Management (and Prevention) of Bleeding on DOACs:

Craig S. Cameron, MD, FACC, FHRS

Oklahoma Heart Institute

* No Disclosures Relevant to This Talk *

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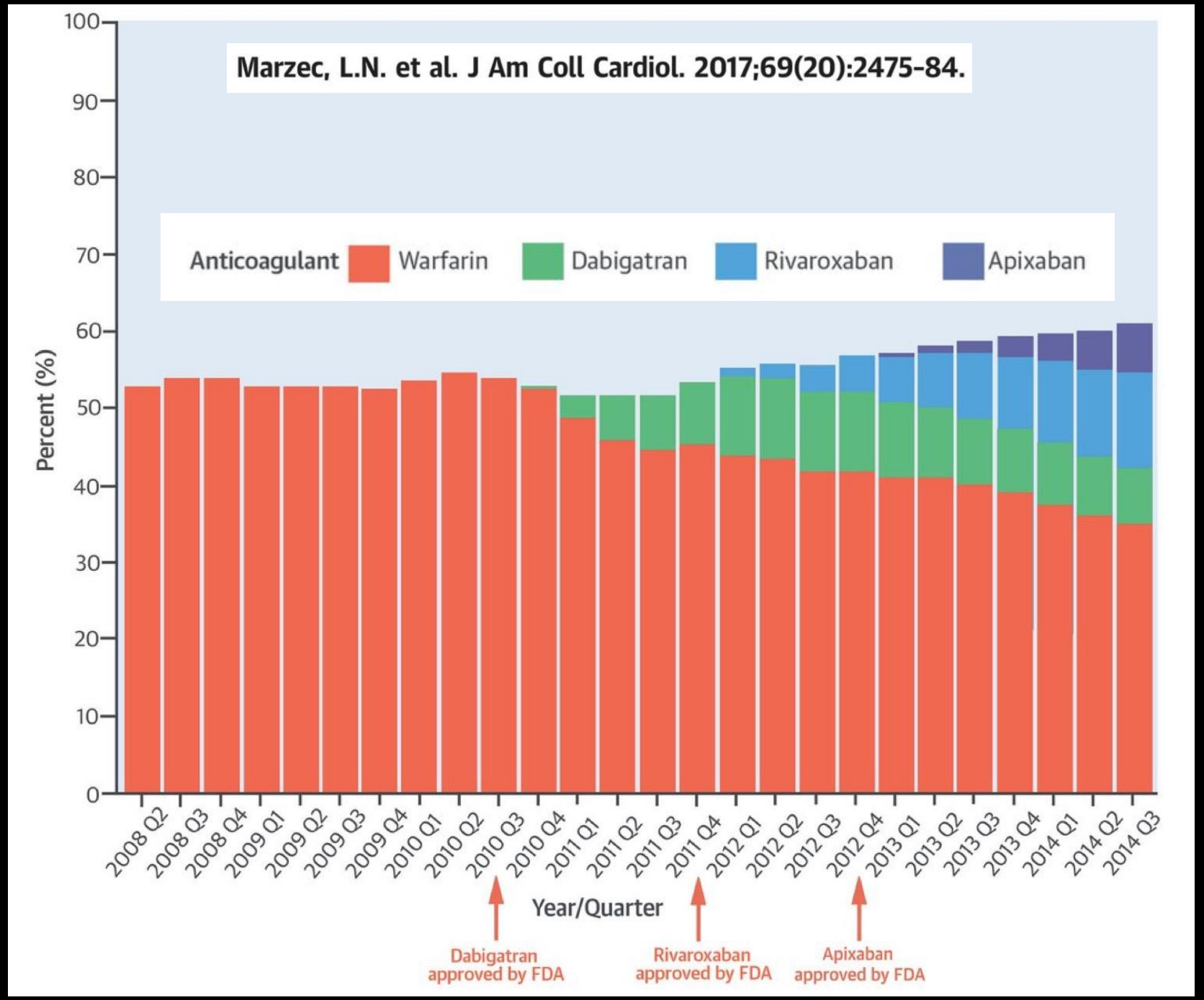

Marzec, L.N. et al. J Am Coll Cardiol. 2017;69(20):2475-84.
Anticoagulant
Warfarin
Dabigatran
Rivaroxaban
Apixaban
Percent (%)
100
90
80
70
60
50
40
30
20
10
0
2008 Q2
2008 Q3
2008 Q4
2009 Q1
2009 Q2
2009 Q3
2009 Q4
2010 Q1
2010 Q2
2010 Q3
2010 Q4
2011 Q1
2011 Q2
2011 Q3
2011 Q4
2012 Q1
2012 Q2
2012 Q3
2012 Q4
2013 Q1
2013 Q2
2013 Q3
2013 Q4
2014 Q1
2014 Q2
2014 Q3
Year/Quarter
Dabigatran approved by FDA
Rivaroxaban approved by FDA
Apixaban approved by FDA

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

January CT, et al. 2019 Focused Update on Atrial Fibrillation

Class of Recommendation	Level of Evidence	Recommendations
I	A	2. 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) (S4.1.1-8– S4.1.1-11).

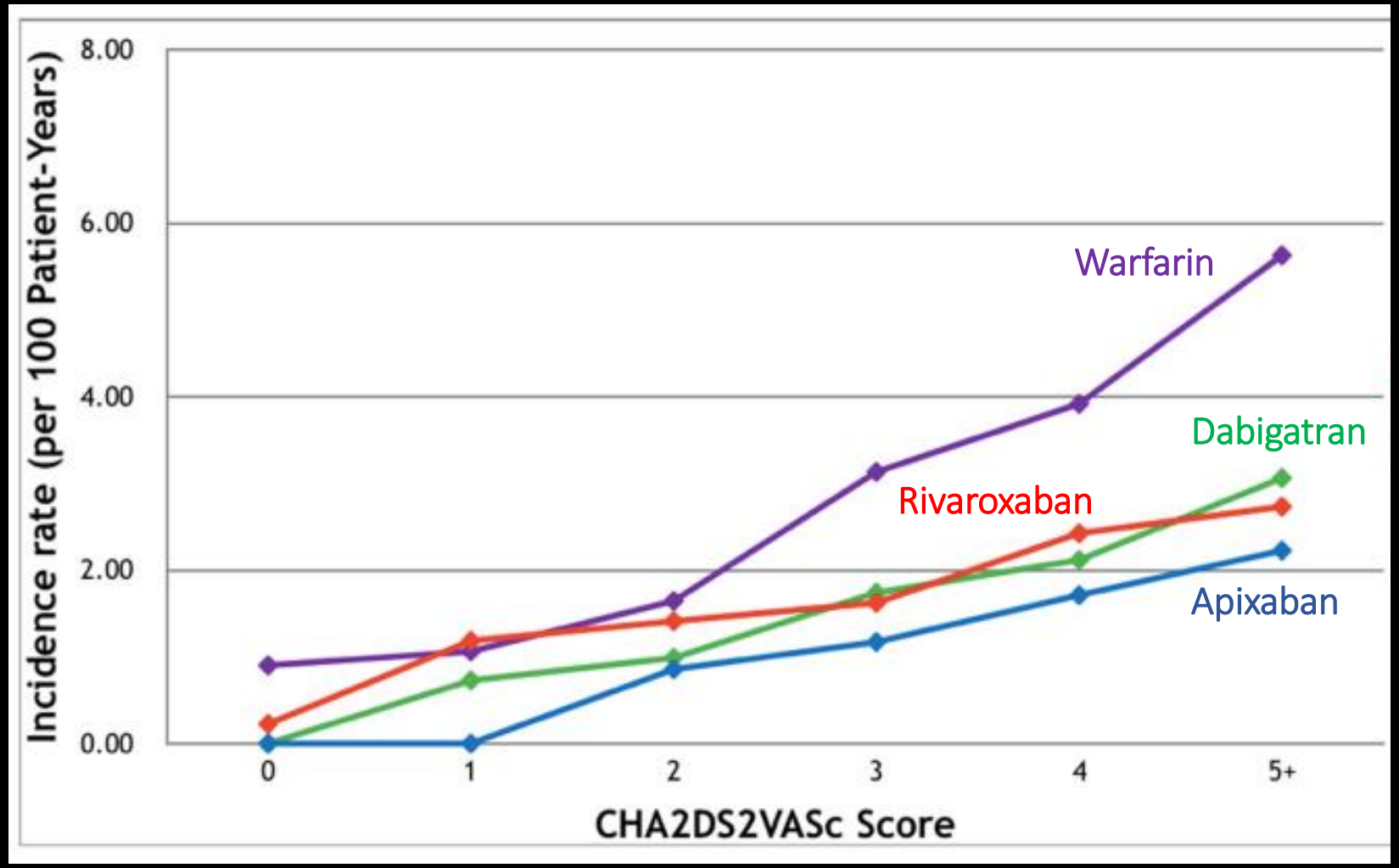
Prevention of Bleeding Complications

- Patient Selection
- Dosing
- “The Company Kept”

Clinical Characteristic	Score
Congestive Heart Failure	1
Hypertension	1
Age > 75	2
Diabetes	1
Stroke/TIA	2
Vascular Disease	1
Age > 65	1
Sex (female gender)	1

Clinical Characteristic	Score
Hypertension	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly age	1
Drugs or alcohol (1 each)	1 or 2

The CHA2DS2-VASc Score Predicts Major Bleeding in Non-Valvular Atrial Fibrillation Patients Who Take Oral Anticoagulants



J. Clin. Med. **2018**, *7*, 338

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS...

Class of Recommendation	Level of Evidence	Recommendations
I	A, B	1. For patients with AF and an elevated CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: • Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7) • Dabigatran (LOE: B) (S4.1.1-8) • Rivaroxaban (LOE: B) (S4.1.1-9) • Apixaban (LOE: B) (S4.1.1-10), or • Edoxaban (LOE: B-R) (S4.1.1-11)
IIb	C	15. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered (S4.1.1-31–S4.1.1-35).

DOAC Dosing Recommendations in AFib

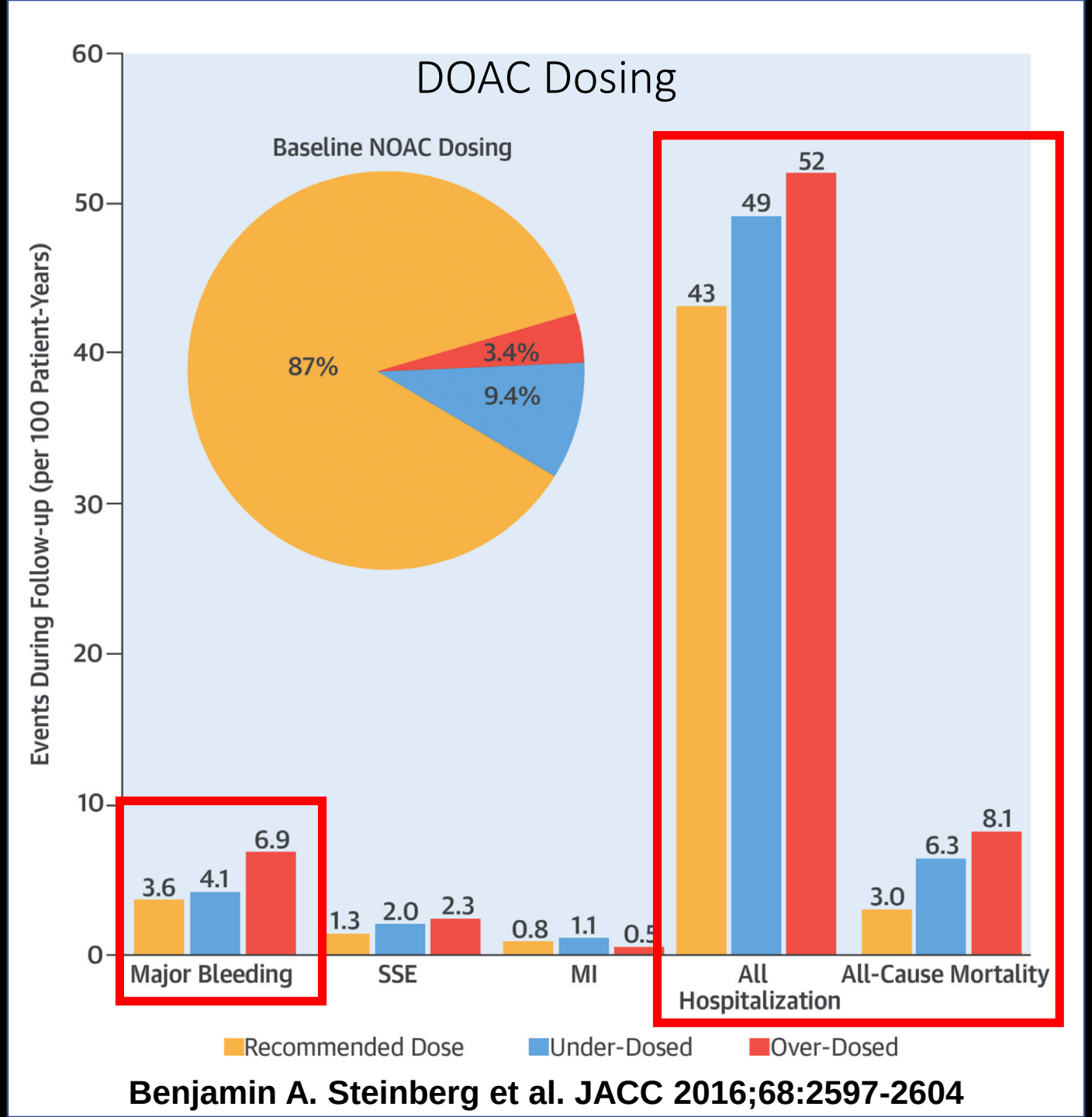
Apixaban	Dabigatran	Edoxaban	Rivaroxaban
5 mg BID	150 mg BID	60 mg daily (contraindicated if CrCl≥95 ml/min)	20 mg daily with food
2.5 mg BID 1. If 2 of 3 factors present: Age ≥80 years, SCr ≥1.5 mg/dL, Weight ≤60 kg	75 mg BID CrCl 15-30 mL/min OR, CrCl 30-50 mL/min with concomitant dronedarone or ketoconazole	30 mg daily CrCl 15-50 mL/min	15 mg daily with food CrCl 15-50 mL/min
2 strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir)			

Substrates for P-glycoproteins

Substrates for CYP3A4

ORBIT AF II

5,738 patients
- 9.4% underdosed
- 3.4% overdosed



Benjamin A. Steinberg et al. JACC 2016;68:2597-2604

Question #1

The addition of aspirin to oral anticoagulation increases the risk of bleeding by:

A. 0%

B. 30%

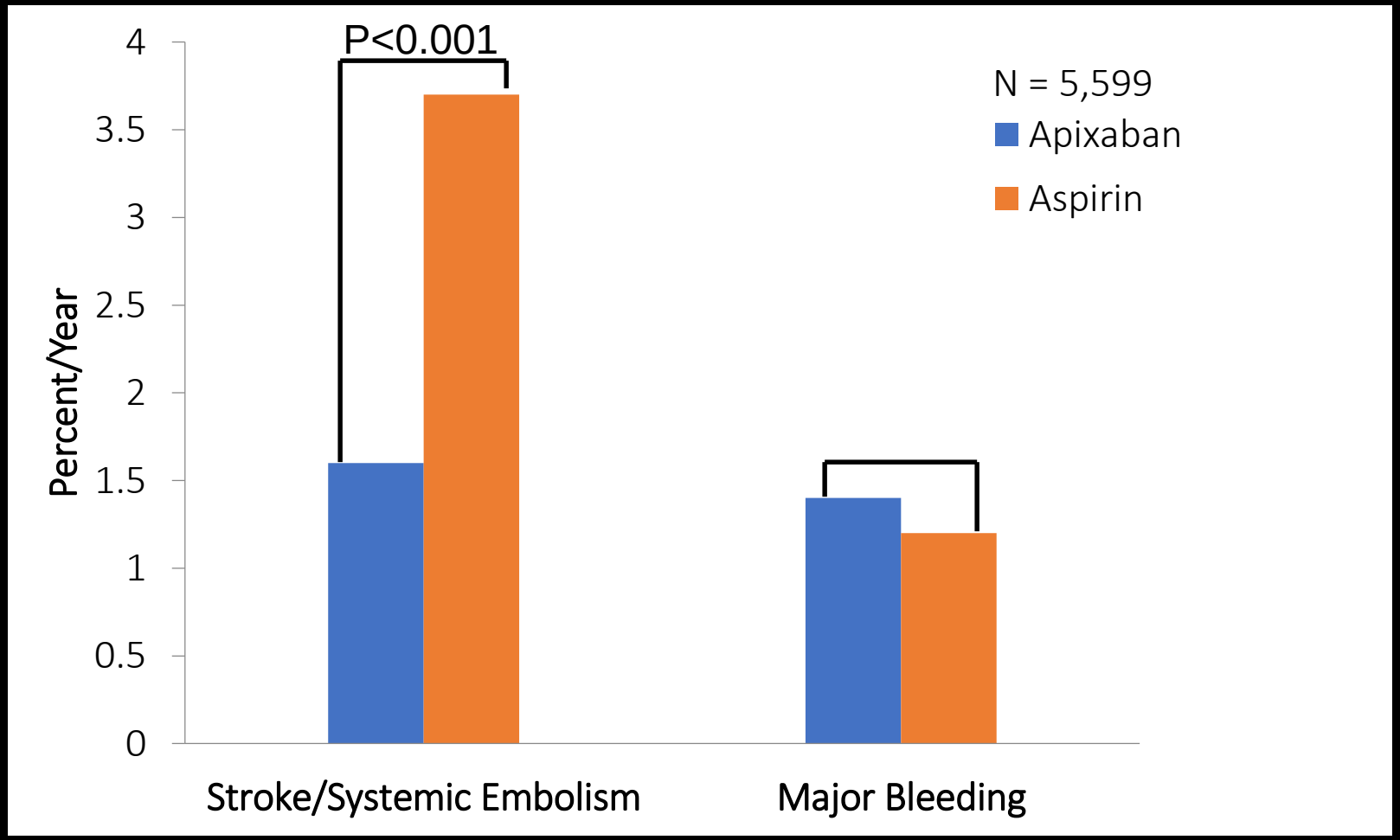
C. 50%

D. 75%

E. 100% (double)

AVERROES

Stroke/Systemic Embolism and Major Bleeding



N Engl J Med 2011;364:806-17

The NEW ENGLAND

CONCLUSIONS

Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

CONCLUSIONS

The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number,

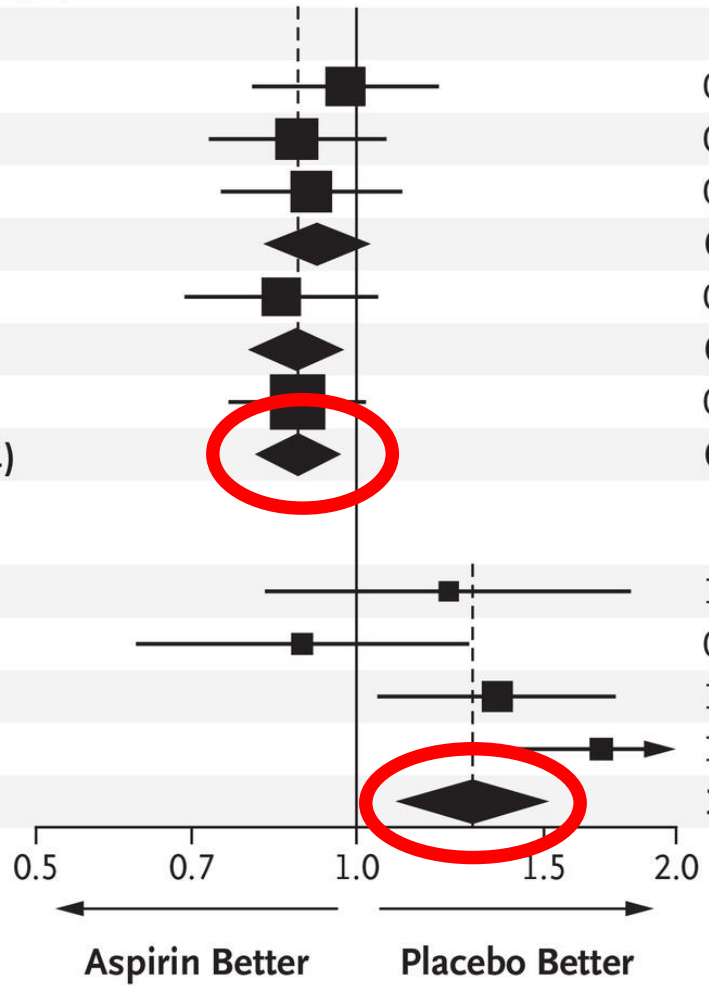
CONCLUSIONS

Higher all-cause mortality was observed among apparently healthy older adults who received daily aspirin than among those who received placebo and was attributed primarily to cancer-related death. In the context of previous studies, this result was unexpected and should be interpreted with caution. (Funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.)

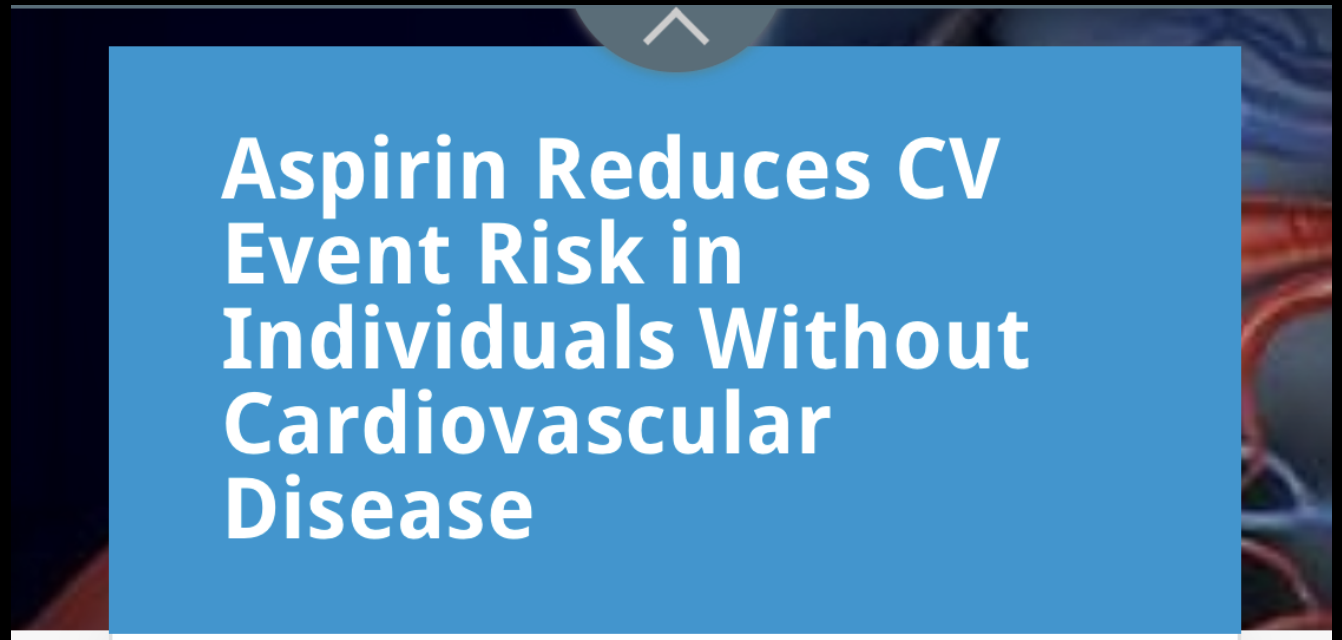
Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASCEND Study Collaborative Group*

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



N Engl J Med 2018;379:1529-39.



Aspirin Reduces CV Event Risk in Individuals Without Cardiovascular Disease

Posted on Feb 6, 2019 in Cardiology

https://www.thecardiologyadvisor.com/asp for-primary-prevention-of-cardiovascular-events/article/831954/

February 06, 2019

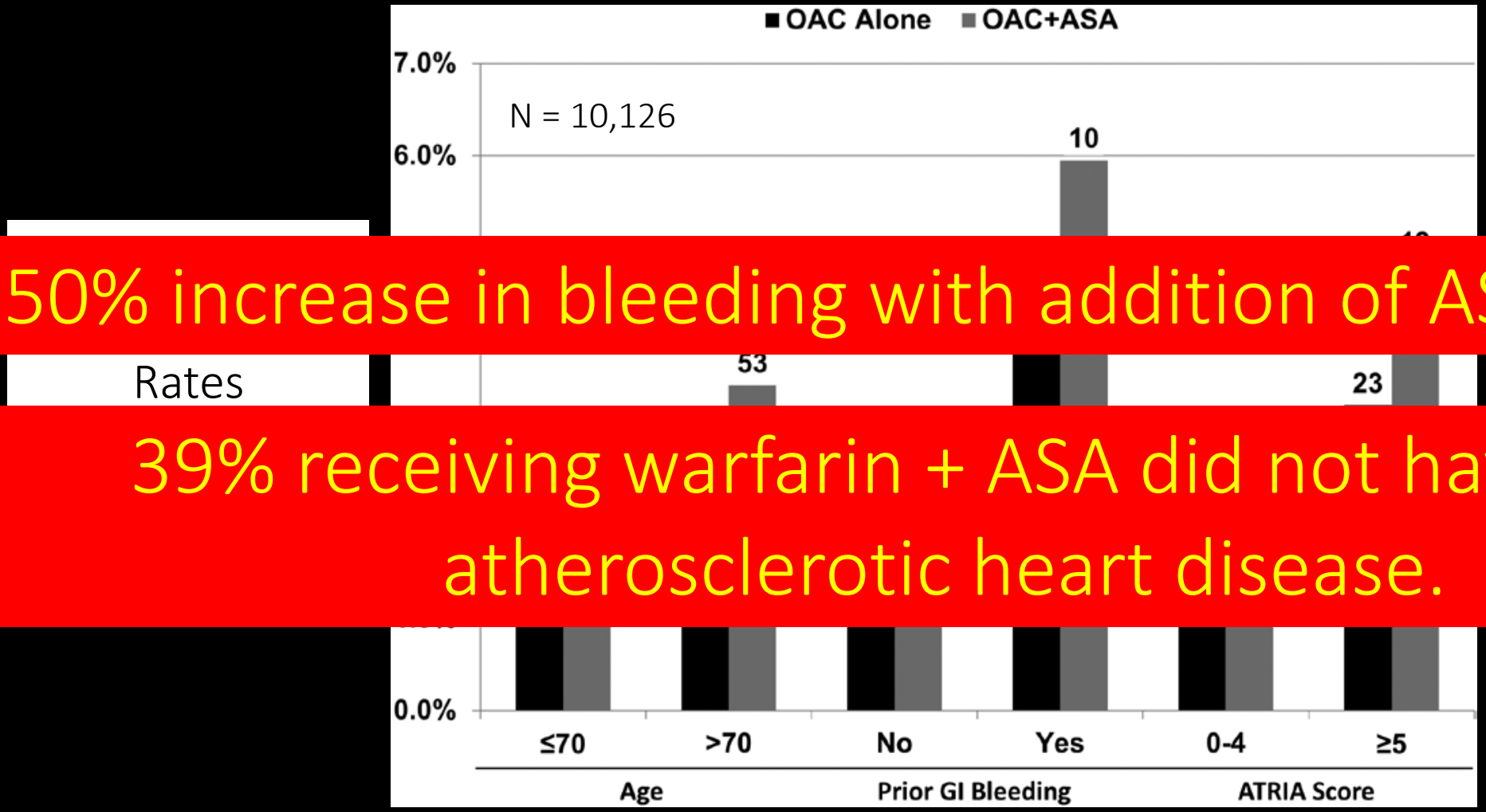
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

January CT, et al. 2019 Focused Update on Atrial Fibrillation

Class of Recommendation	Level of Evidence	Recommendations
IIa	B	For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy (S4.1.1-24, S4.1.1- 25).

Use and Associated Risks of Concomitant Aspirin Therapy With Oral Anticoagulation in Patients With Atrial Fibrillation

Insights From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry



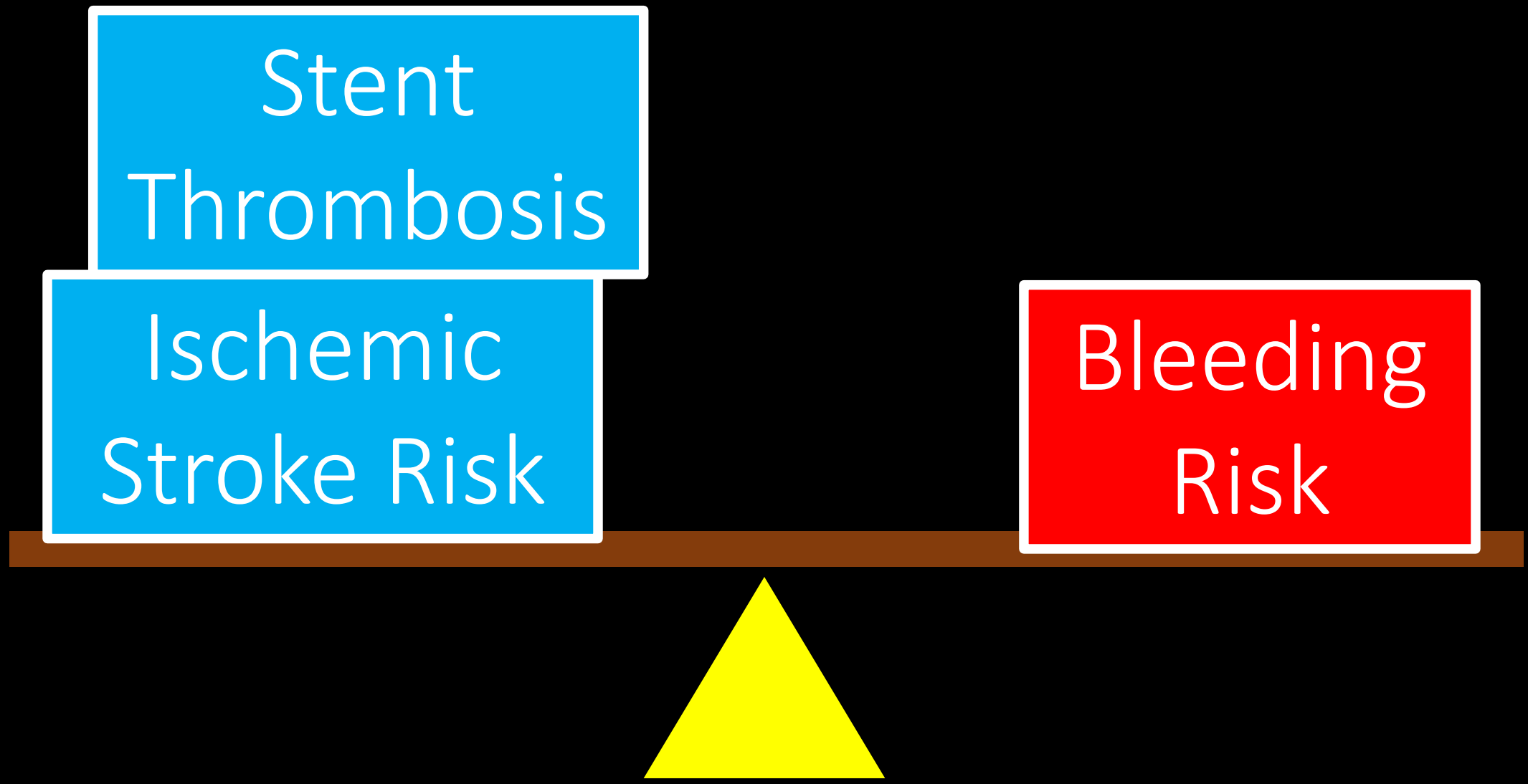
50% increase in bleeding with addition of ASA to OAC!

Rates

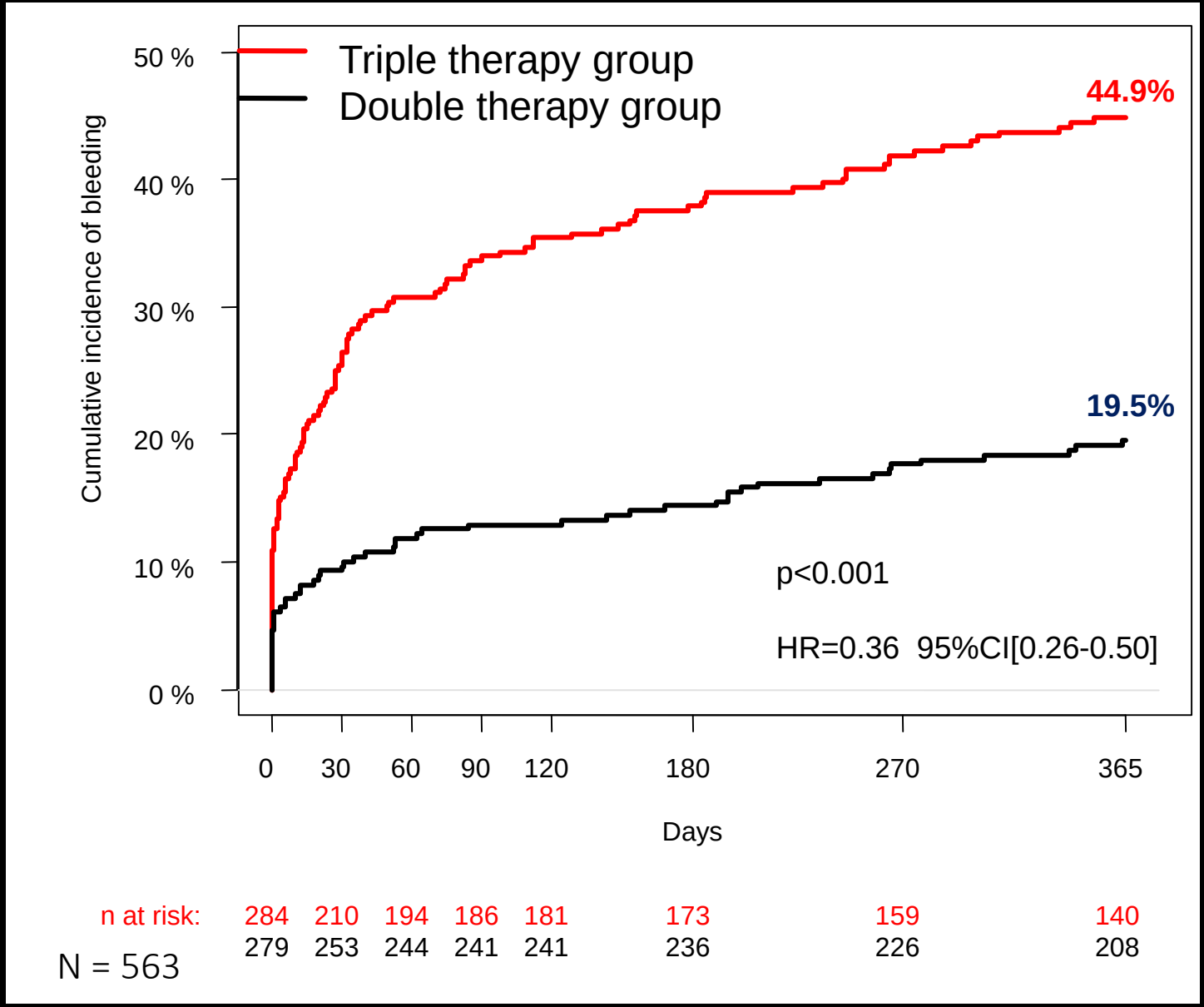
39% receiving warfarin + ASA did not have a h/o atherosclerotic heart disease.

Circulation. 2013;128:721-728.

What about triple therapy?

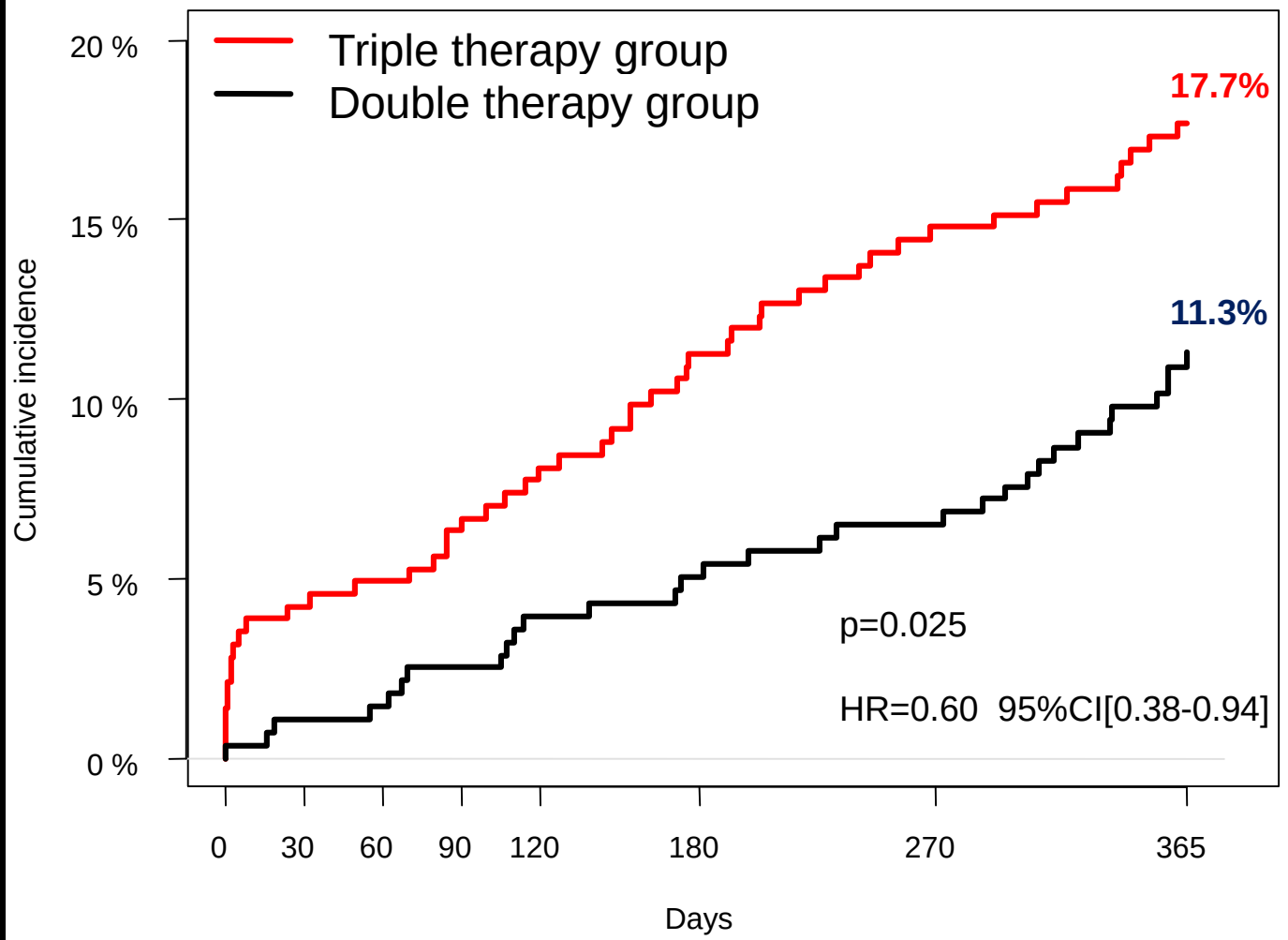

Stent Thrombosis
Ischemic Stroke Risk
Bleeding Risk

WOEST Trial



The Lancet **2013**
381, 1107-1115

Secondary Endpoint (Death, MI,TVR, Stroke, ST)

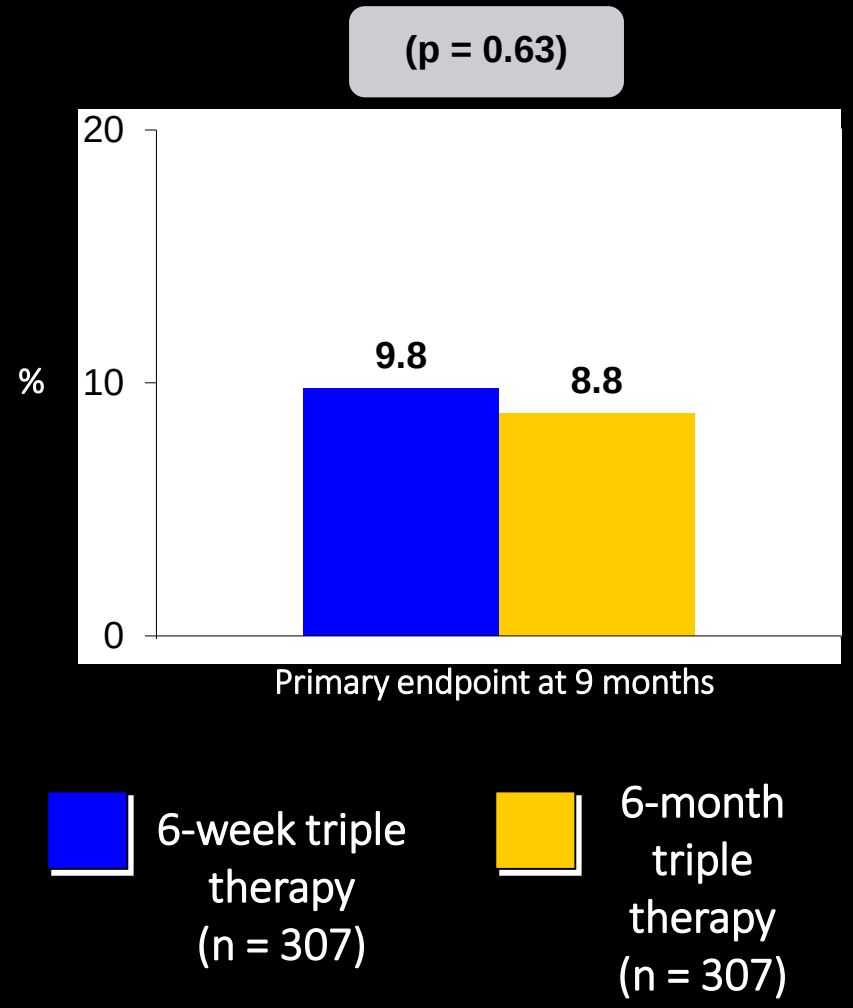


n at risk:								
	284	272	270	266	261	252	242	223
	279	276	273	270	266	263	258	234

The Lancet **2013**
381, 1107-1115

ISAR-TRIPLE

Trial design: Patients with an indication for oral anticoagulation (OAC) and undergoing DES PCI were randomized to either 6 weeks or 6 months of triple therapy (aspirin + clopidogrel + OAC initially, aspirin + OAC indefinitely). Patients were followed for 9 months.



Results

- Primary endpoint: Composite of death, MI, stent thrombosis, stroke, TIMI major bleeding at 9 months for 6 weeks vs. 6 months of triple therapy: 9.8% vs. 8.8%, HR 1.14, 95% CI 0.68-1.91, p = 0.63
- Cardiac death, MI, stent thrombosis, ischemic stroke: 4.0% vs. 4.3%, p = 0.87; TIMI major bleeding: 5.3% vs. 4.0%, p = 0.44
- Stent thrombosis: 0.7% vs. 0%

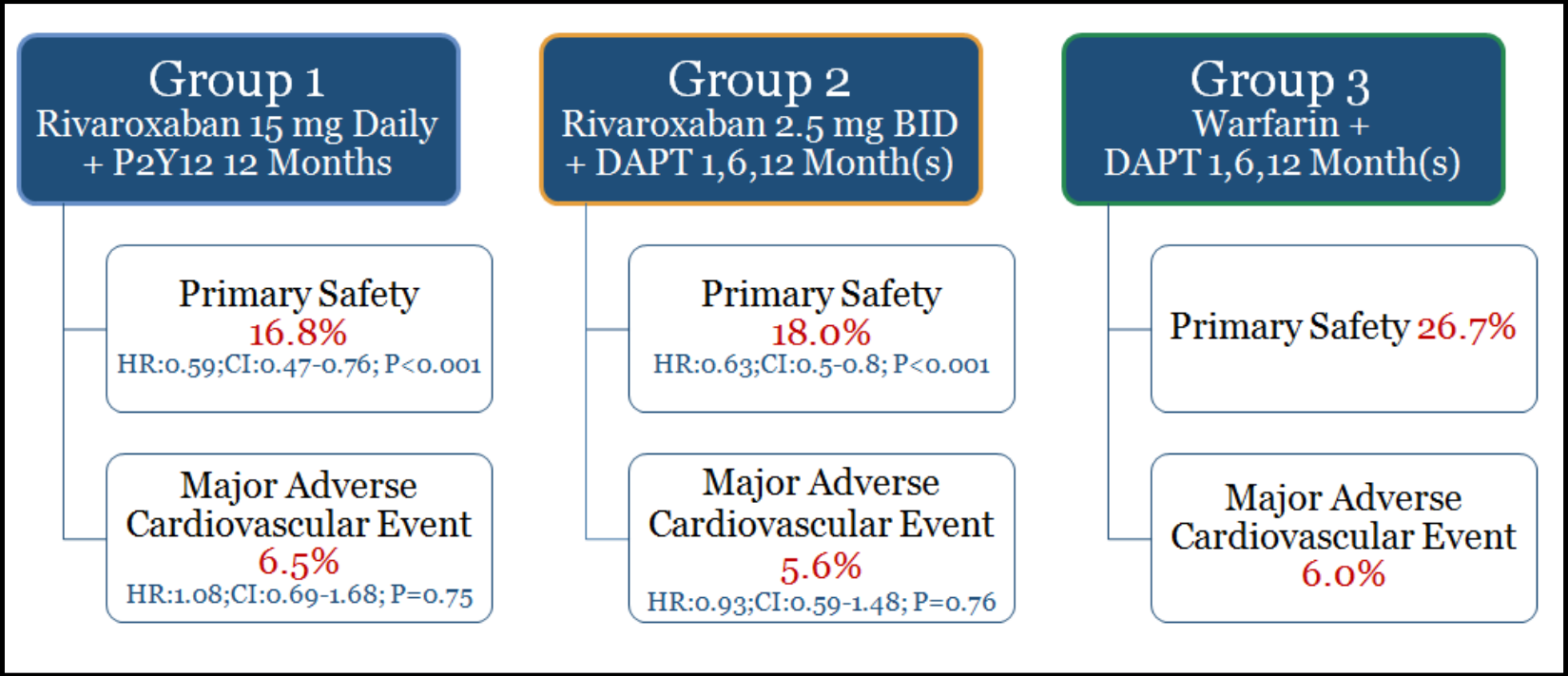
Conclusions

- 6-week duration of triple therapy is not superior to a 6-month duration of triple therapy in patients undergoing DES PCI, who also had an indication for OAC use
- Trial was underpowered to assess smaller bleeding differences

Fiedler, et al. J Am Coll Cardiol **2015**;65:1619 TCT 2014

PIONEER AF-PCI

N=2121 stented pts with nonvalvular AF; ~66% DES



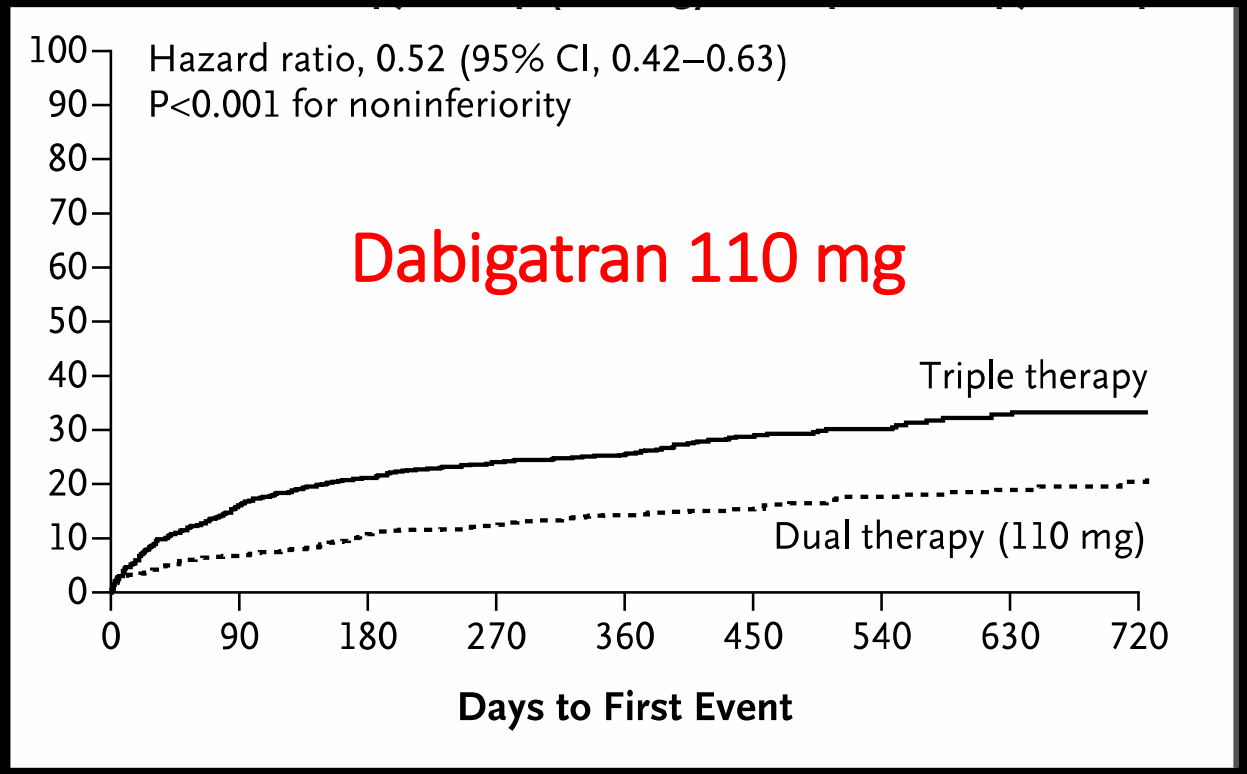
- Low-dose and very-low-dose rivaroxaban was associated with lower risk of clinically significant bleeding than standard triple therapy with warfarin
- The rates of major adverse cardiovascular events were similar
  - Broad confidence intervals make efficacy difficult to assess
  - Cannot truly assess stroke prevention of 15 mg or 2.5 mg BID rivaroxaban doses

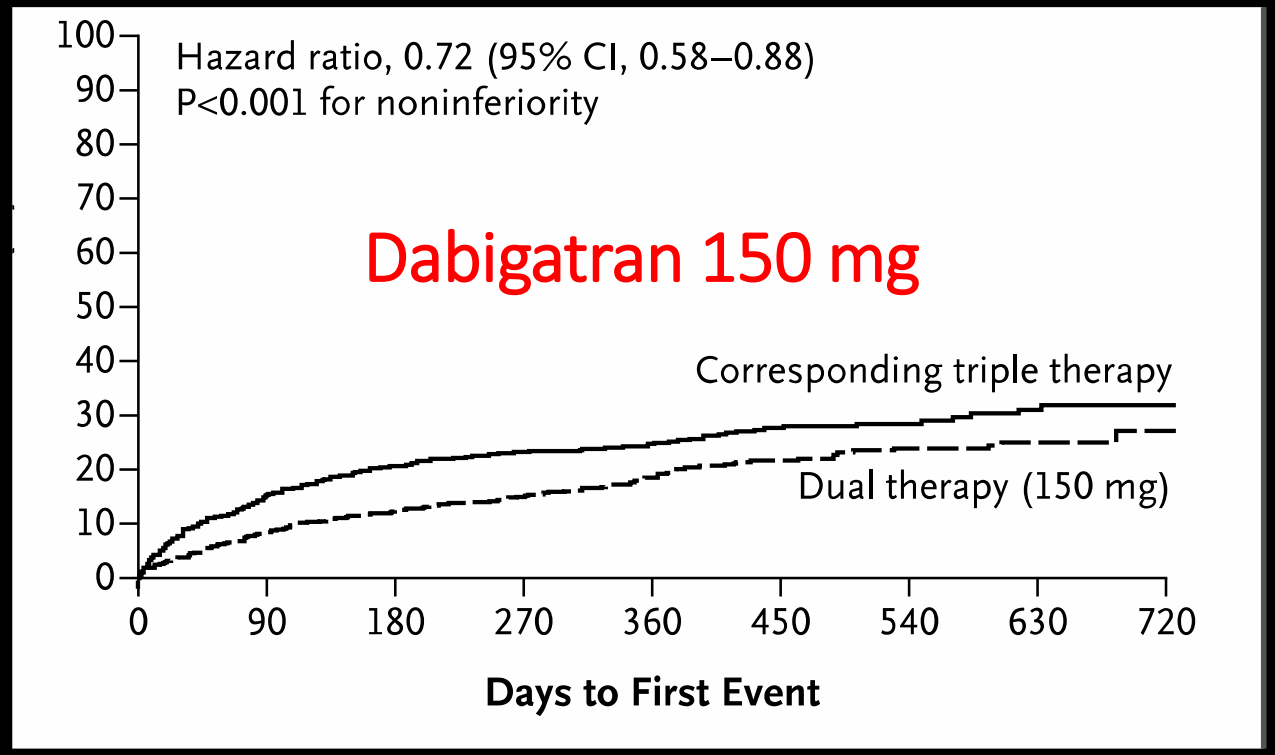
N Engl J Med **2016**; 375:2423-34

RE-DUAL PCI

2,725 patients with nonvalvular AF who had undergone stenting

Primary Endpoint: Major or Clinically Relevant Bleeding





N Engl J Med 2017;377:1513-24

Triple Therapy: Summarizing the Data

- Data to date: double therapy significantly reduces the risk of bleeding without a signal of harm with regard to stent thrombosis in clinical trials that enrolled both patients with stable ischemic disease and patients with ACS.
- Ongoing studies:
  - AUGUSTUS: evaluating the safety of apixaban versus vitamin K antagonist and aspirin versus aspirin placebo in patients with AF and ACS or PCI.
  - ENTRUST-AF-PCI: evaluating edoxaban treatment versus vitamin K antagonist treatment in patients with AF undergoing PCI.

OAC Post-DES: Putting It All Together

- Low thrombotic risk (e.g., elective PCI) and low bleeding risk
  - DOAC + clopidogrel 75 mg + aspirin 81 mg x 1-6 month then drop aspirin
    - Long term: DOAC + aspirin 81 mg
  - DOAC + clopidogrel x 6-12 months
    - Long term: DOAC + aspirin 81 mg
- Low thrombotic risk (e.g., elective PCI) and high bleeding risk
  - DOAC + clopidogrel x 6-12 months
    - Long term- DOAC + aspirin 81 mg
- High thrombotic risk (e.g., ACS) and low bleeding risk
  - DOAC + clopidogrel 75 mg + aspirin 81 mg x 6-12 months
    - Long term- DOAC + aspirin 81 mg vs. DOAC + clopidogrel
- High thrombotic risk (e.g., ACS) and high bleeding risk
  - DOAC + clopidogrel x 6-12 months
    - Long term- DOAC + aspirin 81 mg vs. DOAC + clopidogrel

Some final points to emphasize:

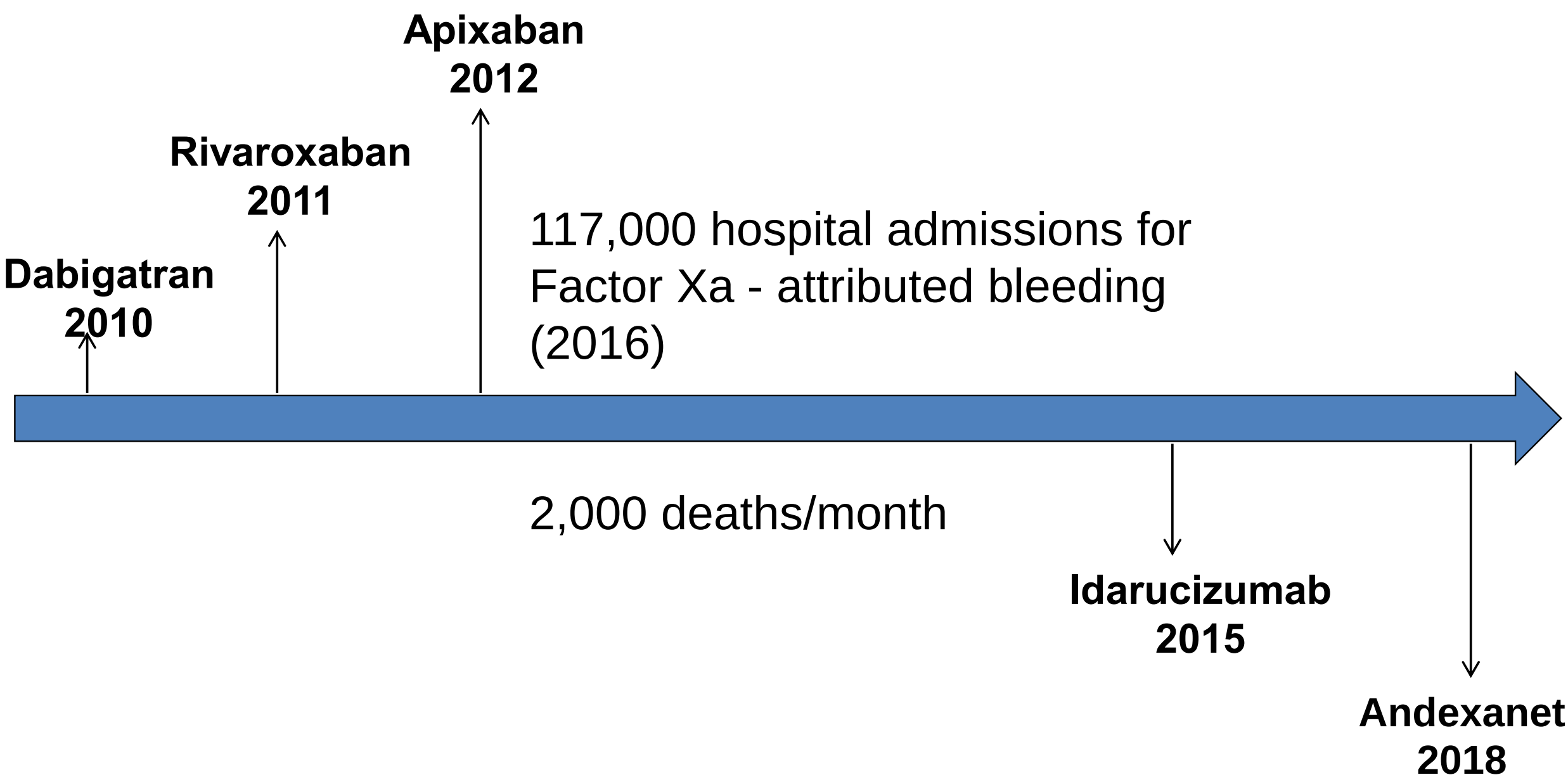
- Major bleeding confers a poor prognosis
- Rates of bleeding on triple therapy:
  - 15-40% per year
  - Major bleed 2-10%/year
- Triple therapy bleeding is 2-5x that of DAPT
- Use gastroprotective therapy to reduce risk of GI bleeding
- Favor DOACs over warfarin
  - We have the most data for dabigatran (RE-DUAL PCI) and rivaroxaban (PIONEER-AF)
  - If warfarin is used, target the lower INR (~2)

Management of Bleeding Complications

Question #2

Which of the following is true regarding the reversal agents Idarucizumab (Praxbind) and Andexanet Alfa (Andexxa)?

A. Both are recombinant antibodies to their respective DOAC agents.
B. Both were approved by the FDA on the basis of surrogate measures of anticoagulation (pharmacodynamic data).
C. Both have large randomized trials supporting their use.
D. Both are relatively inexpensive medications to administer.


Apixaban
2012
Rivaroxaban
2011
Dabigatran
2010
117,000 hospital admissions for Factor Xa - attributed bleeding (2016)
2,000 deaths/month
Idarucizumab
2015
Andexanet
2018

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Practical Management of Anticoagulation in Patients With Atrial Fibrillation

Richard J. Ko
Kim K. Birtch
Christopher I
Kim A. Willia

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

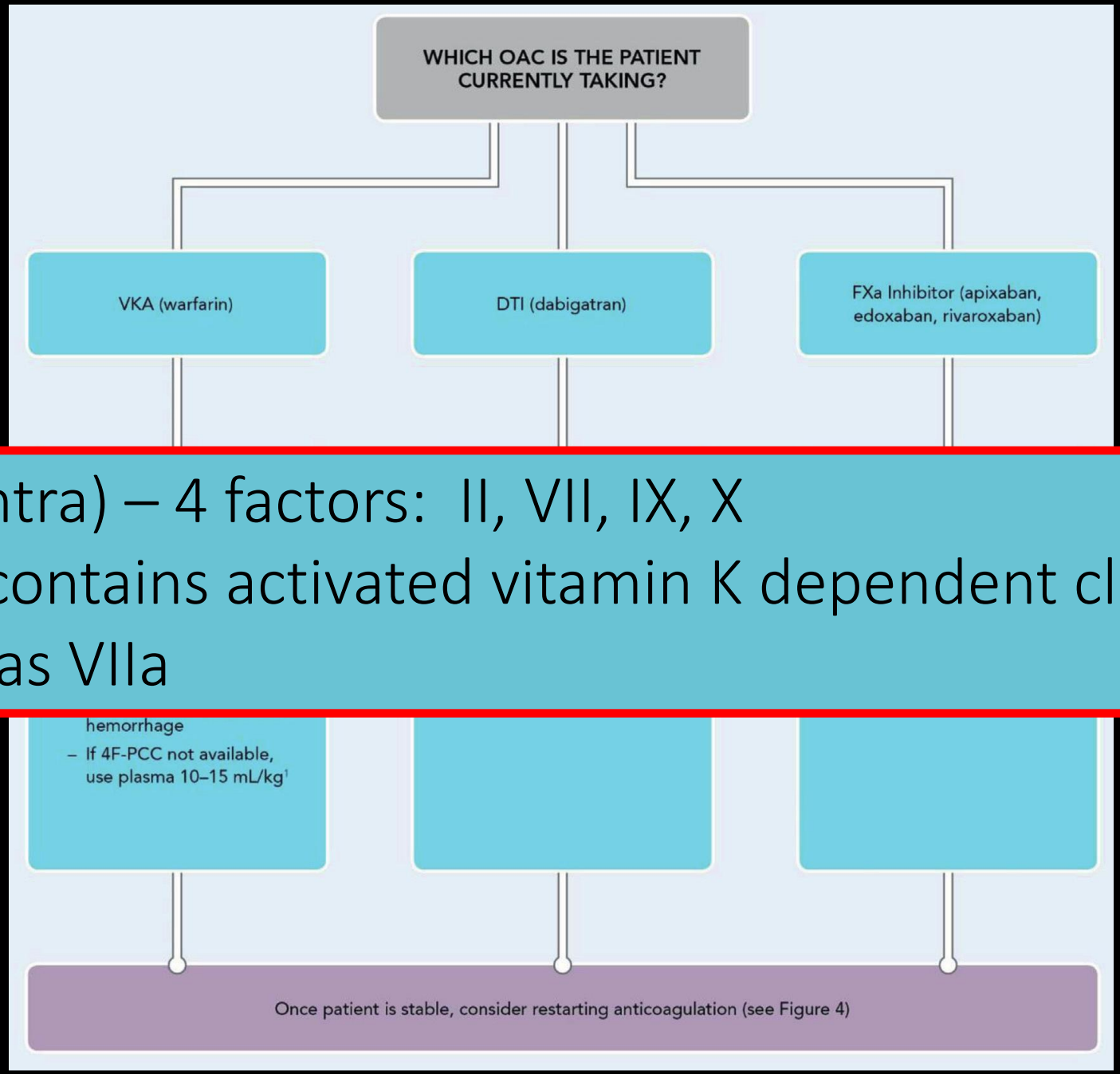
A Repo

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

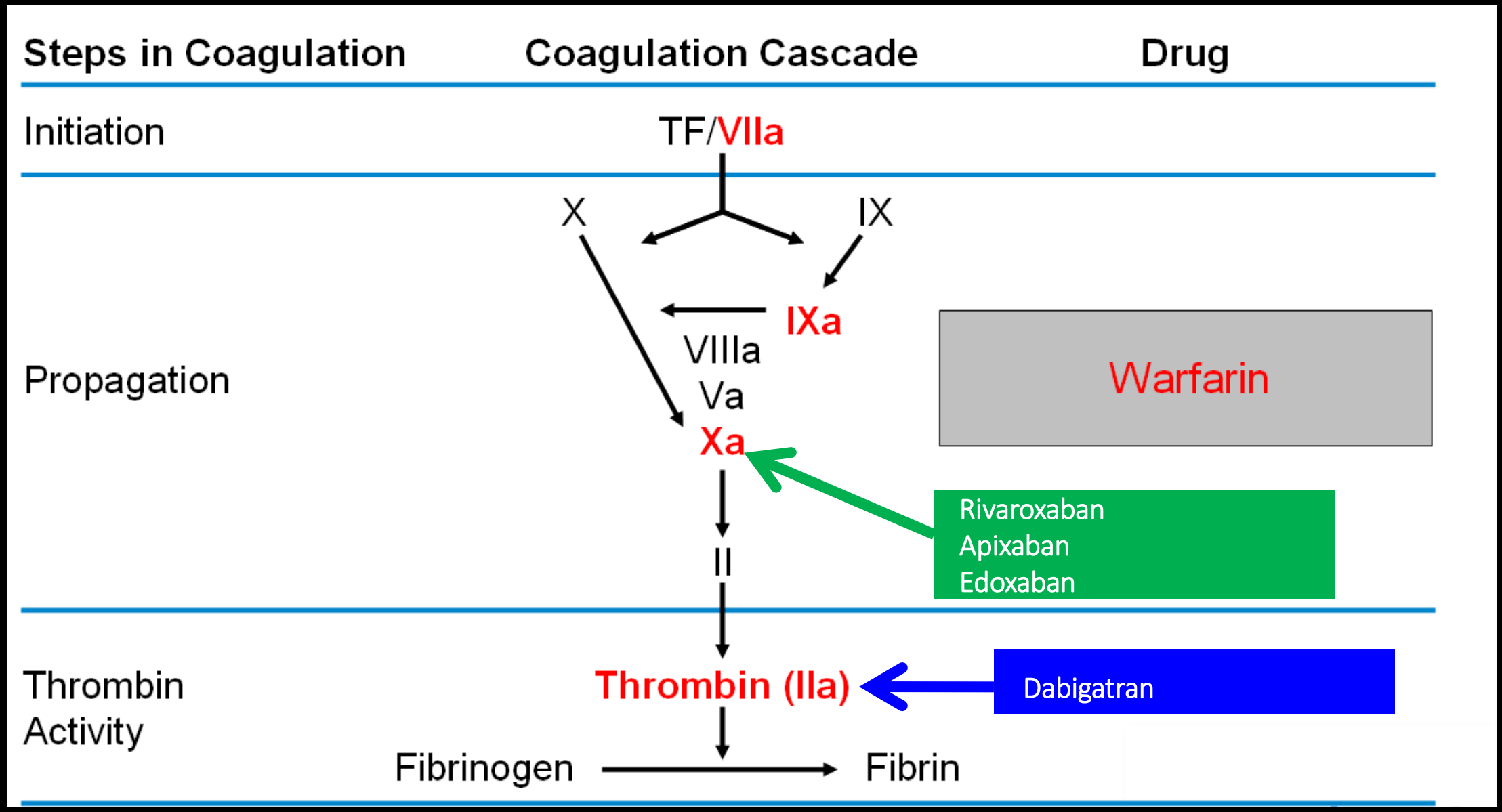
2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in P… A…



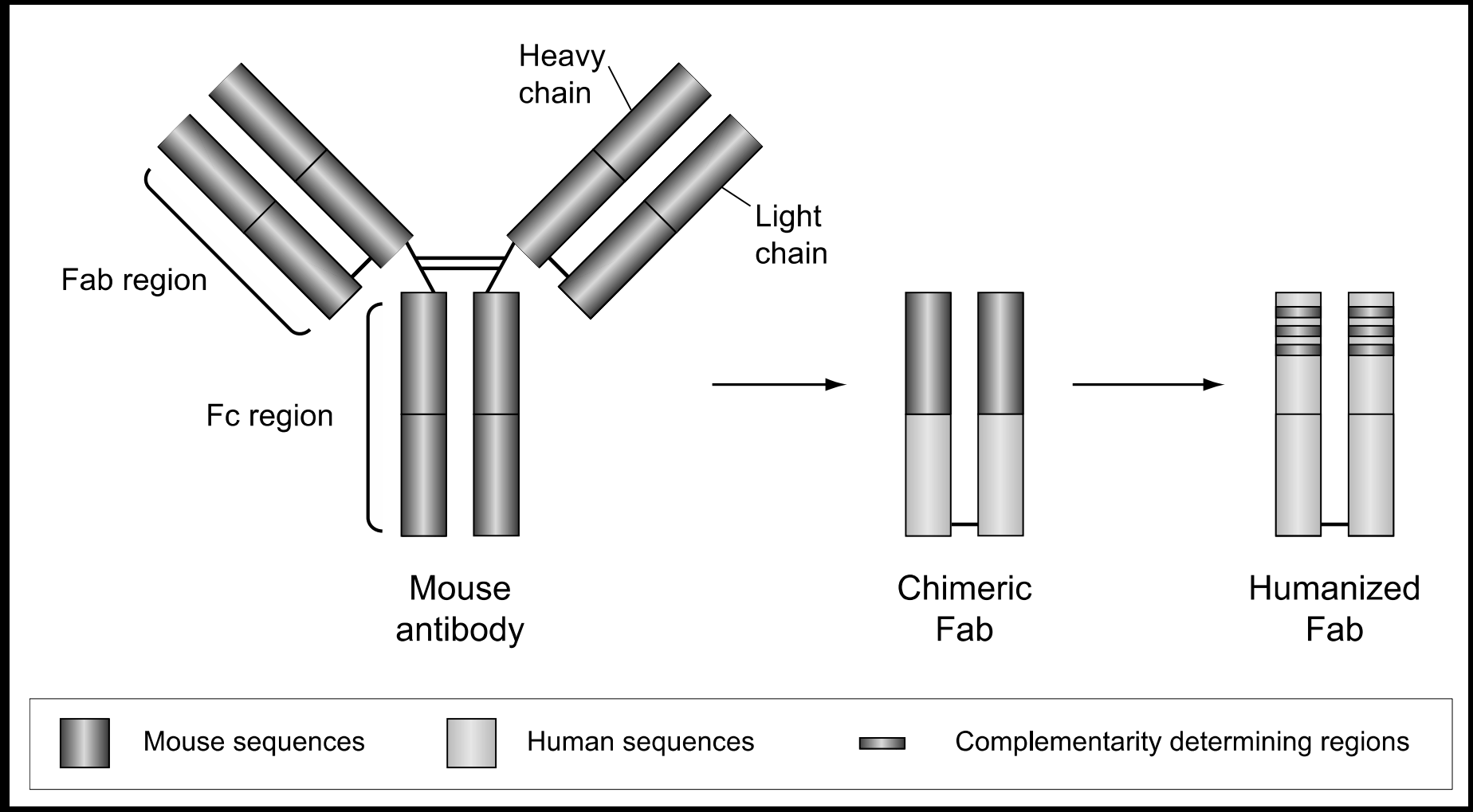
4F-PCC (Kcentra) – 4 factors: II, VII, IX, X

aPCC – also contains activated vitamin K dependent clotting factors, such as VIIa

DOAC: Mechanisms

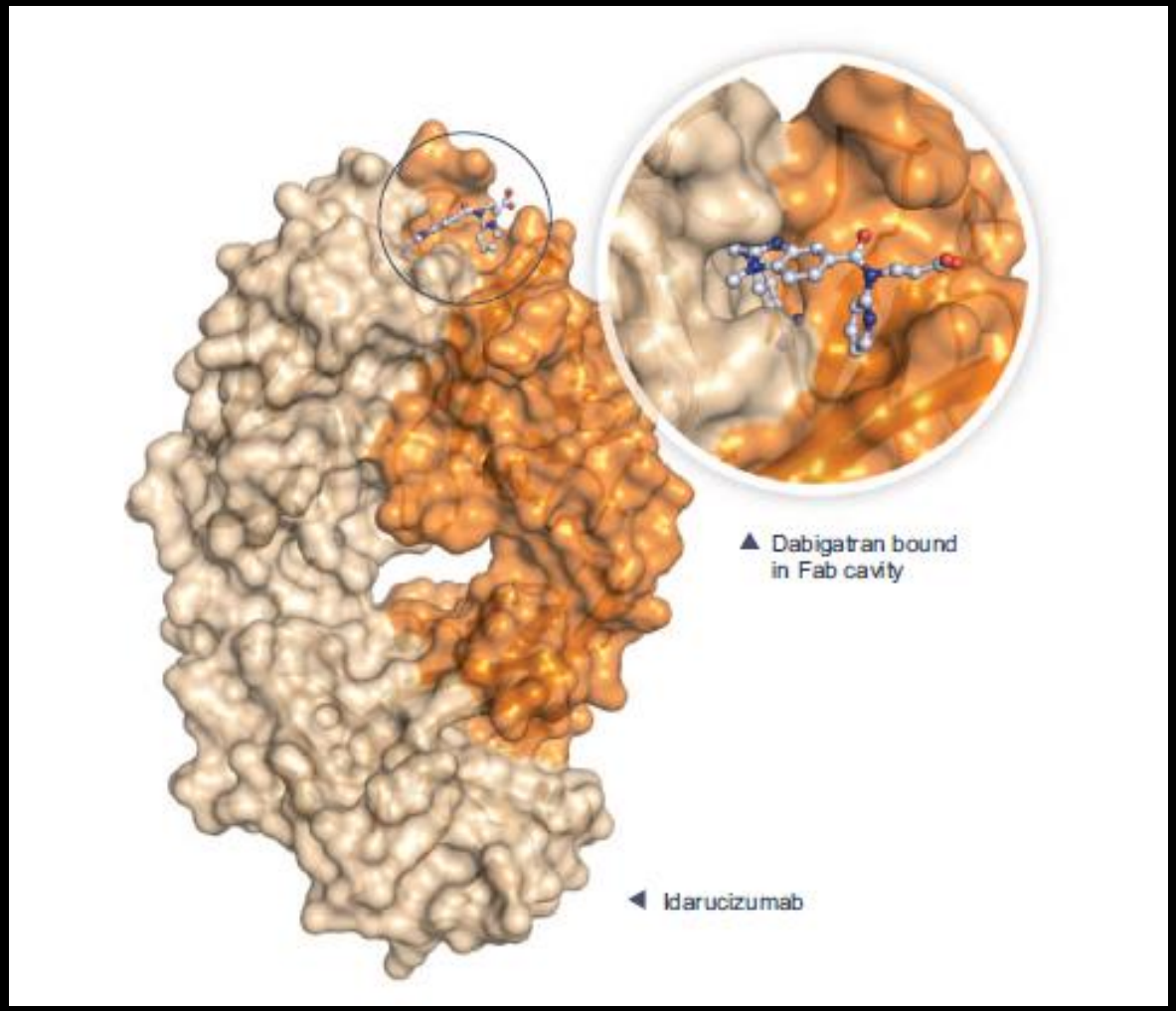


Idarucizumab
The Antidote for Reversal of Dabigatran

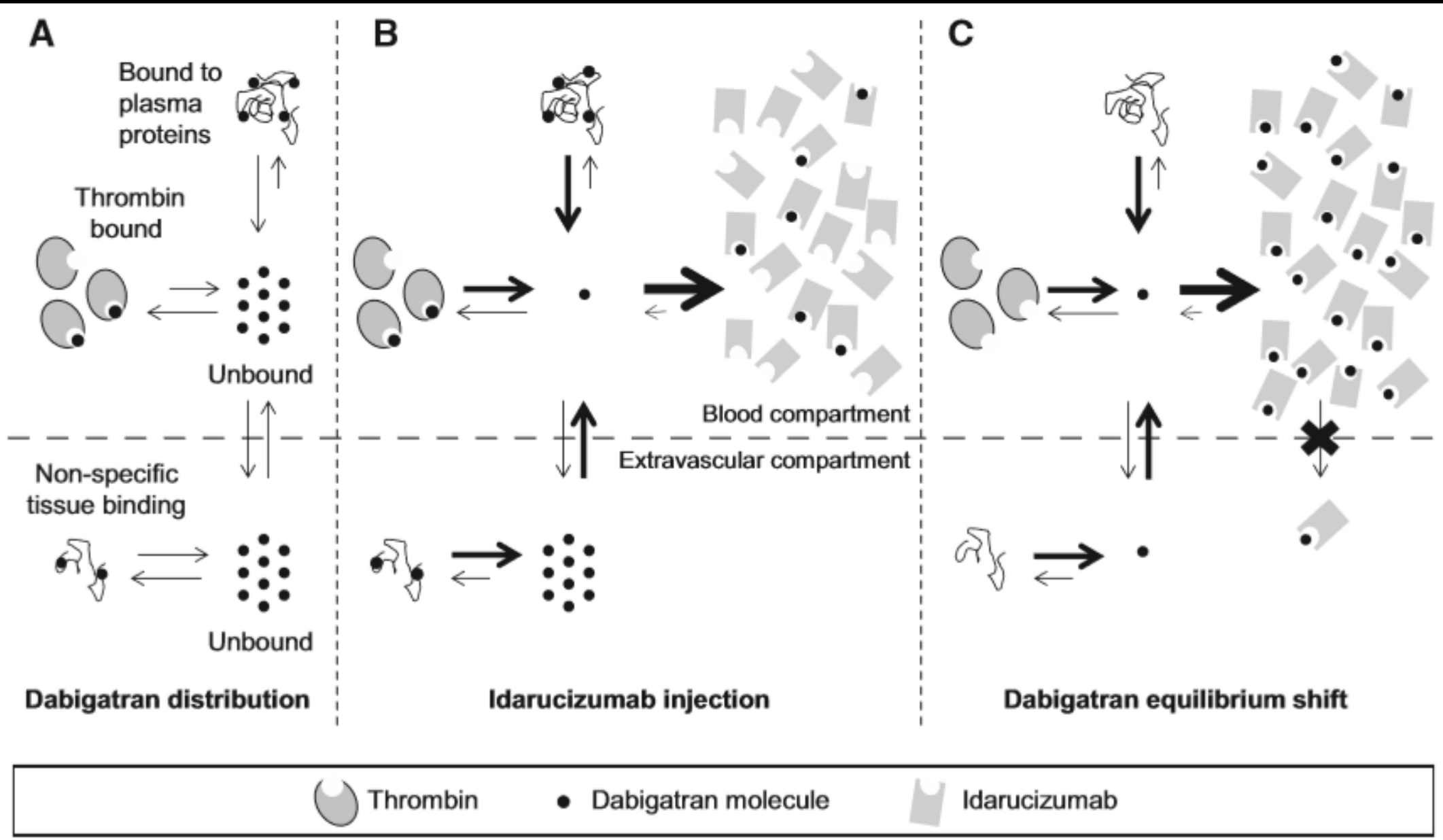


Circulation. 2015;132:2412-2422

Idarucizumab
The Antidote for Reversal of Dabigatran



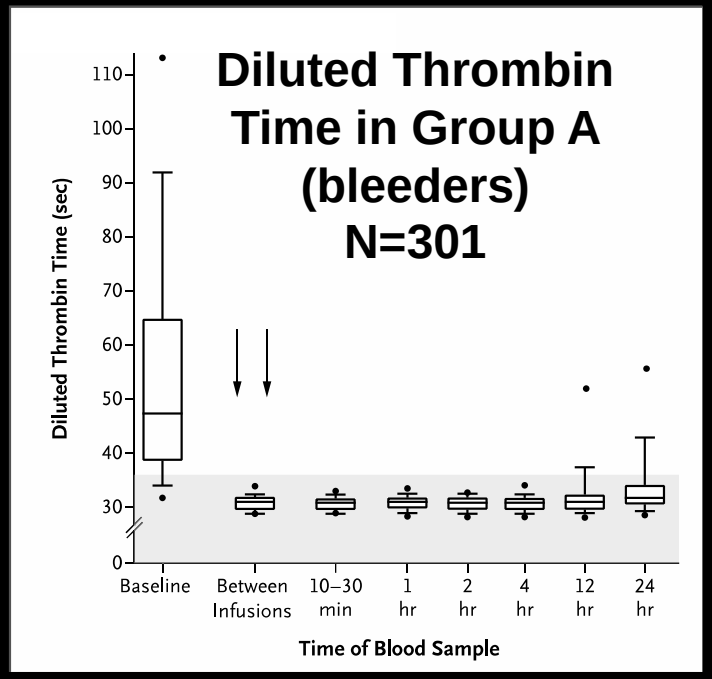
Circulation. 2015;132:2412-2422

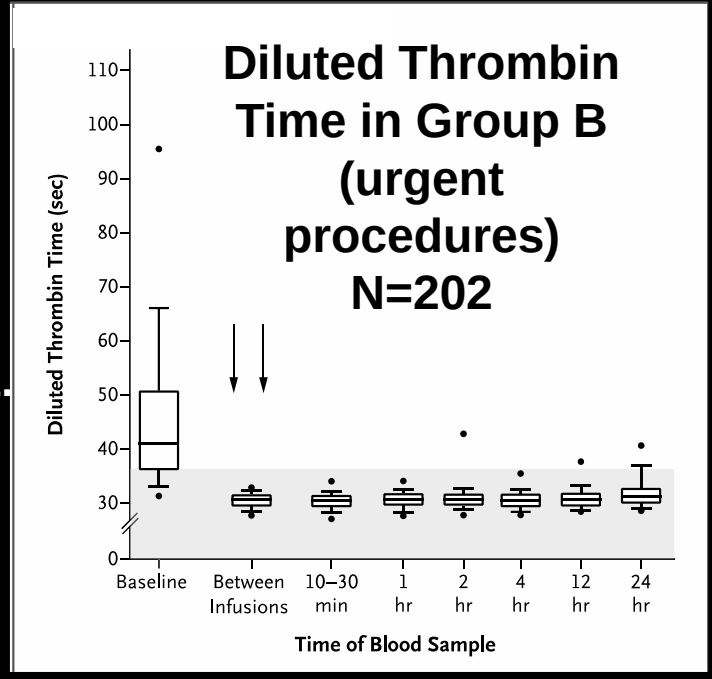


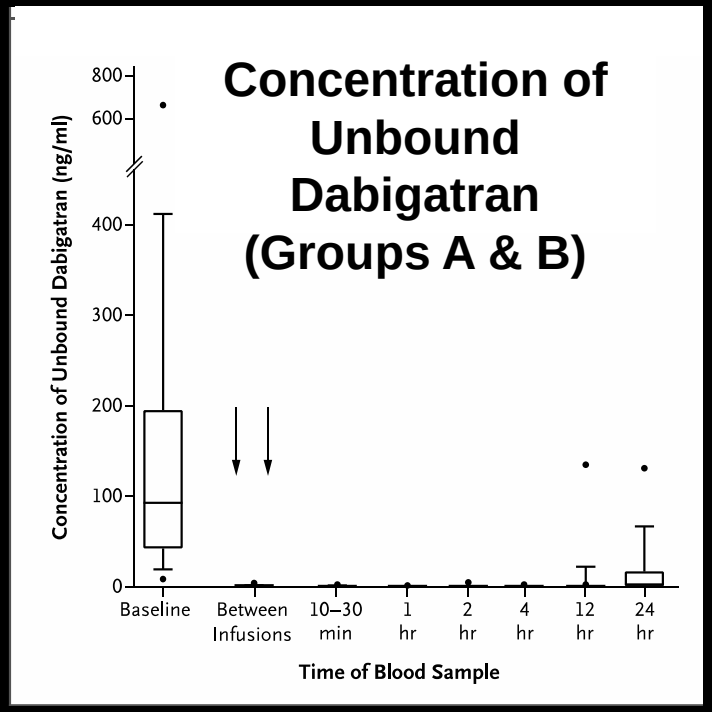
Circulation. 2015;132:2412-2422

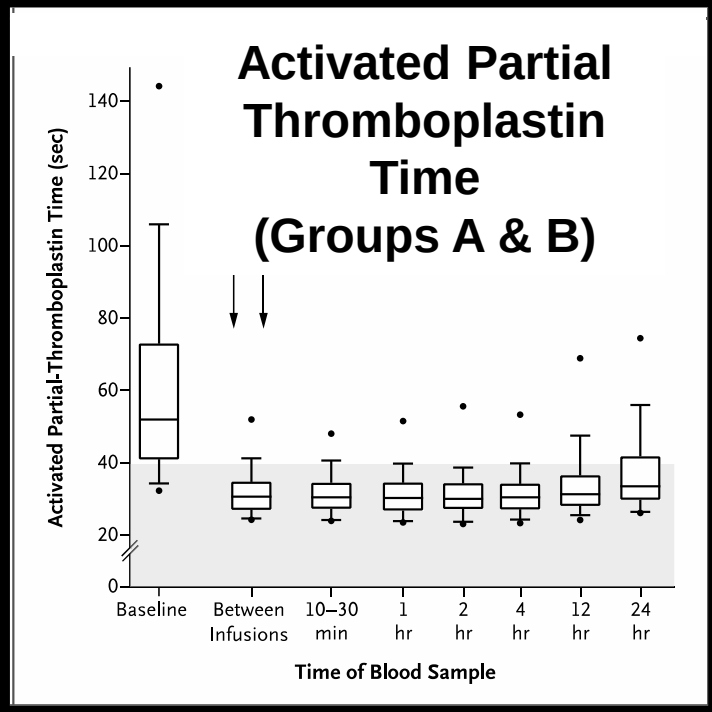
Idarucizumab for Dabigatran Reversal

N Engl J Med 2017;377:431-41.

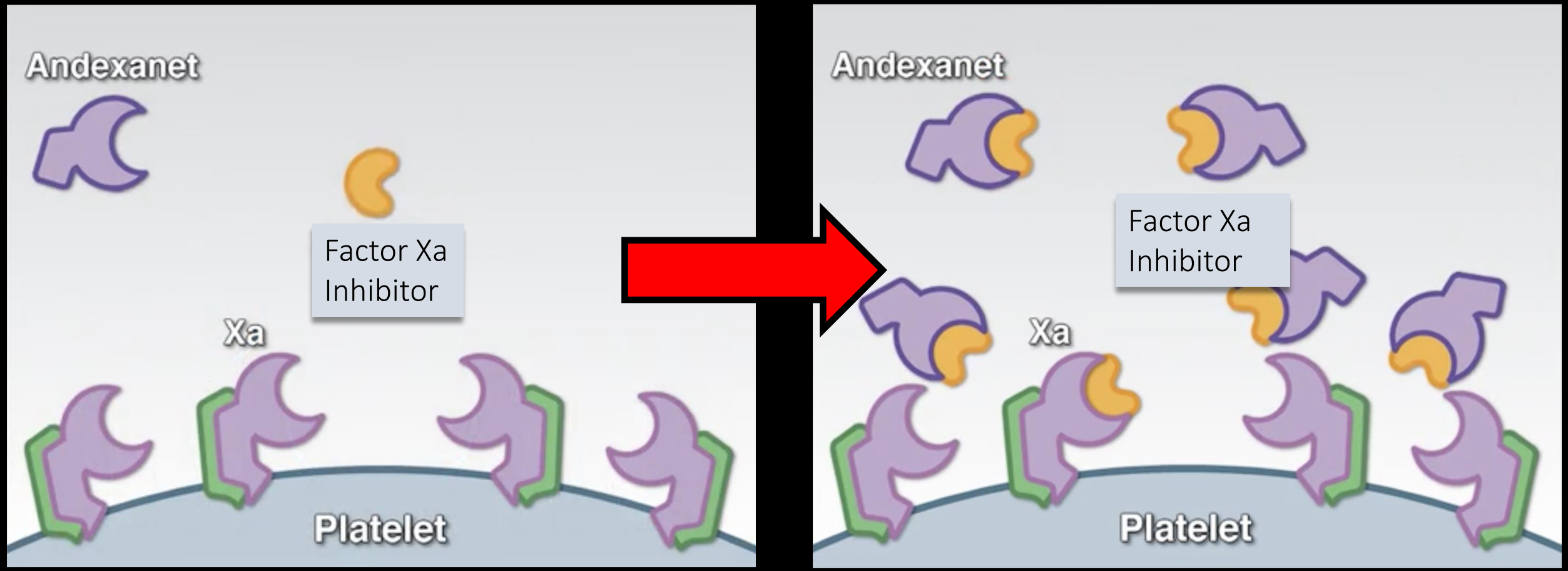








Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity



N Engl J Med 2015;373:2413-24

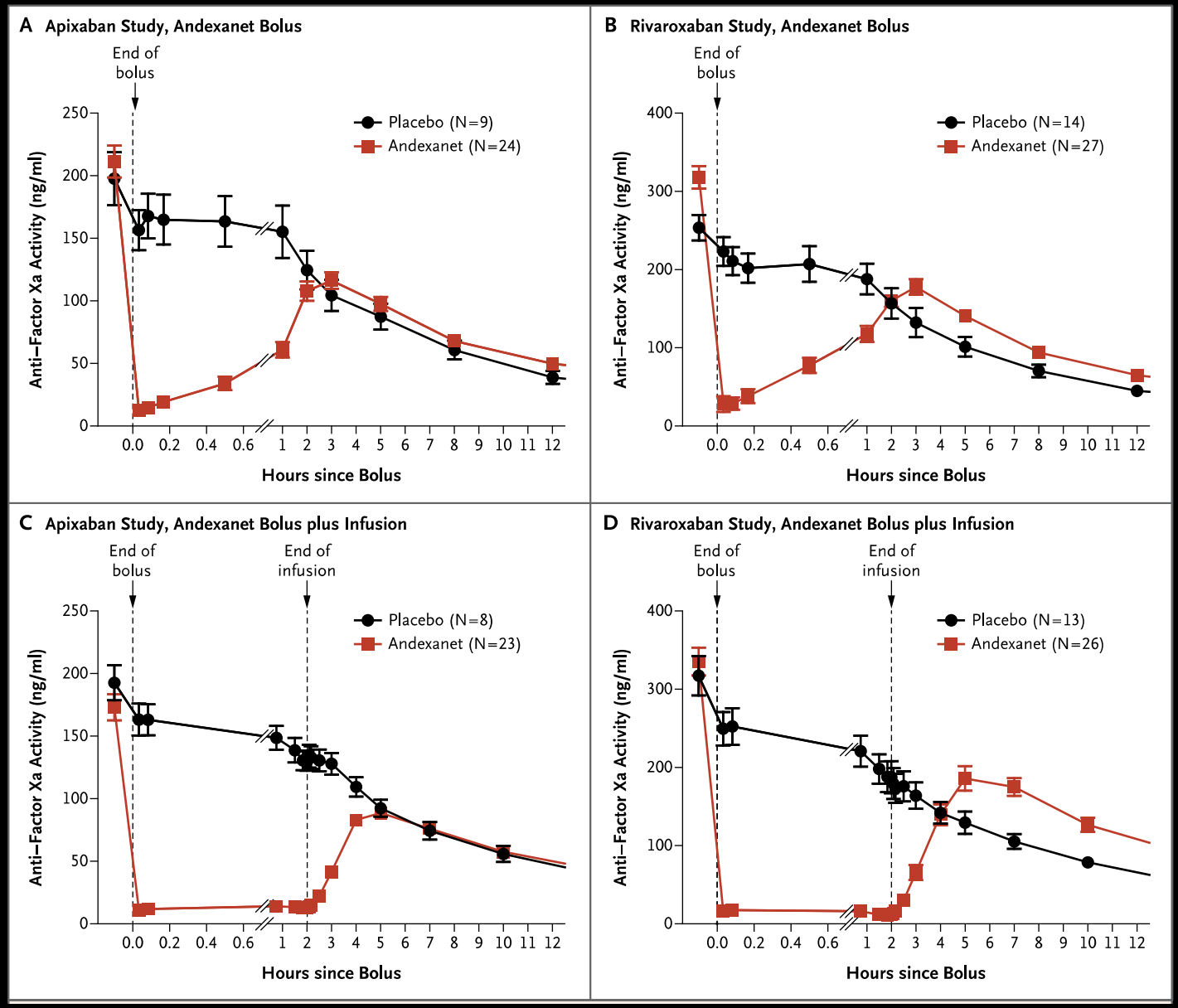
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Apixaban

Rivaroxaban

Bolus

Bolus + Infusion



N Engl J Med 2015;373:2413-24

Summary of Clinical Data for Reversal Agents

		Number		Hemostatic Efficacy		Thrombotic Event Rate	
Pivotal Study	Reversal agent	Total	% ICH	Total	%ICH	Total	ICH
REVERSE AD	Idarucizumab	301	33%	68%	NR	5%	6%
ANNEXA-4	Andexanet	227	61%	83%	81%	11%	12%

Andexxa Package Insert

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

There are 2 OPTIONS for administering PRAXBIND

OPTION 1: INFUSION

Hang vials and administer as two consecutive infusions[1]

OPTION 2: BOLUS INJECTION

Inject both vials consecutively via syringe[1]

ANDEXXA Dosing

Cost of DOAC reversal agents?

The wholesale acquisition cost of two 2.5 g vials of idarucizumab is currently **$3482.50**. To treat 10 or 20 patients per year with a single 5 g dose is estimated to cost $34,825 and $69,650, respectively.

Idarucizumab (Praxbind) Formulary Review. - NCBI

https://

Cost. Initial pricing (AWP) is **$58,000** per reversal (800 mg bolus + 960 mg infusion, **$3,300** per 100 mg vial) which is higher than reversal agents for other DOAC agents (idarucizumab for use in dabigatran reversal is **$4,200** per reversal).

Andexanet alfa - Wikipedia

https://en.wikipedia.org/wiki/Andexanet_alfa

About this result Feedback

Today 12:47 PM

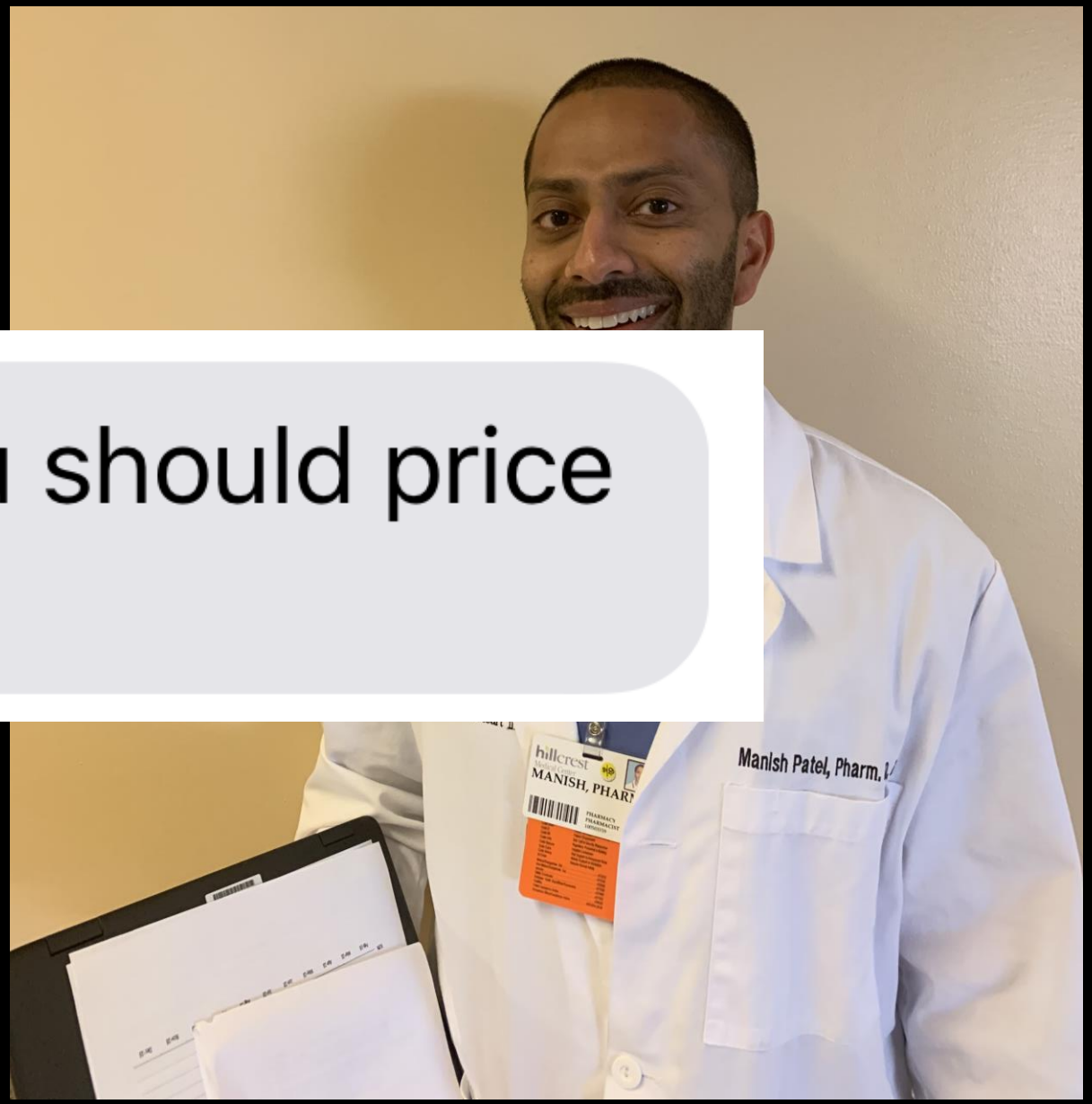
Praxbind - $1845/vial (2.5g)
So 5g dose is $3691

Kcentra- $1713/vial(1034 units)
50unit/kg
Average C
80kg-100
So 4 to 5
$8565

Andexxa- $2800/vial (100mg)
Low dose 9 vials = $25200
High dose 18 vials= $50400

Yw, I think you should price in cars. Lol

Thank you.



CAR AND DRIVER

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Summary of Points for Reversal Agents

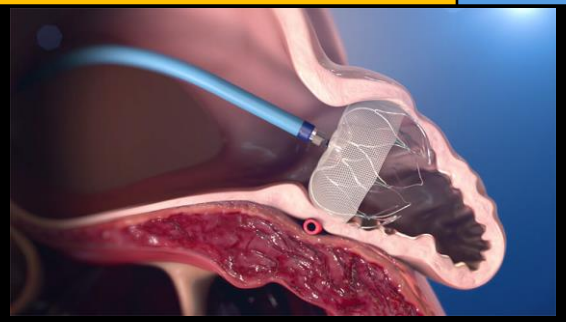
- Specific reversal agents are now available
  - Pharmacodynamic efficacy
  - Limited clinical data
    - None for Edoxaban
  - Post-approval commitments: ongoing collection of data
- Rapidly evolving area of interest
- Benefits, risks, alternatives, and costs will evolve as further data become available

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

January CT, et al. 2019 Focused Update on Atrial Fibrillation

4.4. Nonpharmacological Stroke Prevention

Class of Recommendation	Level of Evidence	Recommendations
IIb	B	1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (S4.4.1- 1–S4.4.1-5).
IIb	B-NR	1. Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery (S4.4.2-1), as a component of an overall heart team approach to the management of AF.



Conclusions

- Proper patient selection and DOAC dosing should help improve outcomes and reduce bleeding complications.
- Adding aspirin or dual antiplatelet therapy to oral anticoagulation significantly increases the risk of bleeding and should be avoided/minimized when possible.
- Specific reversal agents are now a part of our “toolbox,” for managing bleeding complications from DOACs.
  - Limited clinical data
  - Rapidly evolving area with much more to follow.

Congratulations!