial occlusive disease
- Added to traditional therapies, rivaroxaban may reduce ***major adverse cardiac events*** (MACE)
- …..and ***major adverse limb events*** (MALE) in patients with PAD

Case #2

65 y/o right handed male

Ten days ago, he suffered a minor right hemispheric stroke. He has hypertension and smokes. Carotid US showed mild plaque without significant stenosis. TEE, Holter, thrombophilia panel were negative.

65 y/o right handed male

Beyond smoking cessation, hypertension control and statin therapy, which of the following would you recommend?*

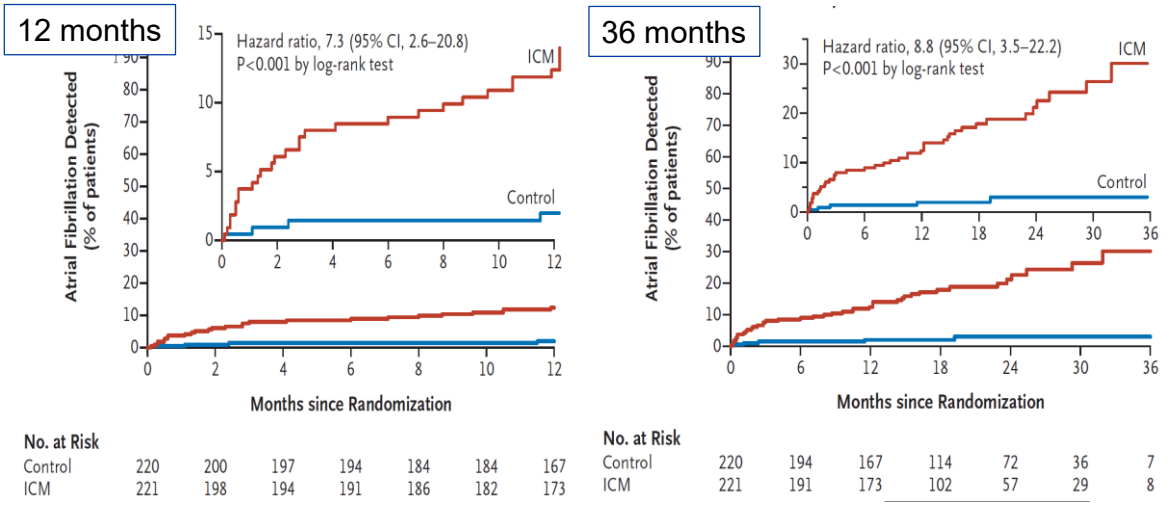
1. Aspirin 81 mg/day
2. Apixaban 5 mg BID
3. Rivaroxaban 5 mg BID
4. Rivaroxaban 15 mg/day
5. Rivaroxaban 20 mg/day
6. Dabigatran 150 mg BID

What is the role of ***Anticoagulant Therapy*** in Patients with ***Cryptogenic Stroke***

Cryptogenic Stroke

- Defined as stroke of undetermined cause
- Common, up to 20% of ischemic strokes (160,000 events/year in US)
- Most are presumed to be from cardiac, arterial, or paradoxic source.
- Risk of recurrent stroke 5% per year.

Cyptogenic Stroke: CRYSTAL AF



Insertable cardiac monitor (ICM)

N Engl J Med 2014;370:2478-86.

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

NAVIGATE ESUS Trial

Patients: Ischemic stroke (7d – 6 mo), < 50% carotid stenosis, No afib, LV thrombus, mech HV, severe MS

7,213 patients → Rivaroxaban 15mg daily

7,213 patients → ASA

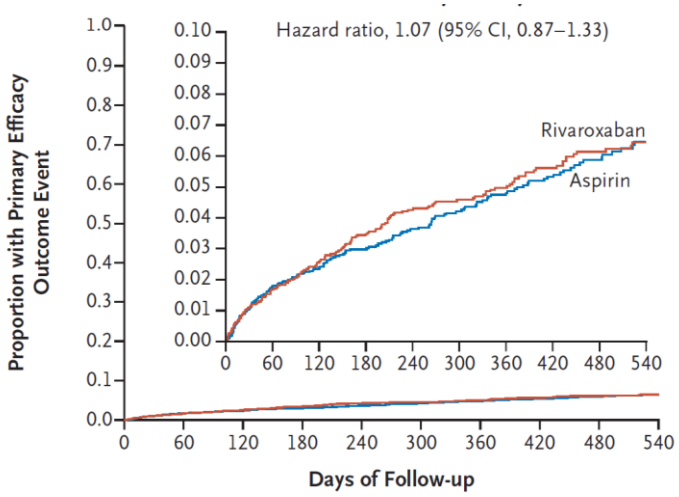
Primary outcome: Recurrent stroke or systemic embolism

N Engl J Med 2018; 378:2191

NAVIGATE ESUS Trial

Efficacy

Terminated early!



any stroke/embolism

N Engl J Med 2018; 378:2191

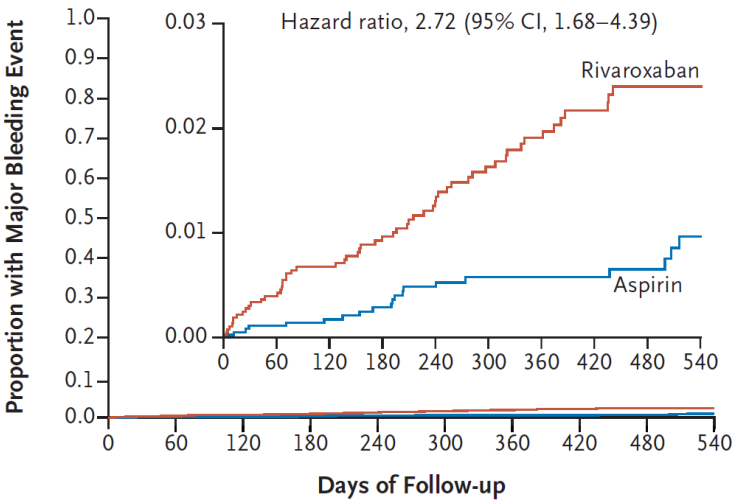
NAVIGATE ESUS Trial

Efficacy	Rivaroxaban	ASA	HR (95% CI)
Primary Outcome (any stroke/embolism)	5.1%	4.8%	1.08 (0.87 – 1.34)
Ischemic Stroke	4.7%	4.7%	1.01 (0.81 – 1.25)
Hemorrhagic Stroke	0.4%	0.1%	6.05 (1.47 – 28.8)
Systemic Embolism	<0.1%	0.1%	0.5 (0.05 – 5.51)

N Engl J Med 2018; 378:2191

NAVIGATE ESUS Trial

Safety



Major bleeding

N Engl J Med 2018; 378:2191

NAVIGATE ESUS Trial

Safety	Rivaroxaban	ASA	HR (95% CI)
Major Bleeding	1.8%	0.7%	2.72 (1.68 – 4.39)
Life threat/fatal bleed	1.0%	0.4%	2.34 (1.28 – 4.29)
ICH	0.3%	0.1%	4.01 (1.51 – 14.2)

N Engl J Med 2018; 378:2191

NAVIGATE ESUS Trial

Pre-specified subset analysis ***favored aspirin!***

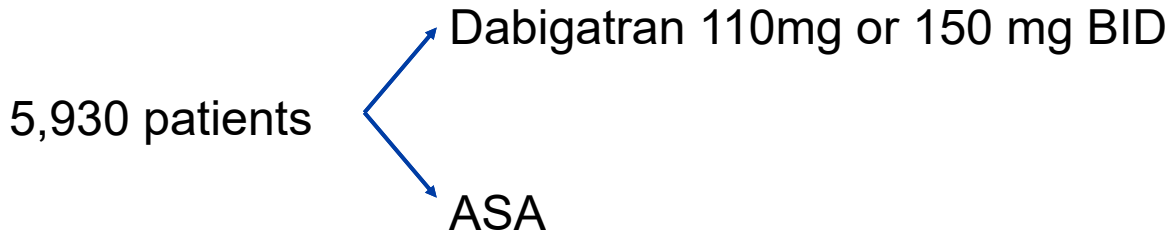
Variable	HR (95%CI)
• < 60 years old	1.73 (1.06 – 2.83)
• Asian ancestry	1.65 (1.08 – 2.52)
• Estimated GFR > 80 ml/min	1.57 (1.11 – 2.23)

N Engl J Med 2018; 378:2191

Dabigatran vs. Aspirin in Embolic Stroke of Undetermined Source

RE-SPECT ESUS Trial

Patients: ≥ 60y/o; Ischemic stroke within 3 mo (or within 6 mo plus ≥ 1 risk factor: mi-mod HF, DM, HTN, PFO, prior TIA)



Primary outcome: Recurrent stroke (Isch, hemorrh or unspec)

Stroke. 2019;50:1032-1033

RE-SPECT ESUS Trial

Outcomes	Dabigatran	ASA	HR (95% CI)
Primary Outcome (any stroke)	4.1%	4.8%	0.85 (0.69 – 1.03)
Ischemic Stroke	4.0%	4.7%	0.84 (0.68 – 1.03)
Major Bleeding			1.19 (0.85 – 1.66)

Stroke. 2019;50:1032-1033

65 y/o right handed male

Beyond smoking cessation, hypertension control and statin therapy, which of the following would you recommend?

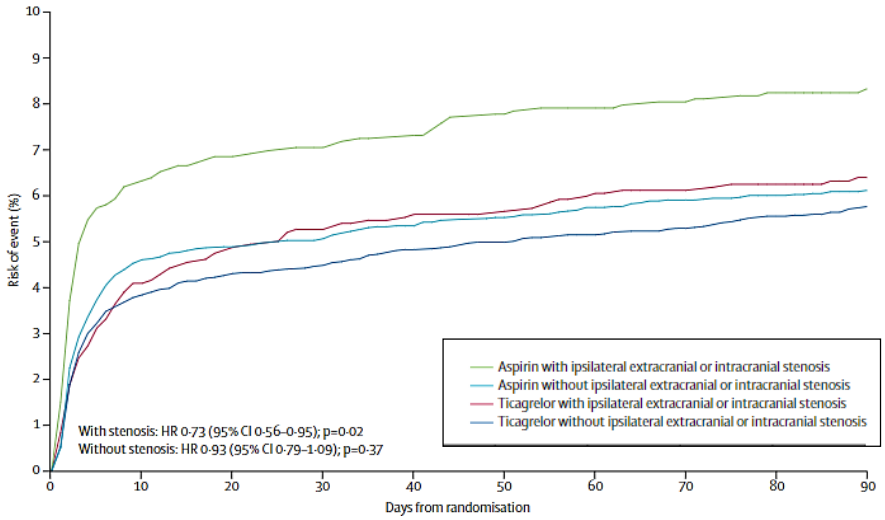
1. Aspirin 81 mg/day
2. Apixaban 5 mg BID
3. Rivaroxaban 5 mg BID
4. Rivaroxaban 15 mg/day
5. Rivaroxaban 20 mg/day
6. Dabigatran 150 mg BID

DOAC ESUS: Bottom Line

- Lack of benefit (Rivaroxaban and Dabigatran) & increased bleeding (Rivaroxaban) argue ***against*** the use of DOACs as a mono-therapy strategy for ESUS.
- These negative trial results may be explained by the ***stroke heterogeneity*** in the ESUS population.

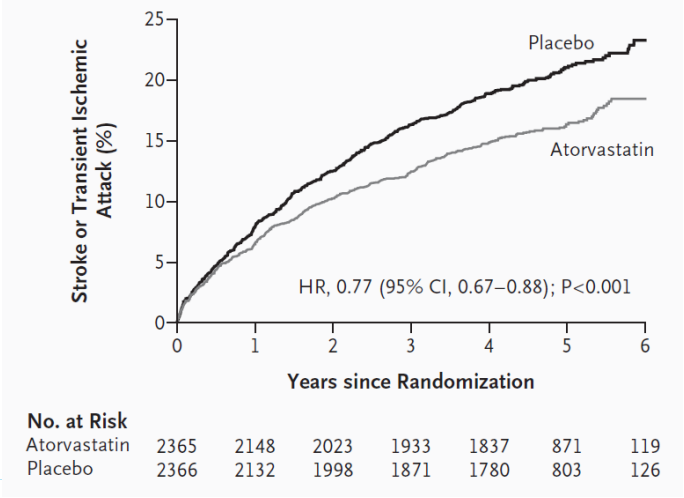
Ticagrelor vs. ASA in Acute Stroke/TIA

Atherosclerotic Subset of SOCRATES Trial



Lancet Neurol 2017;16:301

High-Dose Atorvastatin after Stroke or TIA
SPARCL Trial



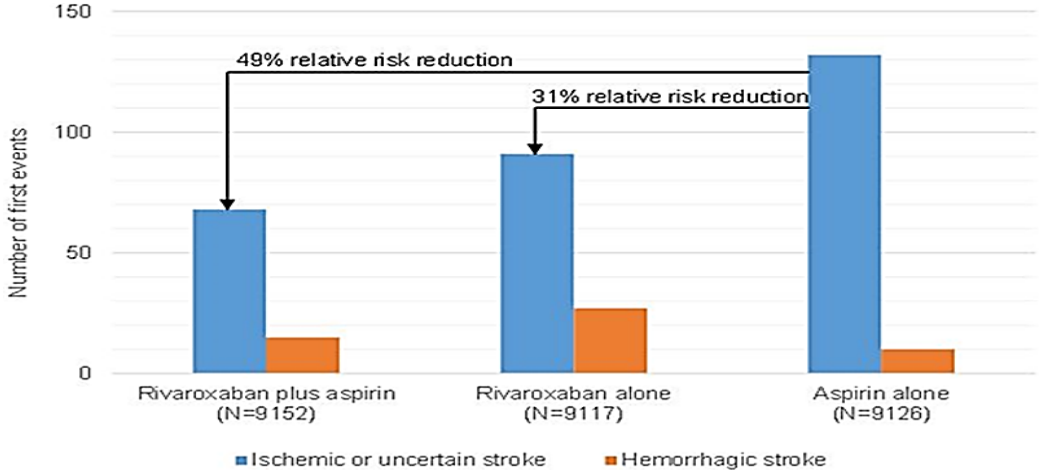
N Engl J Med 2006;355:549

DOAC ESUS: Bottom Line

- ***Aortic arch*** and ***carotid plaque rupture*** with embolization may be better suited for lipid lowering and antiplatelet therapy.

Stroke Outcomes

COMPASS Trial



Circulation 2019;139:1134

DOAC ESUS: Bottom Line

- Combining a ***DOAC*** plus ***aspirin*** plus ***lipid lowering*** (COMPASS trial) may be the most attractive option for these patients.

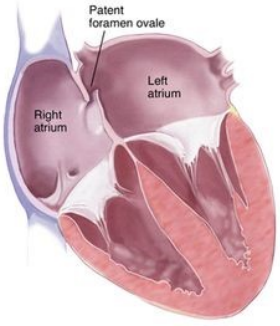
Same 65 y/o right handed male

Ten days ago, he suffered a minor right hemispheric stroke. He has hypertension and smokes. Carotid US showed mild plaque without significant stenosis. Holter, thrombophilia panel were negative.

TEE reveals PFO with small right to left shunt.

PFO & Cryptogenic Stroke

- Potential cause of cryptic stroke
- Device closure studied in 6 trials
  - 3 showed recurrent stroke reduction
  - Enrollment age limit < 60 years of age
  - Benefit compared to anti-platelets in all but 1 trial



CRYSTAL AF study NEJM 2014;370:2478

NAVIGATE ESUS Substudy

534 patients (7.4%) with PFO

Recurrent stroke rates

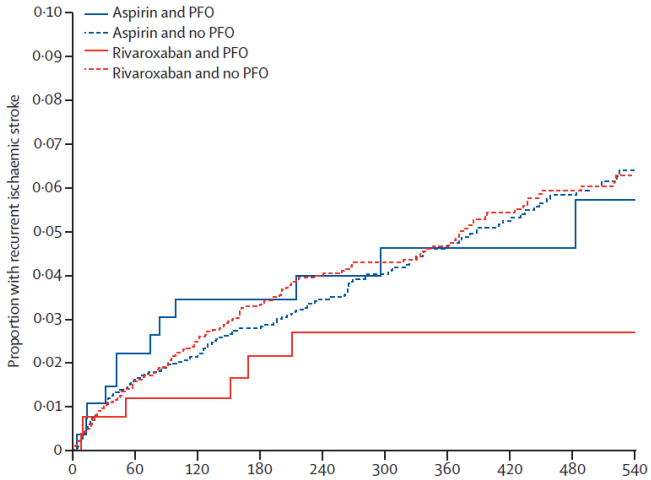
- PFO present 3.7%
- PFO absent 4.8%

HR (95%CI)

0.80 (0.51 – 1.26)

Lancet Neurol 2018;17:1053

NAVIGATE ESUS Substudy



Recurrent Stroke, PFO Subgroup

Rivaroxaban 2.6%
ASA 4.8%

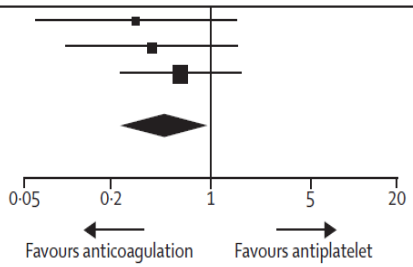
HR 0.54 (0.22 – 1.36)

Lancet Neurol 2018;17:1053

NAVIGATE ESUS Substudy

	Anticoagulation		Antiplatelet therapy		Weight (%)	OR (95% CI)
	Events	Total	Events	Total		
PICSS (2002)	2	42	8	56	19·2	0·30 (0·06–1·49)
CLOSE (2017)	3	187	7	174	26·4	0·39 (0·10–1·53)
NAVIGATE ESUS (2018)	7	182	12	197	54·3	0·62 (0·24–1·60)
Total (95% CI)		**411**		**427**	**100**	**0·48 (0·24–0·96)**
Total events	12		27			

Heterogeneity: τ^2=0·00; χ^2=0·69; df=2 (p=0·71); I^2=0%
Test for overall effect: Z=2·07 (p=0·04)



Lancet Neurol 2018;17:1053

NAVIGATE ESUS Substudy: PFO and Cryptic CVA Bottom Line

- Anticoagulation ***may*** reduce stroke recurrence in patients with PFO.
- Need more data with direct comparison of ***PFO closure and AC***
- Need more data for ***older subjects*** (> 60 years).

Case #3

66 y/o male

Discharged from hospital 2 weeks ago with heart failure. Known CAD with prior MI. Recent Echo reveals EF 30%. He is now NYHA class II. No documented Afib.

Heart failure regimen includes β-blocker, ARB, aldosterone antagonist, diurectic.

Laboratory: NT BNP 1020

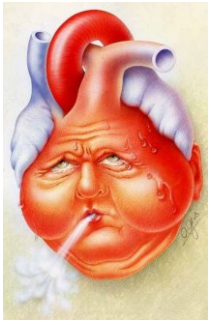
Creatinine 1.4 (Creat clearance 44 ml/min)

66 y/o male

Which of the following have been shown to reduce the composite outcome of death, stroke and MI?*

1. Rivaroxaban 2.5 mg BID
2. Rivaroxaban 5 mg BID
3. Rivaroxaban 15 mg/day
4. Rivaroxaban 20 mg/day
5. None of the above

Heart Failure and Thrombosis



- Heart failure is associated with increased ***prothrombin activation***, ***inflammation, endothelial injury/dysfunction*** and ***platelet activation***.
- Warfarin trials in patients with ***NSR*** have been disappointing.
- Warfarin increases ***bleeding*** outcomes.

Rivaroxaban in recent ACS
ATLAS-ACS-2 TIMI-51 Trial

Patients: Recent ACS/unstable angina (for subjects < 55, DM or prior MI)

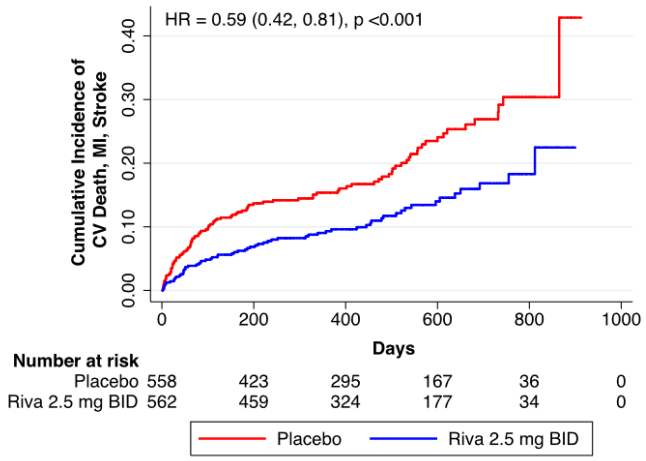
15,526 patients* → Rivaroxaban 2.5mg BID

15,526 patients* → Placebo

Primary outcome: CV Death, MI or stroke

N Engl J Med 2012;366:9

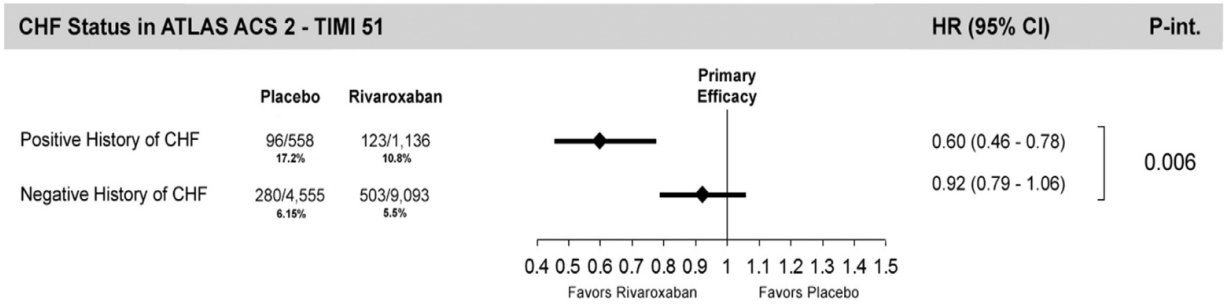
Rivaroxaban in ACS Patients with ***CHF***
Sub-study of *ATLAS-ACS-2* TIMI-51 Trial



N=1694 with HF

Am J Cardiol 2018;122:1896

Rivaroxaban in ACS Patients with CHF
Substudy of ***ATLAS-ACS-2*** TIMI-51 Trial



N=1694 with HF

Am J Cardiol 2018;122:1896

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease
COMMANDER HF Trial

Hypothesis: Rivaroxaban, by reducing thrombin generation, will improve outcomes for patients with worsening chronic heart failure and underlying coronary artery disease.

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease
COMMANDER HF Trial

Patients: ***HFrEF*** with recent worsening, NSR and CAD, elevated BNP/NTBNP
No identified atrial fibrillation

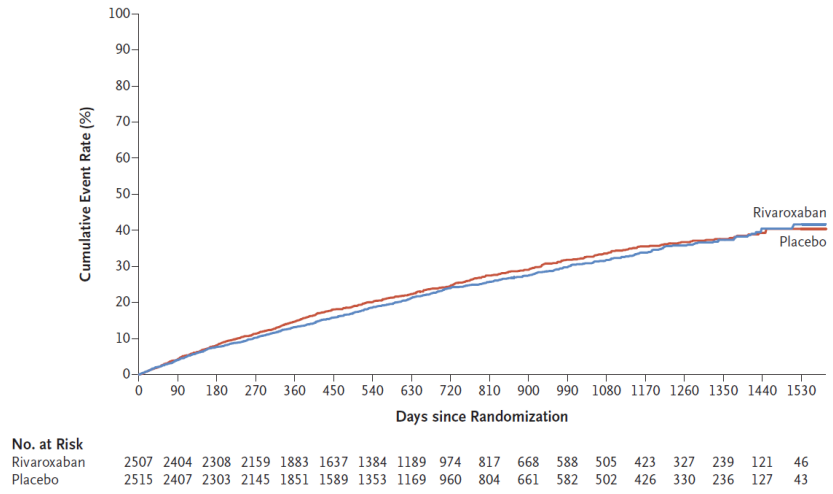
5,022 patients → Rivaroxaban 2.5mg BID
5,022 patients → Placebo

Primary outcome: Death, stroke or MI

N Engl J Med 2018;379:1332

COMMANDER HF Trial

Efficacy



Death, stroke or MI

N Engl J Med 2018;379:1332

COMMANDER HF Trial

Efficacy	Rivaroxaban	Placebo	HR (95% CI)
Primary Outcome (death, stroke, MI)	25%	26.2%	0.94 (0.89 – 1.05)
All cause mortality	21.8%	22.1%	0.98 (0.87 – 1.10)
MI	3.9%	4.7%	0.83 (0.63 – 1.08)
Stroke	2.0%	3.0%	0.66 (0.47 – 0.95)

N Engl J Med 2018;379:1332

COMMANDER HF Trial

Safety	Rivaroxaban	Placebo	HR (95% CI)
Primary Outcome (Fatal, disabling bleed)	0.7%	0.9%	0.80 (0.43 – 1.49)
Fatal bleeding	0.4%	0.4%	1.03 (0.41 – 2.59)
Disabling bleed	0.5%	0.8%	0.67 (0.33 – 1.34)
Major Bleeding (ISTH)	3.3%	2.0%	1.68 (1.18 – 2.39)

N Engl J Med 2018;379:1332

66 y/o male

Which of the following have been shown to reduce the composite outcome of death, stroke and MI in HF patients?

1. Rivaroxaban 2.5 mg BID
2. Rivaroxaban 5 mg BID
3. Rivaroxaban 15 mg/day
4. Rivaroxaban 20 mg/day
5. None of the above

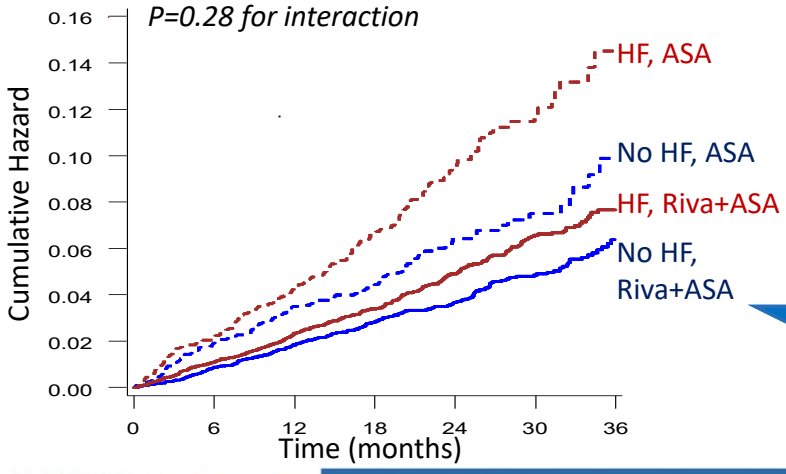
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease
Compass Trial

Patients: Stable cardiovascular disease (CAD, PAD or both)
Exclusion: Severe HF, EF < 30%, NYHA III or IV

5902 HF patients randomized (of 27,325 total subjects)
90% of total randomized subjects had CAD

Lancet 2018;391:205

Primary MACE Outcome by HF Status

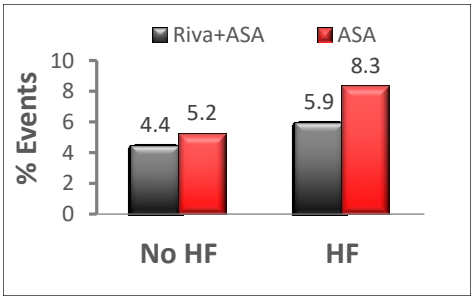


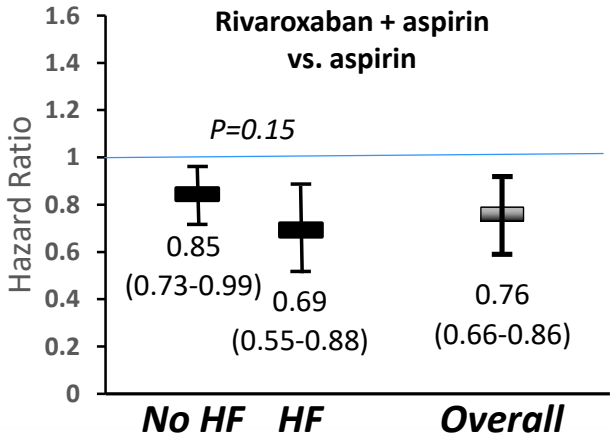
HR 0.68
(95% CI 0.53-0.86)
ARR 2.4%
NNT 42

HR 0.79
(95% CI 0.68-0.93)
ARR 0.9%
NNT 111

Net Clinical Benefit: Hazard Ratios

(Primary outcome + Severe bleeding events)





- Net clinical benefit of patients with HF and no HF are consistent with overall trial
- Higher absolute risk reduction for patients with HF

Heart Failure & DOACs: Bottom Line

- Like prior trials with warfarin, low dose rivaroxaban ***does not*** appear to lower death or MI in HFrEF patients with NSR.
- Low dose rivaroxaban may reduce the absolute risk of ***stroke*** by ***1%***.
- In patients with HFpEF, a strategy of low dose rivaroxaban ***may*** have a safety and efficacy signal (COMPASS, ATLAS ACS).

Case #4

43 year old female RN

- Diplopia with severe “searing” headache.
- “I have an unstable right PCOM aneurysm”.
- CTA head: right PCOM aneurysm.
- Neurosurgery: “story worrisome for sentinel bleed or recent aneurysm enlargement”. “Needs emergent coiling vs. craniotomy with clip”.

43 year old female RN

- Recurrent DVT
- Heterozygous Factor V Leiden
- Last DVT, 6 months ago
- She takes ***apixaban 5 mg*** twice daily.

What would be the next most appropriate step in managing this patient?*

1. Take the patient immediately to surgery
2. Activated charcoal
3. FFP/Vitamin K
4. Prothrombin Complex Concentrate
5. Idarucizumab
6. Andexanet alpha

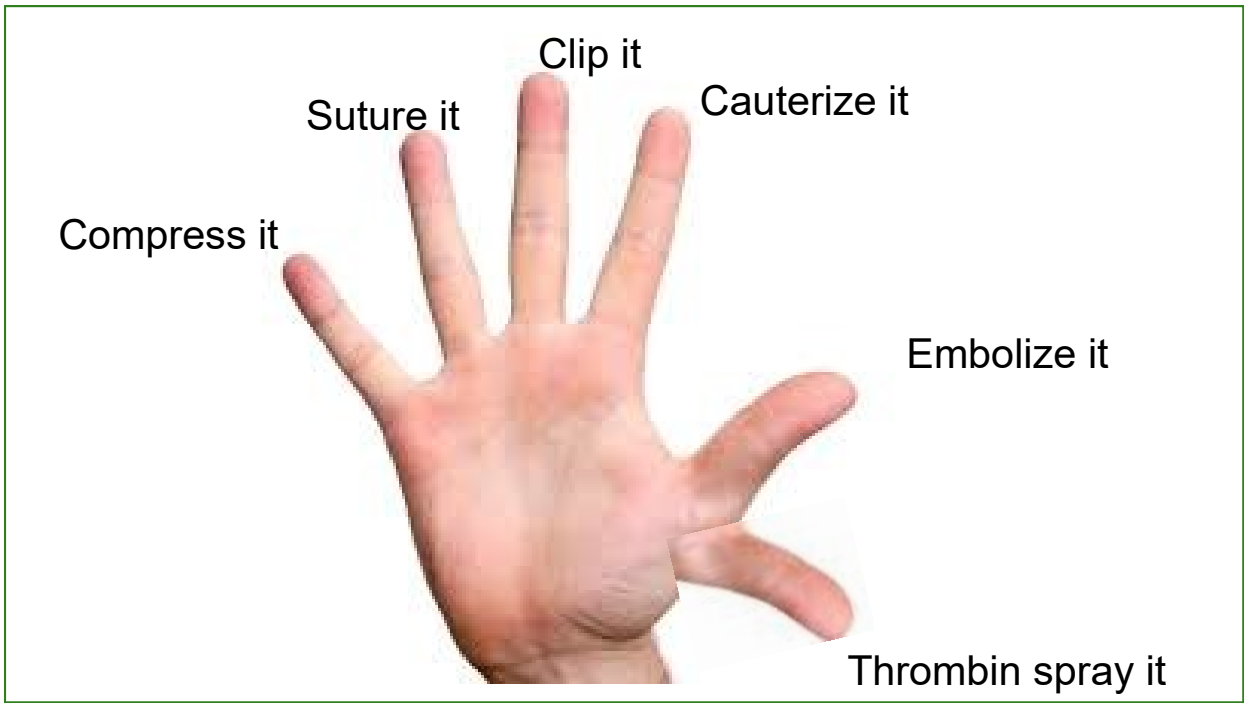
How do you manage a patient with:

Major Bleeding

or

Urgent/Emergent Surgery

…..if they are on a DOAC



Management Decision Tree

Establish
Baseline Thrombotic Risk

↓

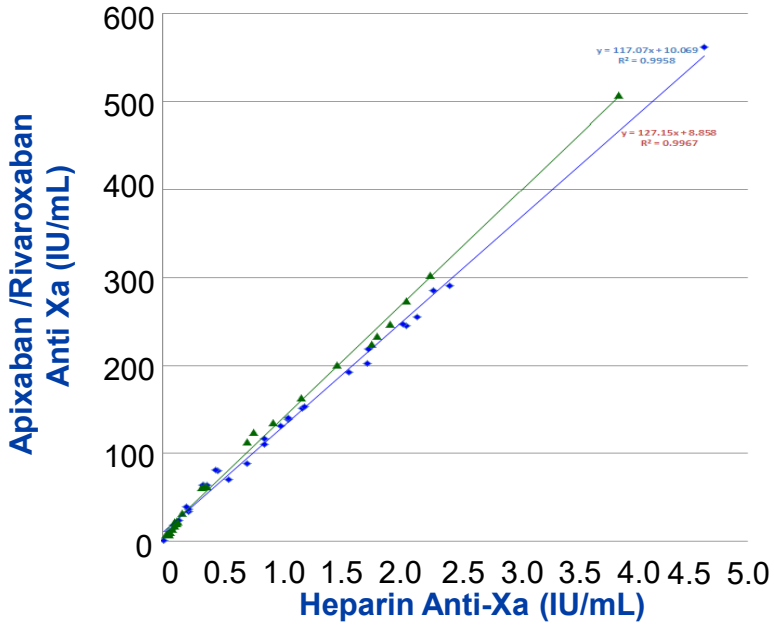
Define
Timing of last dose
Rate of metabolism
Inhibitor concentration

Direct Factor Inhibitors

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Factor Target	Thrombin	Xa	Xa	Xa
T½ (hrs)	12-17	7-11	7-11	11
Elimination	Renal	Renal Hepatic	Renal Hepatic Enteric	Renal Hepatic Enteric

How do you assess ***drug levels*** if you don't have the ***direct assay***?

Approximate ***DOAC levels*** using ***Heparin Anti Xa***



Management Decision Tree

Establish
Baseline Thrombotic Risk

↓

Define
Timing of last dose
Rate of metabolism
Inhibitor concentration

↓

Weigh
Risks and Benefits of Reversal

Antidotes: Direct Factor Inhibitors

	Idarucizumab	Andexanet alpha	Aripazine
Chemical Structure	Humanized Monocl FAB	Truncated rFXa	Cationic molecule
Target	Dabigatran	DXi	DXi, DTI, Heparins
Company	Boehringer Ingelheim	Portola	Perosphere

Idarucizumab for Dabigatran Reversal

ABSTRACT

N Engl J Med 2015;373:511

Idarucizumab (Praxbind)
Dabigatran Reversal

90 Patients

Group A Major bleeding (n=51)

Group B Urgent surgery (n=39)

Major Bleeding Group

- ***Mortality rate 18%***

Urgent Surgery Group

- ***Mortality rate 23%.***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

ABSTRACT

BACKGROUND

Bleeding is a complication of treatment with factor Xa inhibitors, but there are no specific agents for the reversal of the effects of these drugs. Andexanet is designed to reverse the anticoagulant effects of factor Xa inhibitors.

METHODS

Healthy older volunteers were given 5 mg of apixaban twice daily or 20 mg of ri- varoxaban daily. For each factor Xa inhibitor, a two-part randomized placebo- controlled study was conducted to evaluate andexanet administered as a bolus or as a bolus plus a 2-hour infusion. The primary outcome was the mean percent change in anti-factor Xa activity, which is a measure of factor Xa inhibition by the anticoagulant.

RESULTS

Among the apixaban-treated participants, anti-factor Xa activity was reduced by 94% among those who received an andexanet bolus (26 participants), as compared with 23% among those who received placebo (9 participants) ($P<0.001$), and unbound apixaban concentration was reduced by 0.5 ng per milliliter versus 1.9 ng per milliliter ($P<0.001$); thrombin generation was fully restored in 100% versus 11% of the participants ($P<0.001$) within 2 to 5 minutes. Among the rivaroxaban-treated participants, anti-factor Xa activity was reduced by 92% among those who received an andexanet bolus (27 participants), as compared with 38% among those who received placebo (14 participants) ($P<0.001$), and unbound rivaroxaban concentration was reduced by 25.4 ng per milliliter versus 4.2 ng per milliliter ($P<0.001$); thrombin generation was fully restored in 86% versus 7% of the participants ($P<0.001$). These effects were sustained when andexanet was administered as a bolus plus an infusion. In a subgroup of participants, transient increases in levels of D-dimer and prothrombin fragments 1 and 2 were observed, which resolved within 24 to 72 hours. No serious adverse or thrombotic events were reported.

CONCLUSIONS

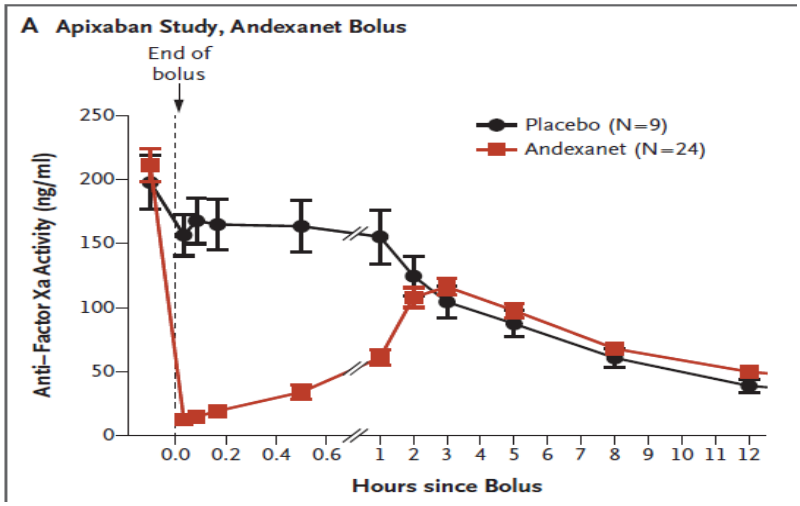
Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects. (Funded by Portola Pharmaceuticals and others; ANNEXA-A and ANNEXA-R ClinicalTrials.gov numbers, NCT02329725 and NCT02329275.)

Andexanet alpha

- Recombinant modified factor Xa
- Catalytically inactive
- Binds:
  - Rivaroxaban, apixaban, edoxaban
  - LMWH
  - Fondaparinux

N Engl J Med. 2015

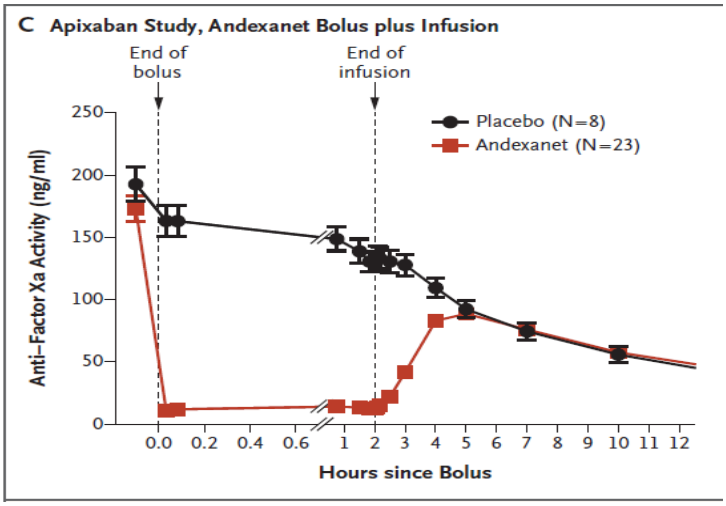
Apixaban: Bolus Only



Anti-Xa activity reduced by 90%.

N Engl J Med. 2015 [Epub].

Effects maintained for infusion duration



Anti-Xa activity reduced by 90%.

N Engl J Med. 2015 [Epub].

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

ORIGINAL ARTICLE

ABSTRACT

ANNEXA-4 Study

352 patients: major bleed

64% ICH, 26% GI

Riv (36%), Apix (55%)

- Hemostasis, good/excellent: 82%
- ***Mortality 14%***
- ***Thromboembolism 10%***

N Engl J Med 2019; Feb 7

PCCs: Warfarin Reversal

- 165 ***warfarin*** treated patients
- Reason for reversal

Major bleed	56%
Emergent Procedure	44%

- Complications

Thromboembolic events	***21%***
Death	***16%***

Thromb Res. 2016;139:160-5

Which agent?

Andexanet or ***K-Centra?***

Which agent?

K-Centra

- Bleeding is not ICH or intraspinal
- Patient is hemodynamically stable
- Drug levels are low and falling (serial testing)
- Renal function is normal
- No drug – drug interactions (Strong CYP3A4 Inhibitors)

Which agent?

Andexanet

- ICH or intra-spinal bleeding
- Hemodynamic instability
- Drug levels are elevated and stagnant (serial testing)
- Acute renal failure
- Significant drug interactions (Strong CYP3A4 Inhibitors)

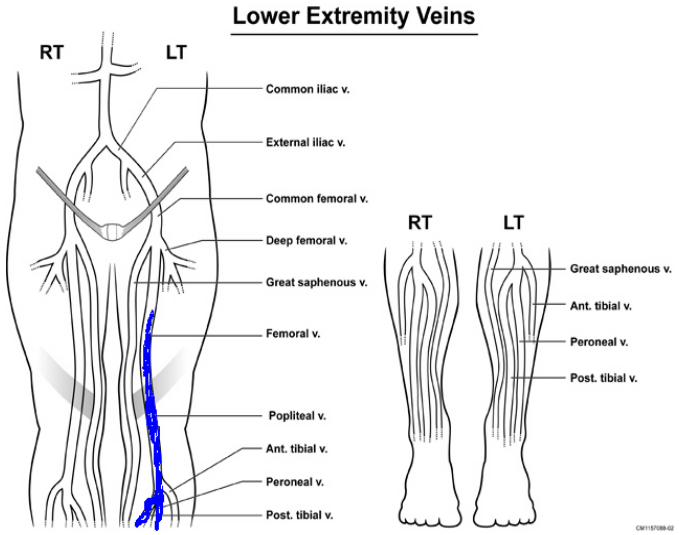
- Future direct comparison RCT is needed and coming!

43 year old female

What would be the next most appropriate step in managing this patient?

1. Take the patient immediately to surgery
2. Activated charcoal
3. FFP/Vitamin K
4. Prothrombin Complex Concentrate
5. Idarucizumab
6. Andexanet alpha

43 year old female RN: Rest of story?



DOAC Antidotes: Bottom Line

- Efficacy in ***major bleeding*** or ***procedure related bleeding*** reversal is promising.
- Each carries a ***high mortality (~20%)*** and ***thromboembolism (~20%)*** rate (pause)
- Underscores the seriousness of major bleeding or urgent surgery ***while on anticoagulants!***

Stable CAD/PAD: Last words

- A strategy of rivaroxaban 2.5 mg BID plus ASA reduce ***MACE*** and ***MALE*** (COMPASS).

Cryptic Stroke: Last words

- ***Do not benefit*** from DOAC monotherapy (NAVIGATE, RE-SPECT ESUS).
- A strategy of ***prolonged monitoring*** (CRYSTAL AF), ***lipid lowering*** (SPARCL), and ***rivaroxaban 2.5 mg BID plus aspirin*** (COMPASS) may be reasonable.

Heart Failure: Last words

- ***HFrEF does not appear to benefit*** from rivaroxaban 2.5 mg BID (COMMANDER HF).
- ***HFpEF may benefit*** from rivaroxaban 2.5 mg BID plus aspirin (COMPASS, ATLAS).

BLEEDING: Last words

- Use a ***step wise approach*** to evaluation and management.
- Consider ***PCC*** for low risk patients and reserve ***Andexanet*** alpha for life threatening bleeding.
- Use ***caution*** when considering reversal.