Stroke Prevention with the Expanded Use of NOACs

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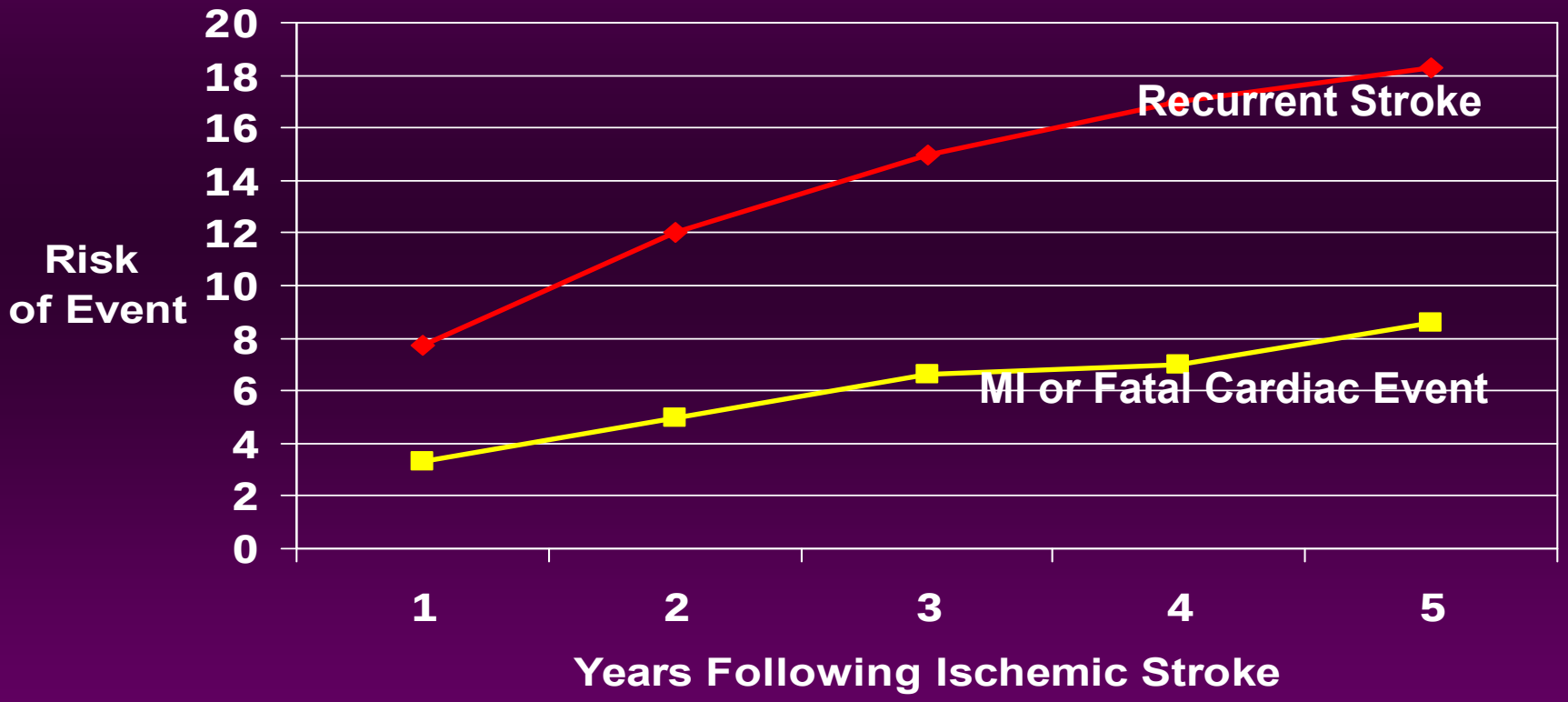
Treatment vs. Prevention

- 750,000 strokes per year in U.S.
- How many can get acute treatment?
- 100% can get secondary prevention

The Problem: Stroke Prognosis



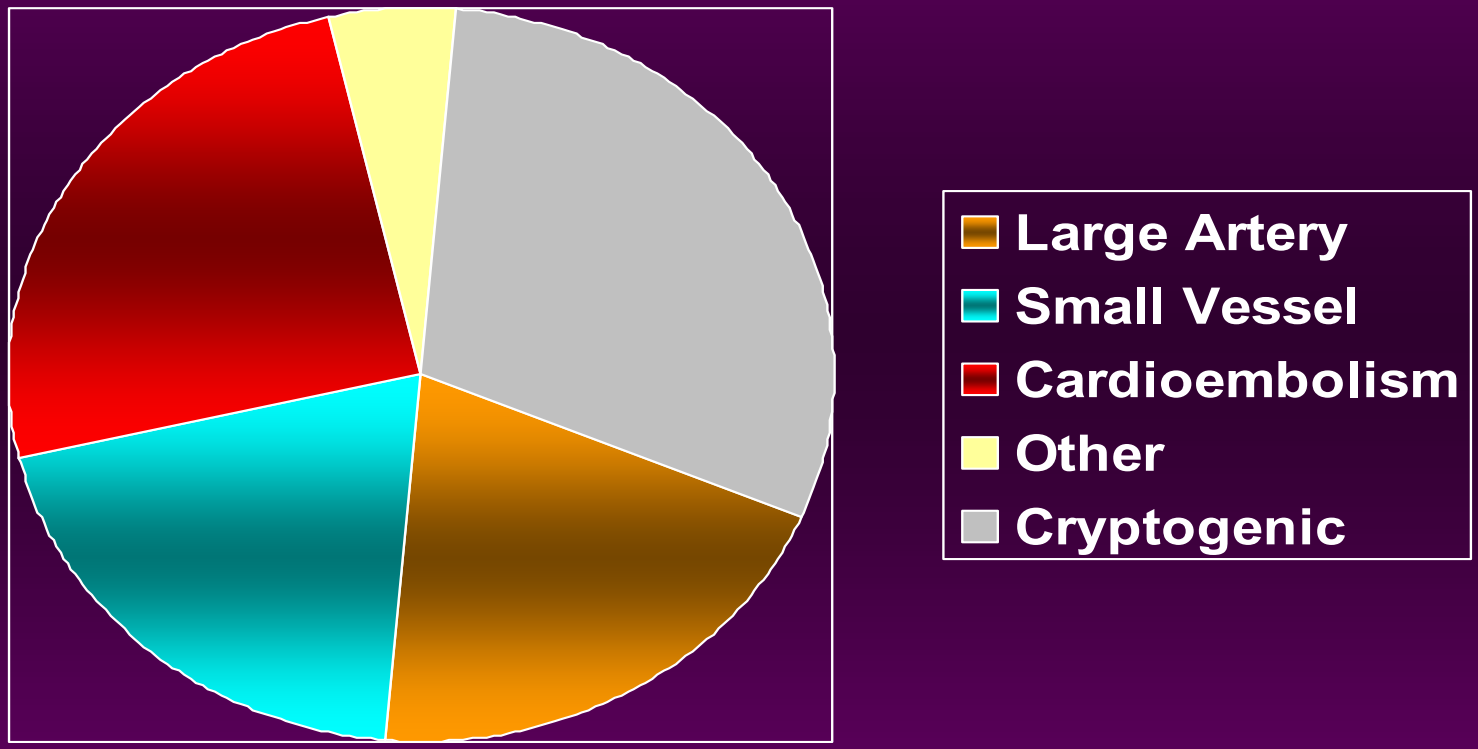
MS Dhamoon *Stroke* 2006;66:641

TIA/Stroke
Evaluation and Prevention

What is the cause of the
TIA or stroke?

Prevention depends on it!

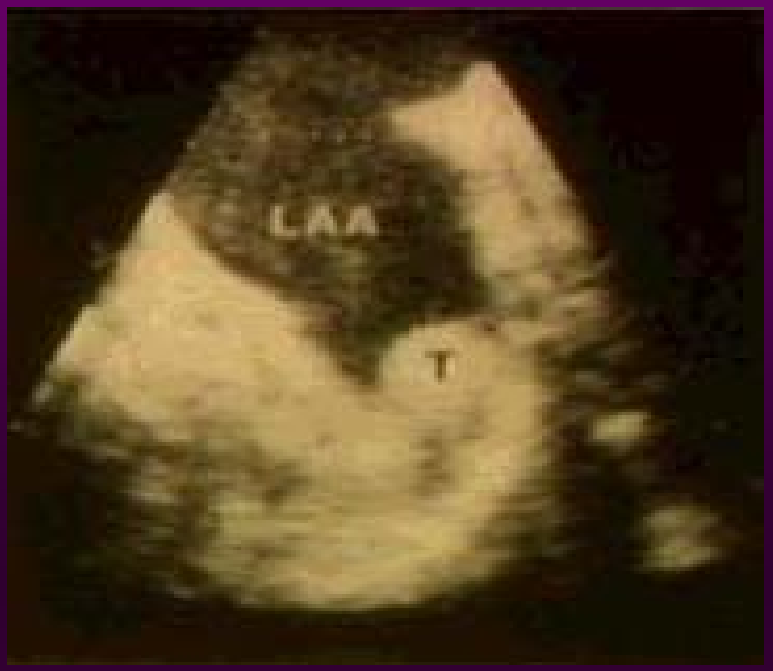
Ischemic Stroke Subtypes

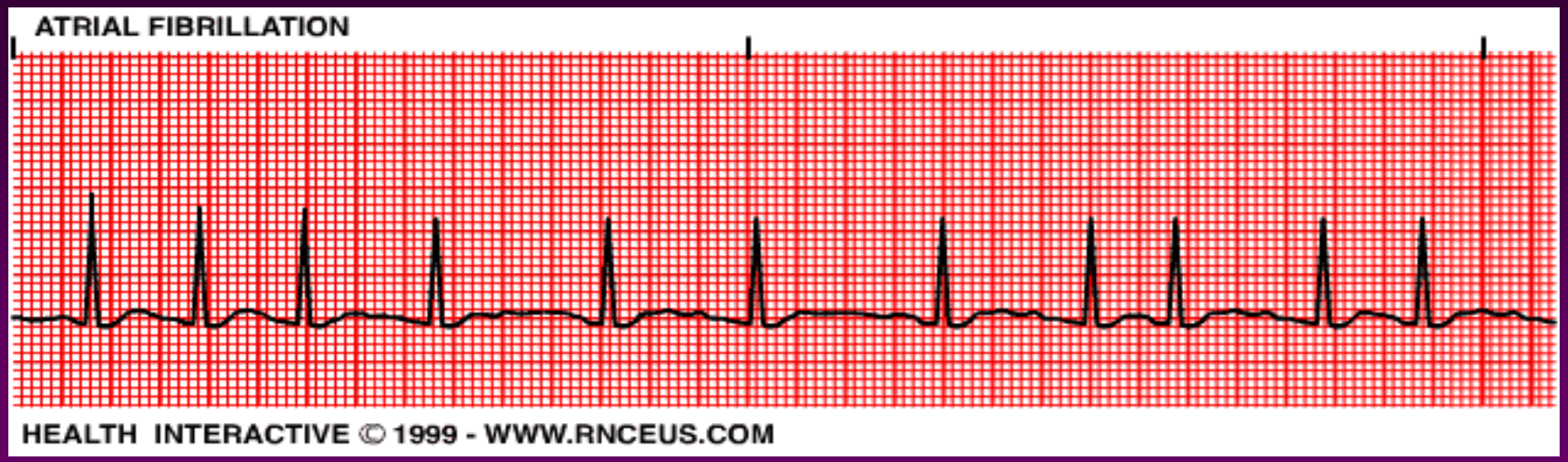


NINCDS Stroke Data Bank:
Foulkes et al. Stroke. 1988;19:547.

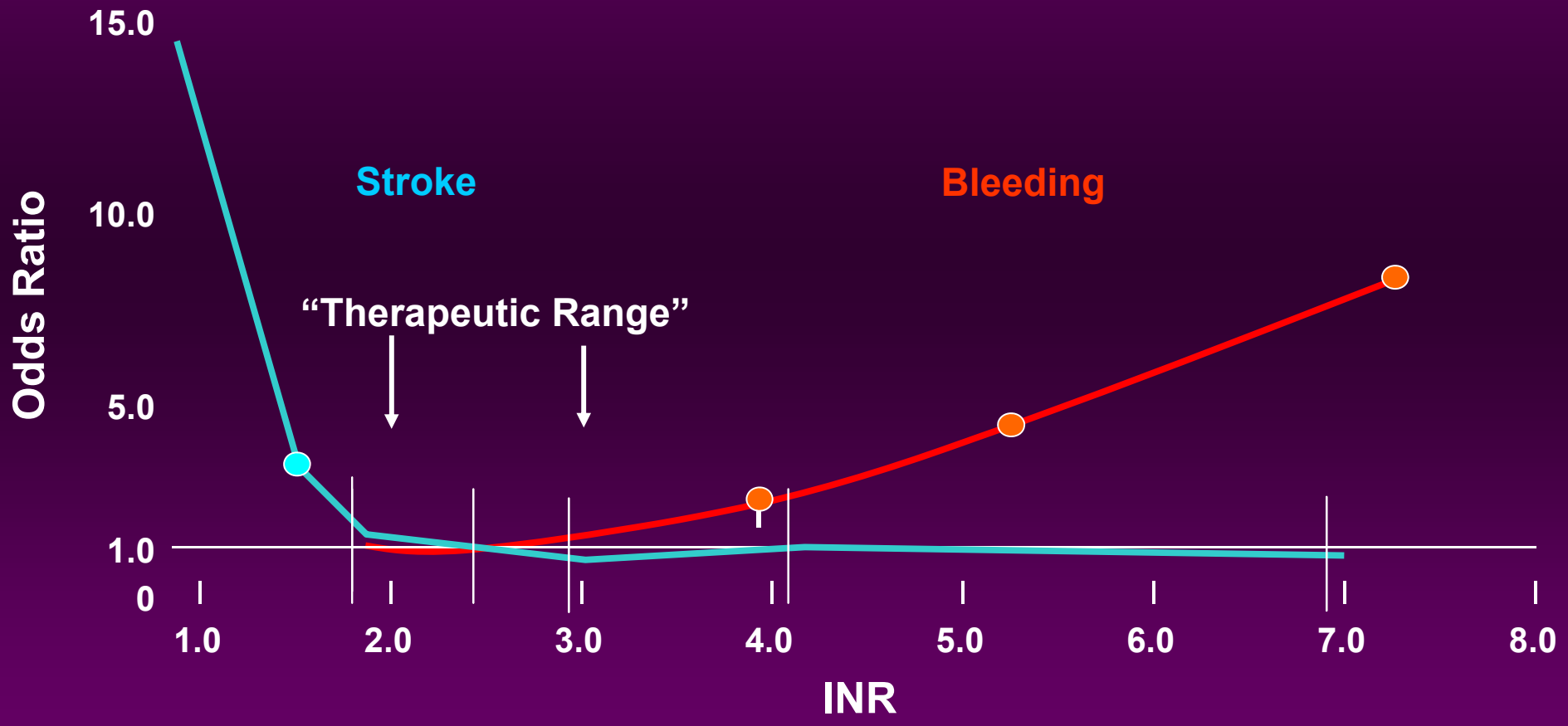
German Stroke Data Bank
Grau A.J. et al. Stroke 2001;32:2559-2566

Cardioembolism



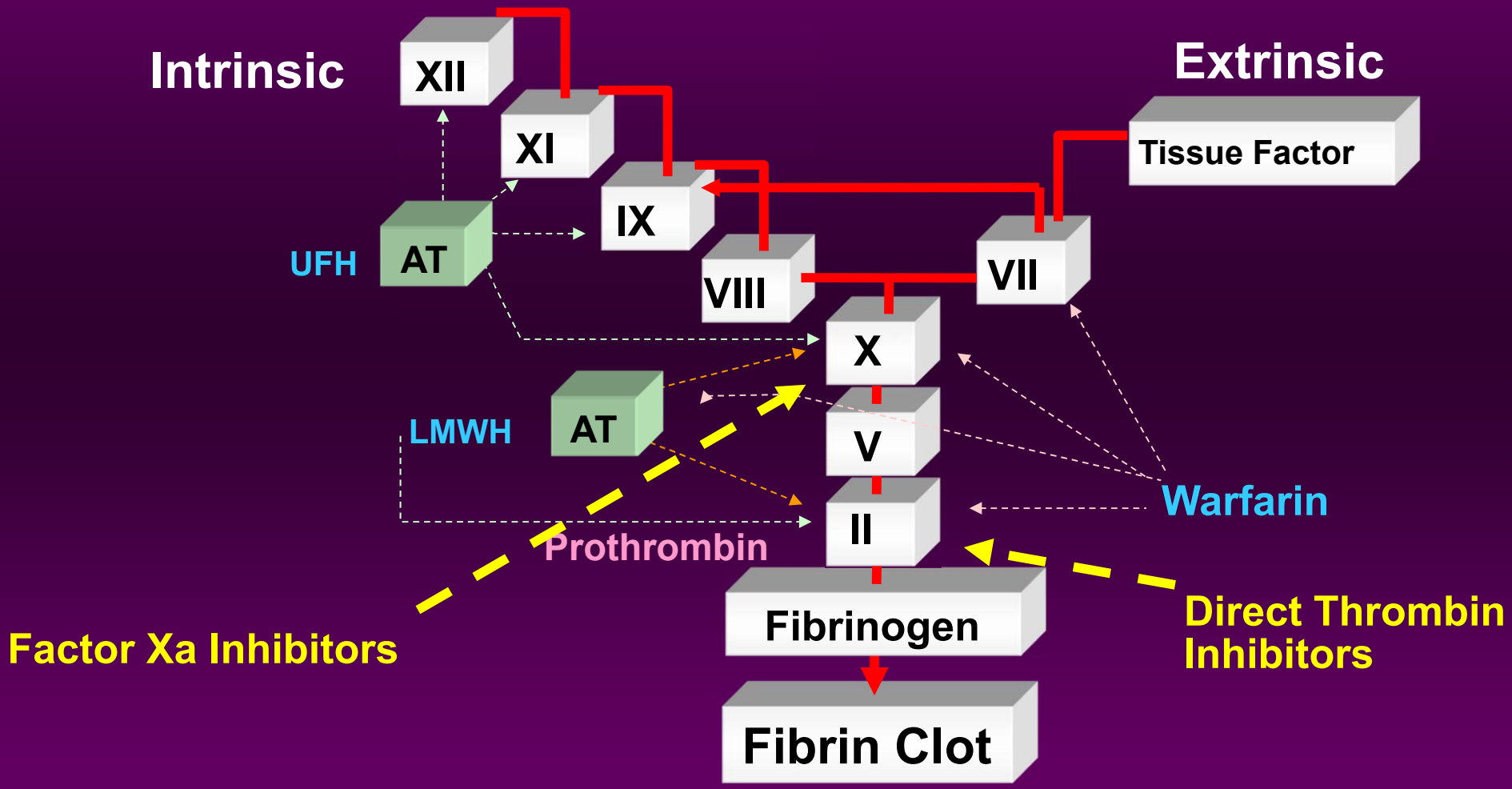


Therapeutic Range for Warfarin Balancing Safety and Efficacy



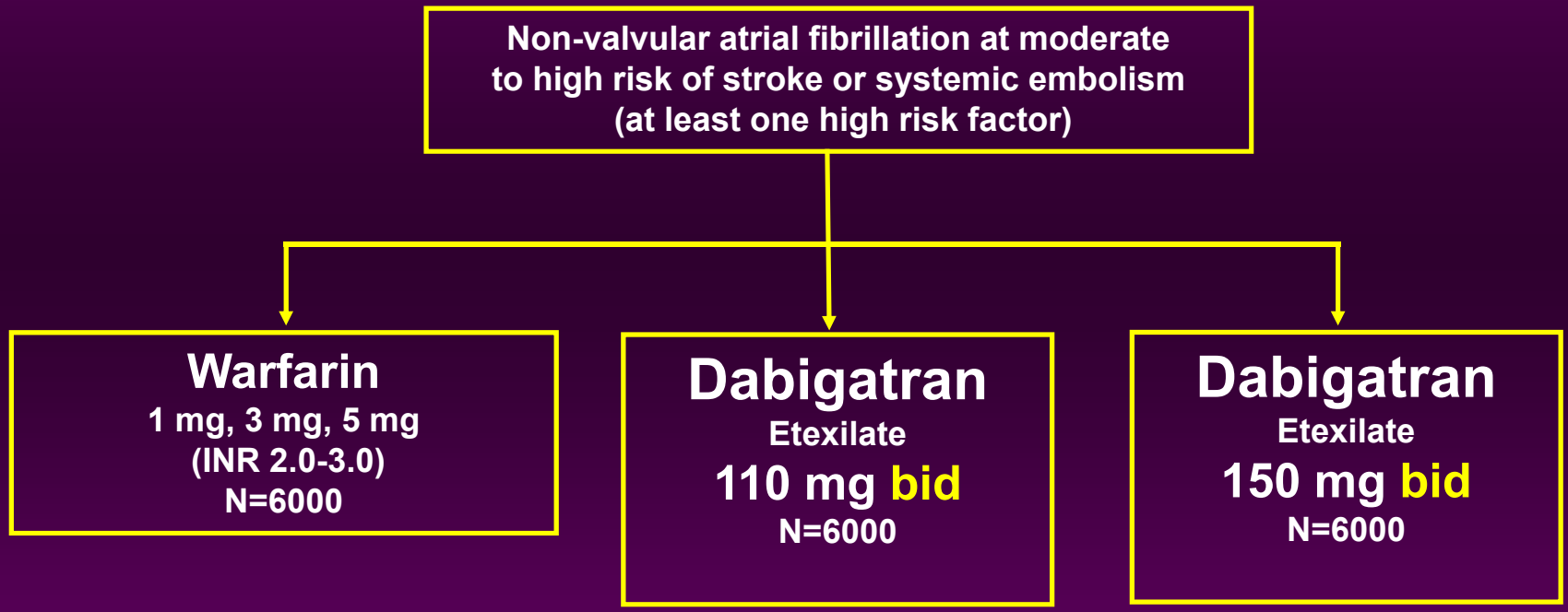
Hylek EM, et al. *Ann Intern Med.* 1994;120:897-902.
Hylek EM, et al. *N Engl J Med.* 2003;349:1019-1026.

Anticoagulants



RE-LY Trial

Dabigatran for Stroke Prevention in Atrial Fibrillation

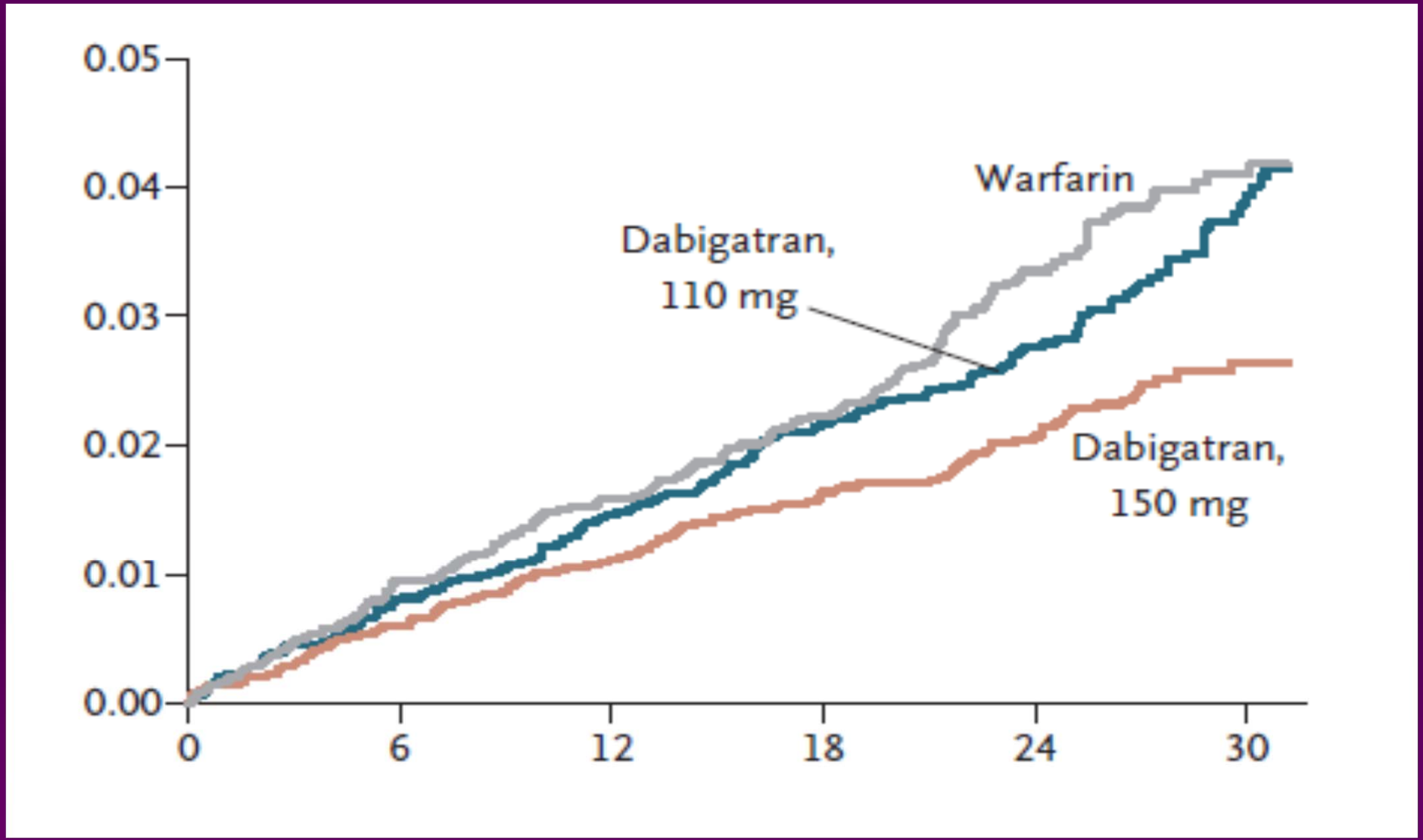


Primary objective: Noninferiority to warfarin

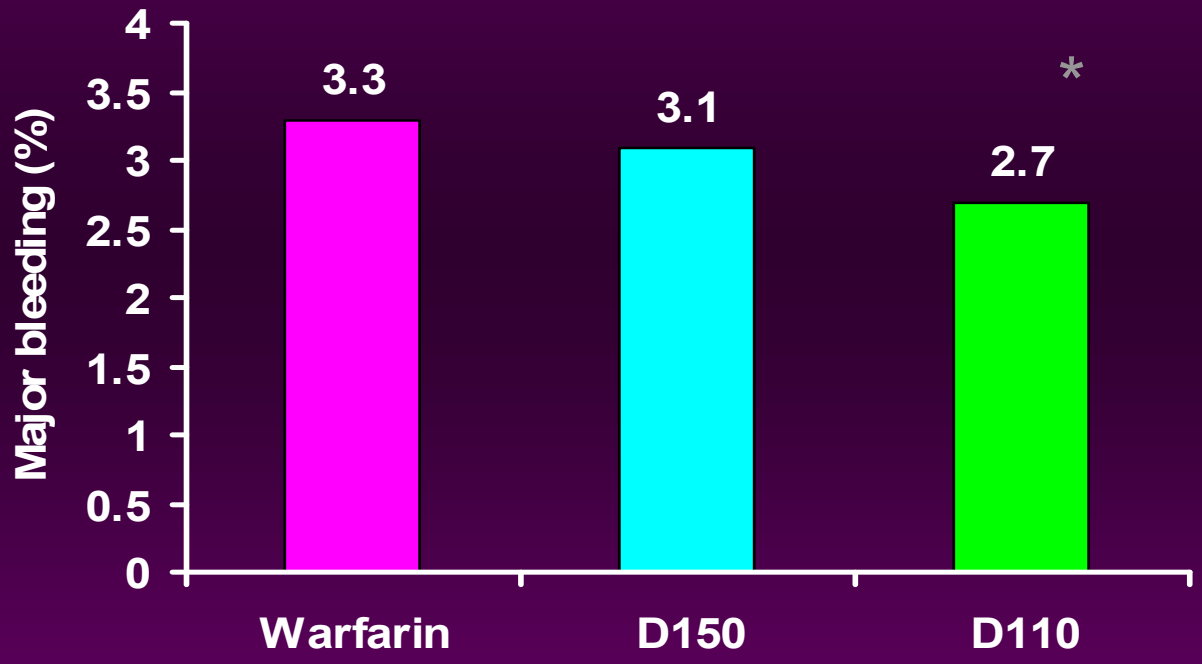
Primary end point: Stroke + systemic embolism

Minimum 1 year of follow-up, maximum of 3 years and mean of 2 years of follow-up

Stroke or Systemic Embolism



Dabigatran: Major Bleeding



Compared to warfarin:

D110: RR=0.80; 95% CI, 0.69-0.93; *P*=0.003 *

D150: RR=0.93; 95% CI, 0.81-1.07; *P*=0.31

Dabigatran

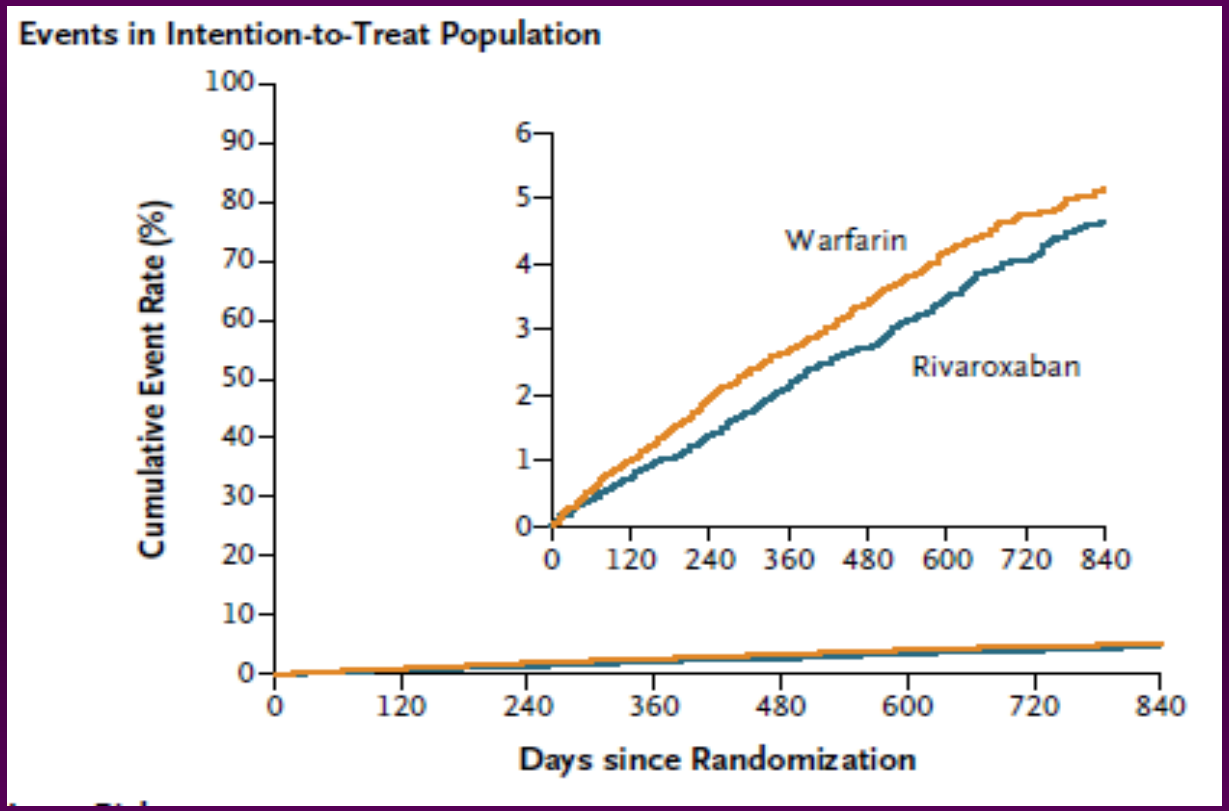
- Dabigatran 150 mg bid
  - reduces the risk of stroke and systemic embolism by ~25% compared to warfarin
  - risk of major bleeding is similar to warfarin

- Dabigatran 110 mg bid
  - about the same efficacy as warfarin
  - risk of major bleeding about 20% lower than warfarin
  - (not approved in U.S.)

ROCKET-AF: Rivaroxaban

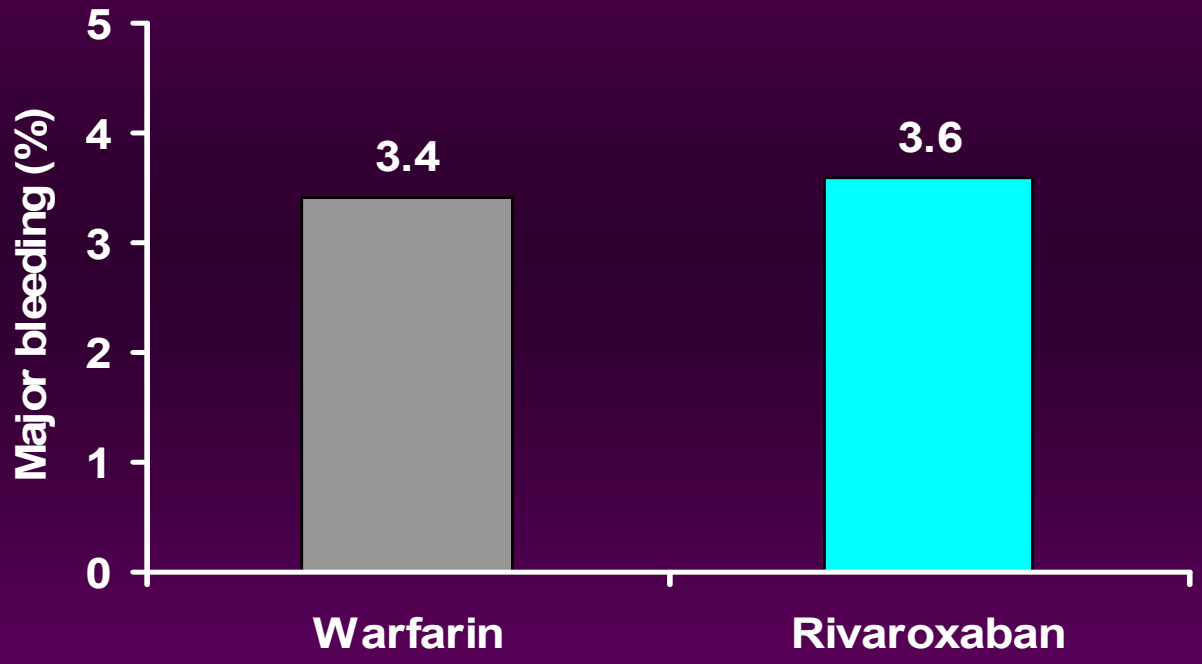
- AFib and at high risk for stroke
- Randomized 14,264 subjects
  - Rivaroxaban 20 mg once daily
  - Warfarin to INR 2.0-3.0
- Primary Outcome: stroke and non-CNS embolism

Rivaroxaban:
Similar Risk of Stroke or Systemic Embolism



HR 0.88 (0.74-1.03), p<0.001 for non-inferiority,
p=0.12 for superiority

Rivaroxaban: Similar Major Bleeding



Compared to warfarin:
Rivaroxaban: 1.04 (0.90-1.20); p=0.58

Rivaroxaban

- Rivaroxaban non-inferior to warfarin for prevention of stroke and non-CNS embolism
- Similar rates of bleeding with both, but less ICH and fatal bleeding with rivaroxaban

ARISTOTLE: Apixaban vs Warfarin

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

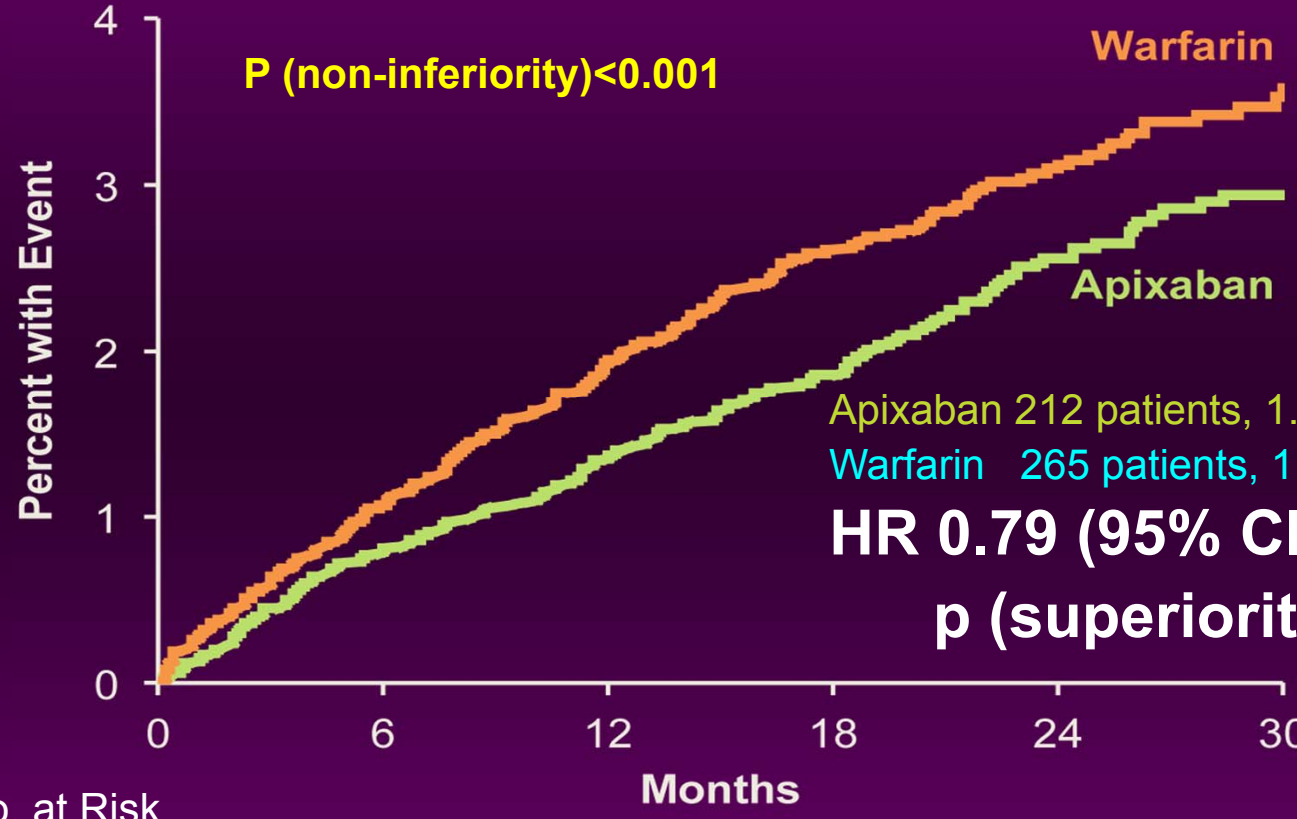
Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

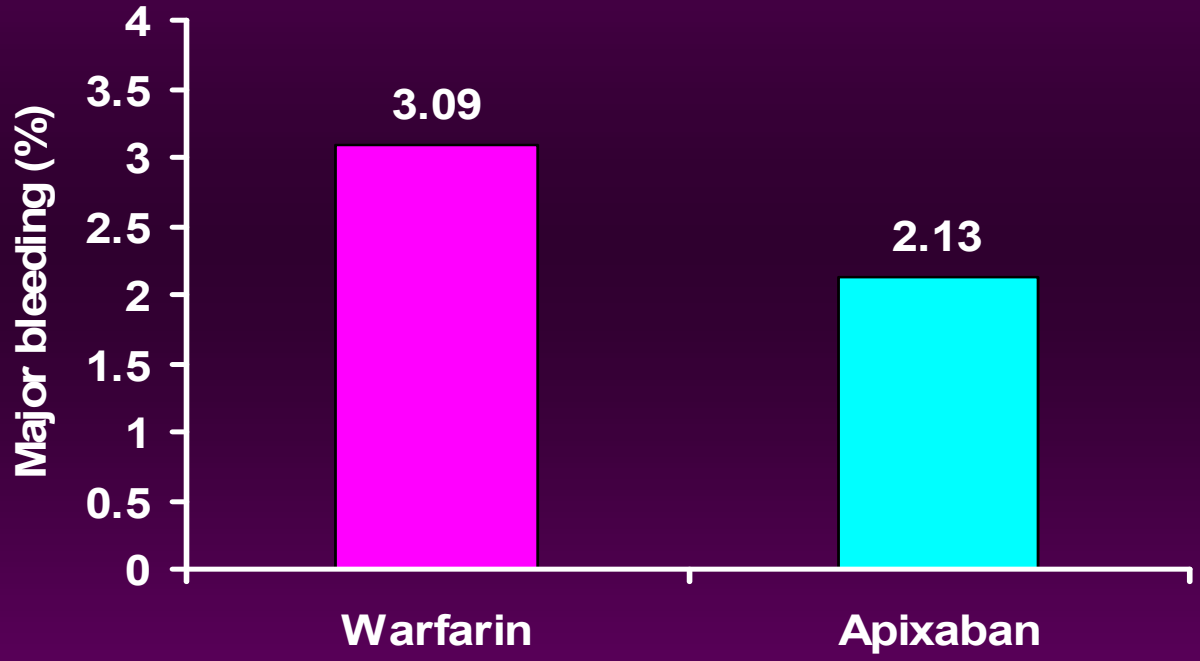
Primary outcome: stroke or systemic embolism

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Apixaban: Major Bleeding



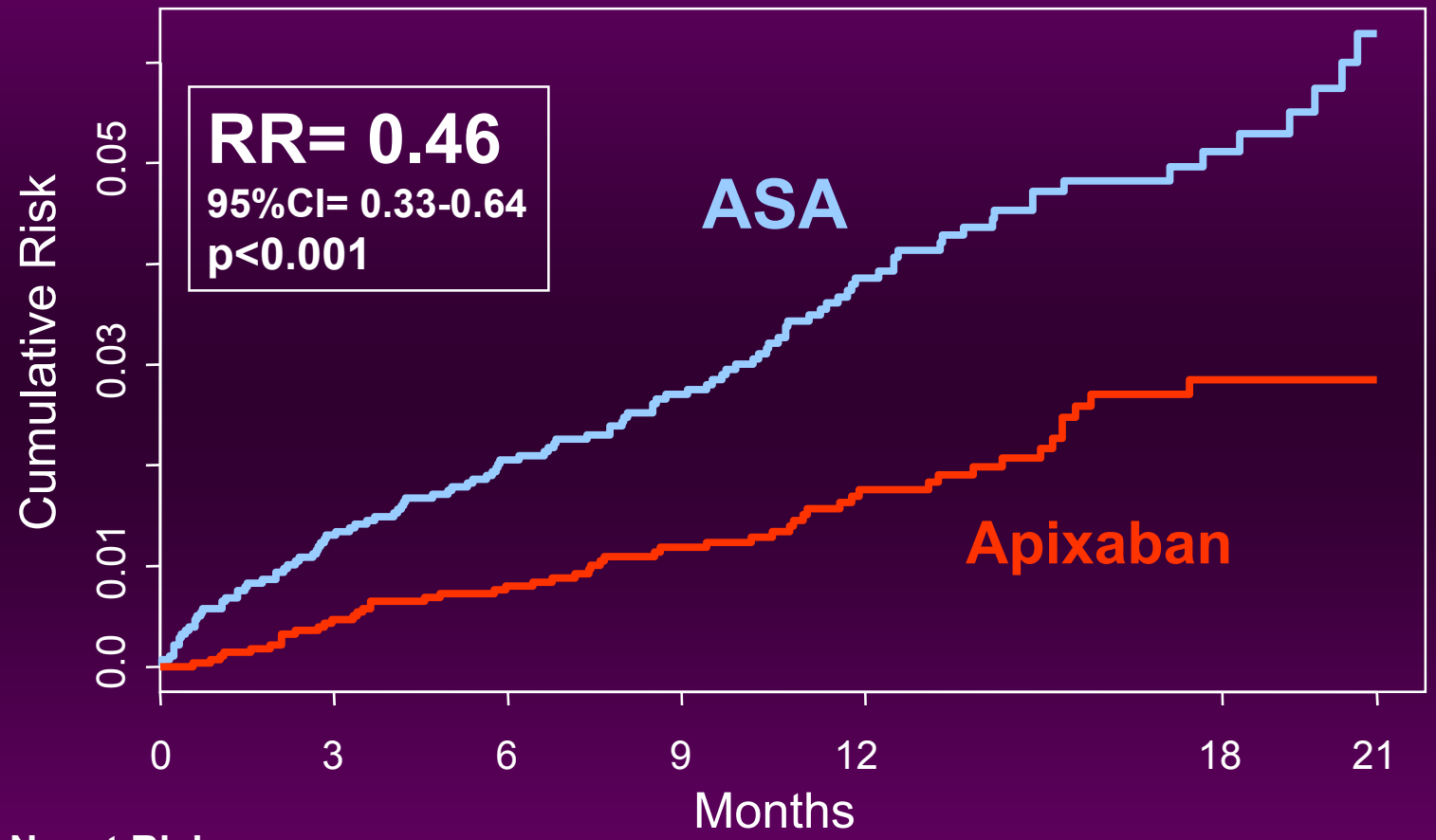
Compared to warfarin

RR 0.69 (0.60-0.80)

AVERROES: Apixaban vs. Aspirin

- Patients with AFib, unsuitable for VKA
- Randomized 5600 subjects
  - Apixaban 5 mg twice daily
  - ASA 81-324 mg daily

Stroke or Systemic Embolism

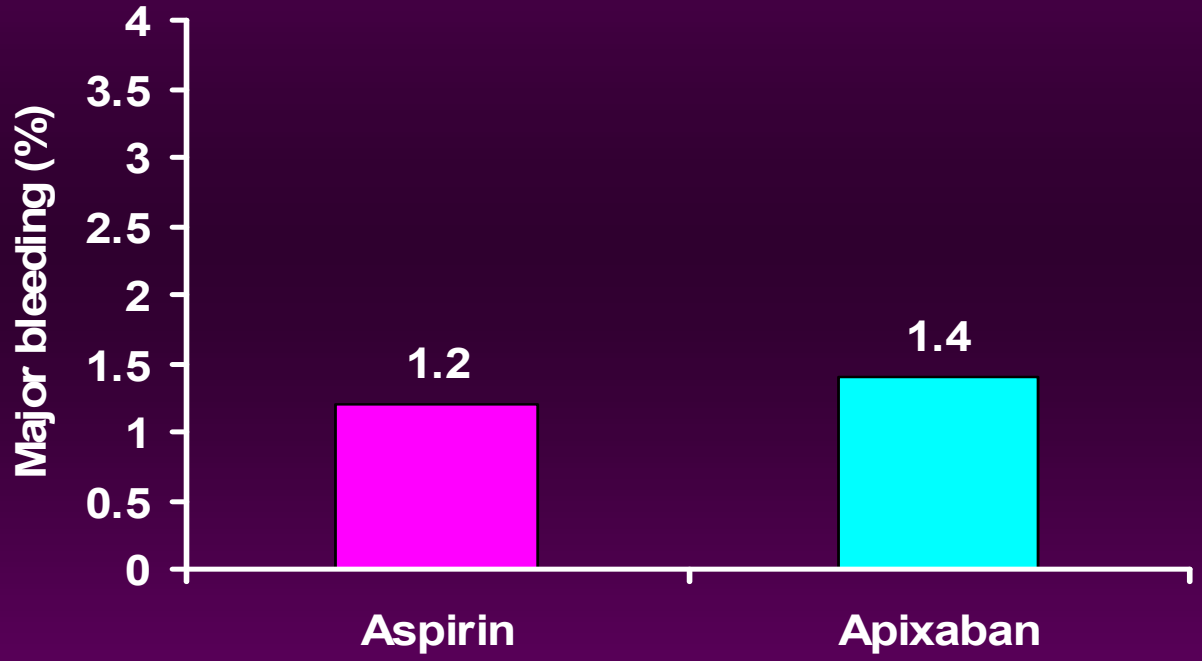


No. at Risk

ASA	**2791**	**2720**	**2541**	**2124**	**1541**	**626**	**329**
Apix	**2809**	**2761**	**2567**	**2127**	**1523**	**617**	**353**

Preliminary Results

Apixaban: Major Bleeding



Compared to aspirin

RR 1.14 (0.74-1.75)

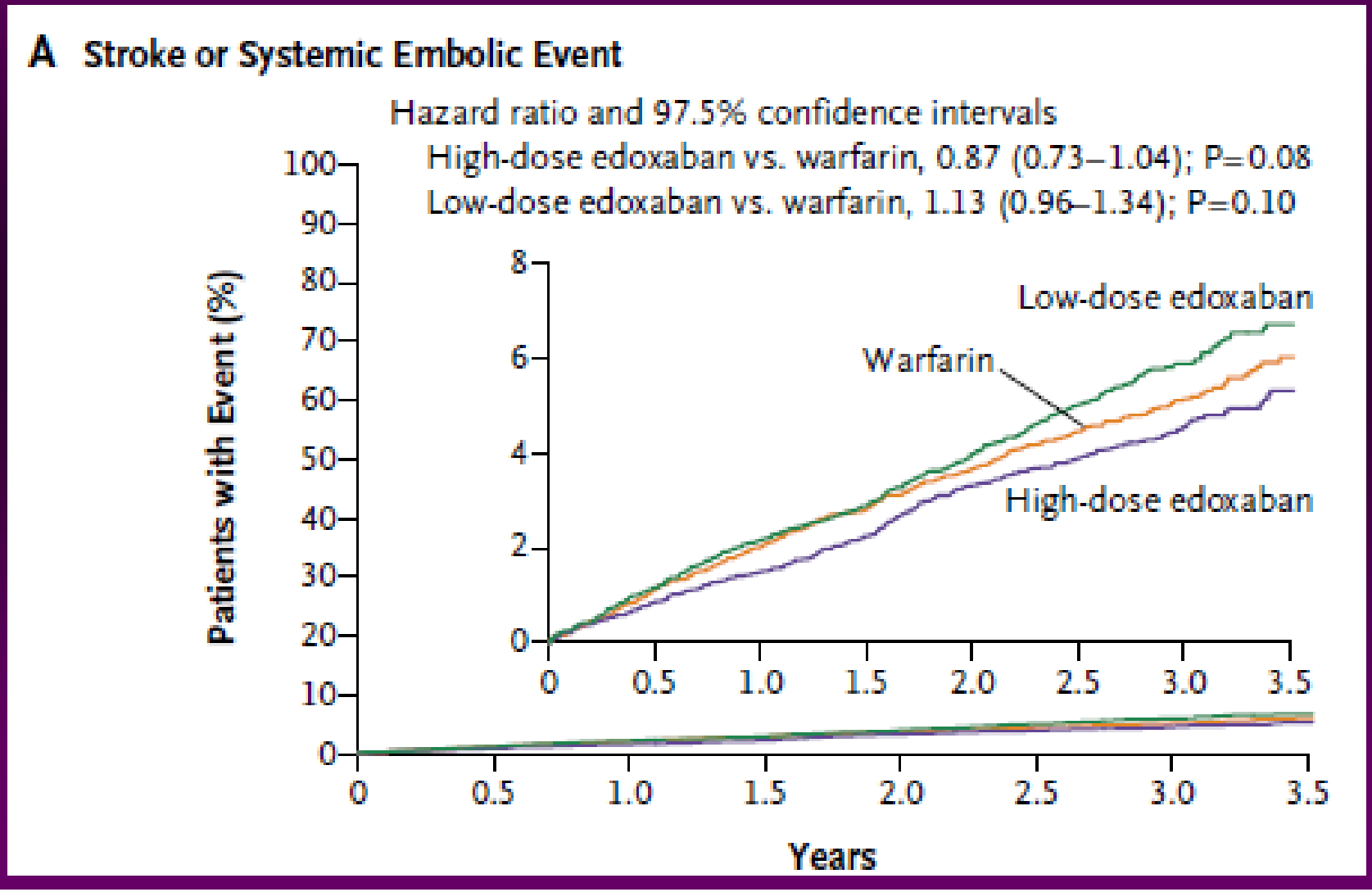
Apixaban

- In patients unsuitable for VKA:
  - Apixaban reduced stroke by ~50% compared to aspirin
  - Without a significant increase in major bleeding
- In patients suitable for VKA:
  - Apixaban reduced stroke by about 20% compared to warfarin
  - With about 30% less major bleeding

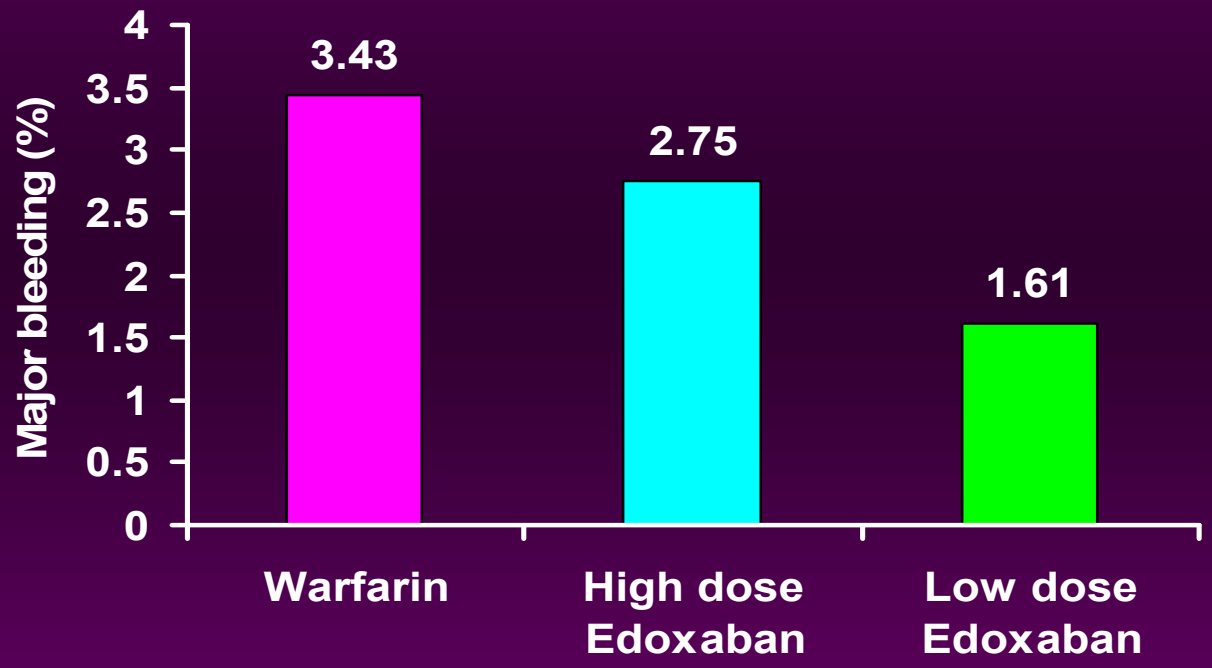
Edoxaban

- AFib and at moderate-to-high risk for stroke
- Randomized 21,105 subjects
  - Edoxaban 60 mg (high) or 30 mg (low dose) once daily
  - Warfarin to INR 2.0-3.0
- Primary Outcome: stroke and systemic embolism

Edoxaban—Stroke or Systemic Embolism



Edoxaban: Major Bleeding



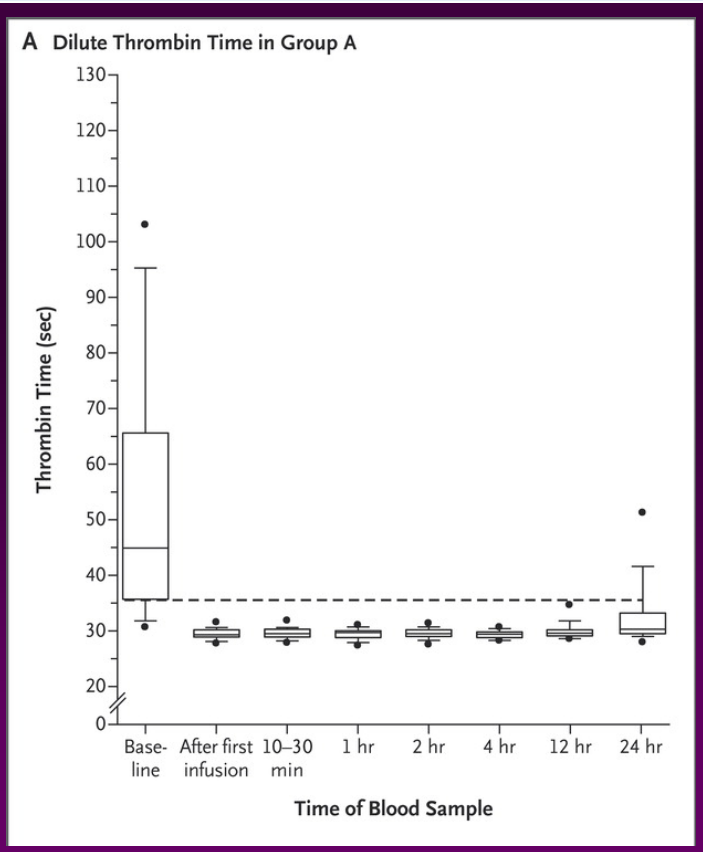
Compared to warfarin:

RR 0.80 (0.71-0.91) **RR 0.47 (0.41-0.55)**

DOAC Reversal

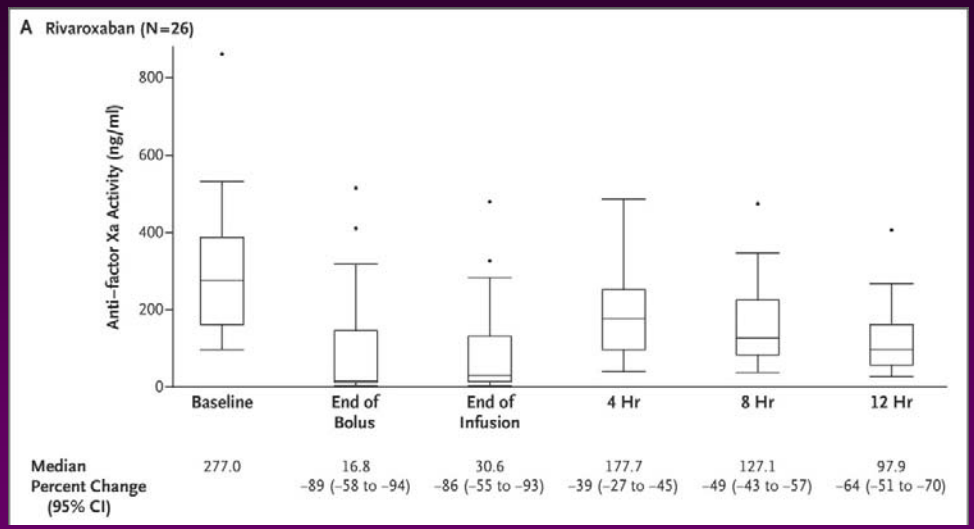
FDA Approves Praxbind® (idarucizumab), Specific Reversal Agent for Pradaxa® (dabigatran etexilate)

- First FDA approval of a specific reversal agent for a novel oral anticoagulant (NOAC)[1]
- Praxbind® immediately reverses the anticoagulant action of dabigatran[2,3]



PORTOLA PHARMACEUTICALS

U.S. FDA Approves Portola Pharmaceuticals' Andexxa®, First and Only Antidote for the Reversal of Factor Xa Inhibitors



Cautions/Uncertainties

- No need to monitor = no way to monitor
- No need to monitor = less interaction with patients
- Thrombolysis?
- Uses or indications beyond Afib and VTE?

Which DOAC?

- Cost/insurance
- Tolerability

Dabigatran (Pradaxa)

- Twice daily
- Reversal agent widely available
- Cannot be crushed

Rivaroxaban (Xarelto)

- Once daily

Apixaban (Eliquis)

- Twice daily
- Lowest risk of bleeding?

Other Cardioembolic Sources

- Extrapolation of Afib data to other high risk sources:
  - Mechanical prosthetic valve
  - Left atrial/atrial appendage thrombus
  - Sick sinus syndrome
  - Recent myocardial infarction (<4 weeks)
  - Left ventricular thrombus
  - Dilated cardiomyopathy
  - Akinetic left ventricular segment
  - Others?

Anticoagulation for "Low-to-Medium Risk" Sources of Cardioembolism

Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis

Atrial septal aneurysm
Patent foramen ovale

Congestive heart failure

Atrial flutter
Left atrial turbulence (smoke)
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, <6 months)

Embolic Stroke of Uncertain Source (ESUS)

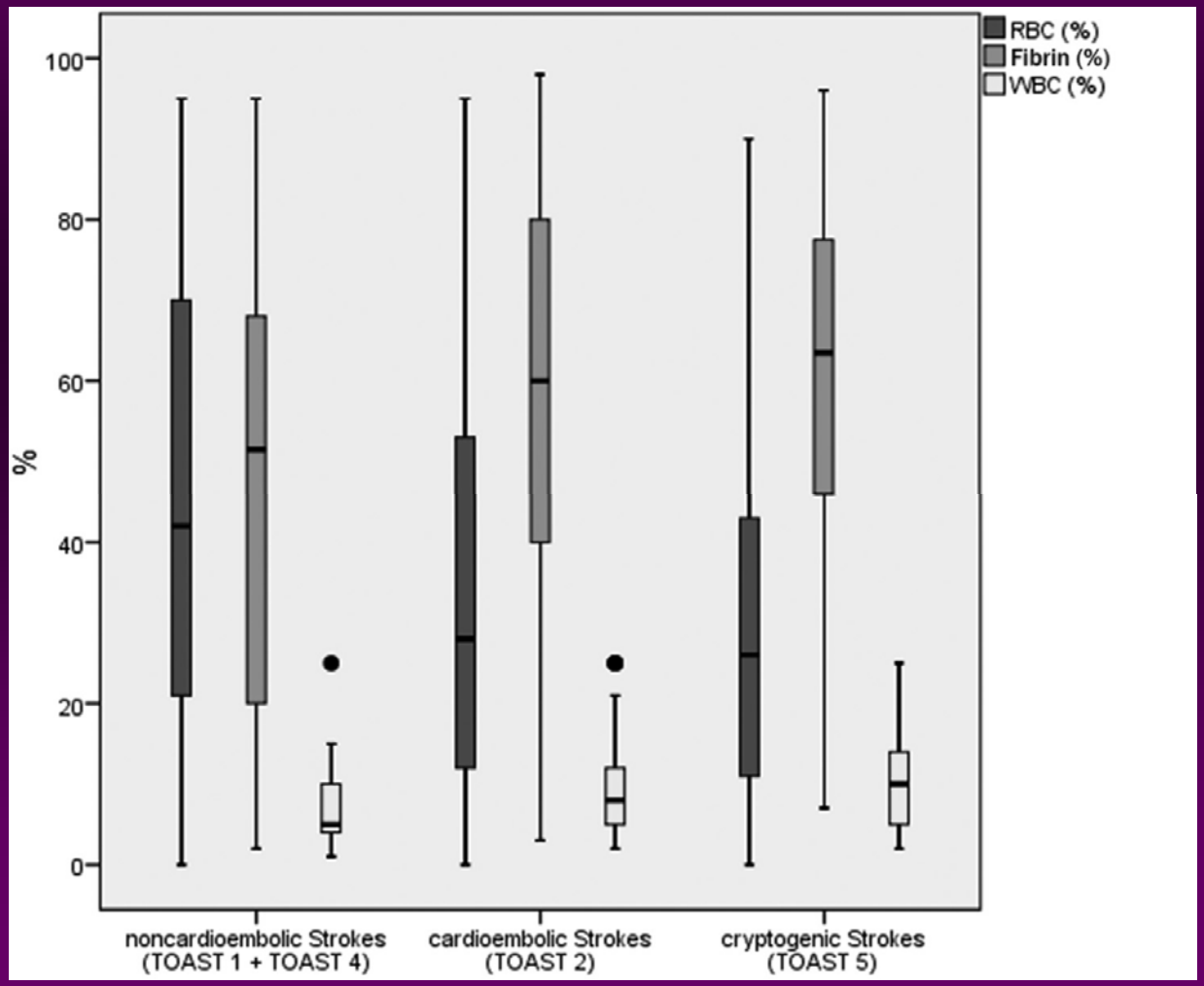
- Stroke detected by CT or MRI that is not lacunar
  - Subcortical infarct ≤1.5 cm (≤2.0 cm on DWI) in largest dimension, and in the distribution of the small, penetrating cerebral arteries.
- Absence of extracranial or intracranial atherosclerosis
  - Causing a ≥50% luminal stenosis in arteries supplying the area of ischemia
- No major-risk cardioembolic source of embolism
  - AF, intracardiac thrombus, prosthetic valve, myxoma/tumors, mitral stenosis, recent MI, EF<30%, vegetation
- No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug misuse)

Lancet 2014

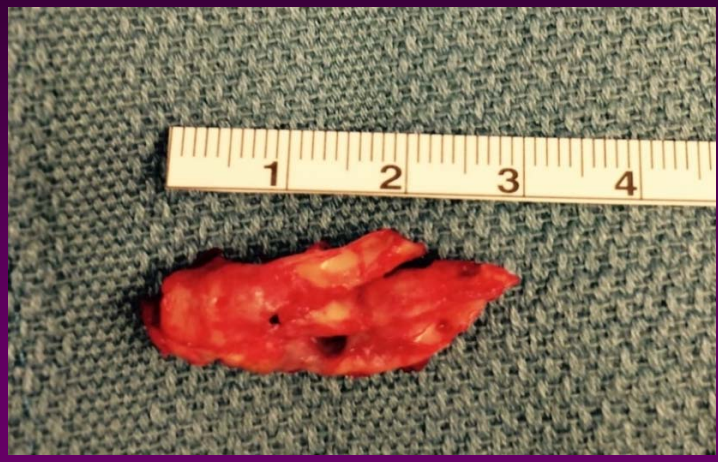
ESUS Components

- Truly unexplained ischemic stroke
- Stroke with undetected/occult AF
- Stroke due to "low-to-medium" risk cardiac sources
- Stroke due to arch atheroma
- Stroke due to <50% extra- or intracranial atherosclerosis

What's in an ESUS?



Nearly identical to cardiogenic emboli



Anticoagulation For ESUS? Post hoc subgroups from WARSS

Subgroup	Cryptogenics			
	proportion with event, % (n)		hazard ratio (95% CI)[1]	p value[2]
	warfarin	aspirin		
Infarct topography				
Superficial, cortical or cerebellar, large deep (i.e., basal ganglia, etc.), or superficial and deep combined	11.9 (168)	17.8 (170)	0.66 (0.37–1.15)	0.14
Small deep	14.8 (27)	12.5 (33)	1.17 (0.29–4.69)	0.82
Brainstem only, brainstem and/or cerebellum	36.8 (19)	10.3 (29)	4.14 (1.07–16.05)	0.04
No primary lesion on scan	17.5 (57)	17.5 (58)	1.06 (0.44–2.54)	0.90
	Interaction (treatment/ brainstem topography)			0.09

Sacco, 2006

Anticoagulation for ESUS?

- NAVIGATE-ESUS
  - Rivaroxaban vs. aspirin for all ESUS
  - Terminated October 2017 due to lack of efficacy
- RESPECT-ESUS
  - Dabigatran vs. aspirin for all ESUS
  - Results expected October 2018
- ARCADIA
  - Apixaban vs. aspirin for ESUS with “atrial cardiopathy”
  - Launched 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

R.G. Hart, M. Sharma, H. Mundl, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, B. Swaminathan, P. Lavados, Y. Wang, Y. Wang, A. Davalos, N. Shamalov, R. Mikulik, L. Cunha, A. Lindgren, A. Arauz, W. Lang, A. Czlonkowska, J. Eckstein, R.J. Gagliardi, P. Amarenco, S.F. Ameriso, T. Tatlisumak, R. Veltkamp, G.J. Hankey, D. Toni, D. Bereczki, S. Uchiyama, G. Ntaios, B.-W. Yoon, R. Brouns, M. Endres, K.W. Muir, N. Bornstein, S. Ozturk, M.J. O'Donnell, M.M. De Vries Basson, G. Pare, C. Pater, B. Kirsch, P. Sheridan, G. Peters, J.I. Weitz, W.F. Peacock, A. Shoamanesh, O.R. Benavente, C. Joyner, E. Themeles, and S.J. Connolly, for the NAVIGATE ESUS Investigators*

NAVIGATE ESUS Study Design

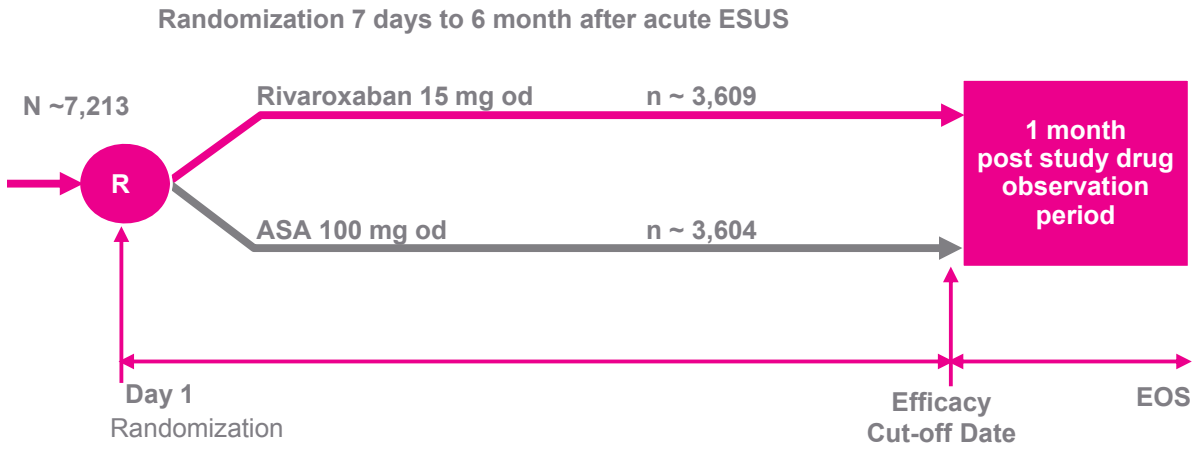
Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Patients with recent ischemic stroke and

1. visualized by brain CT or MRI that is not lacunar (subcortical infarct ≤1.5 cm)
2. absence of cervical carotid atherosclerotic artery stenosis > 50% or occlusion
3. no atrial fibrillation after ≥ 24 hours cardiac rhythm monitoring
4. no intra-cardiac thrombus on echocardiography
5. no other specific etiology for cause of stroke (eg, arteritis, dissection, migraine/ vasospasm, drug abuse)

Age ≥ 50 years

459 sites in 31 countries



Primary efficacy endpoint: Stroke, systemic embolism (ITT)
Primary safety endpoint: ISTH major bleeding (ITT)

Study was halted on 5 October 2017 at the 2nd interim analysis at the recommendation of the DMC:

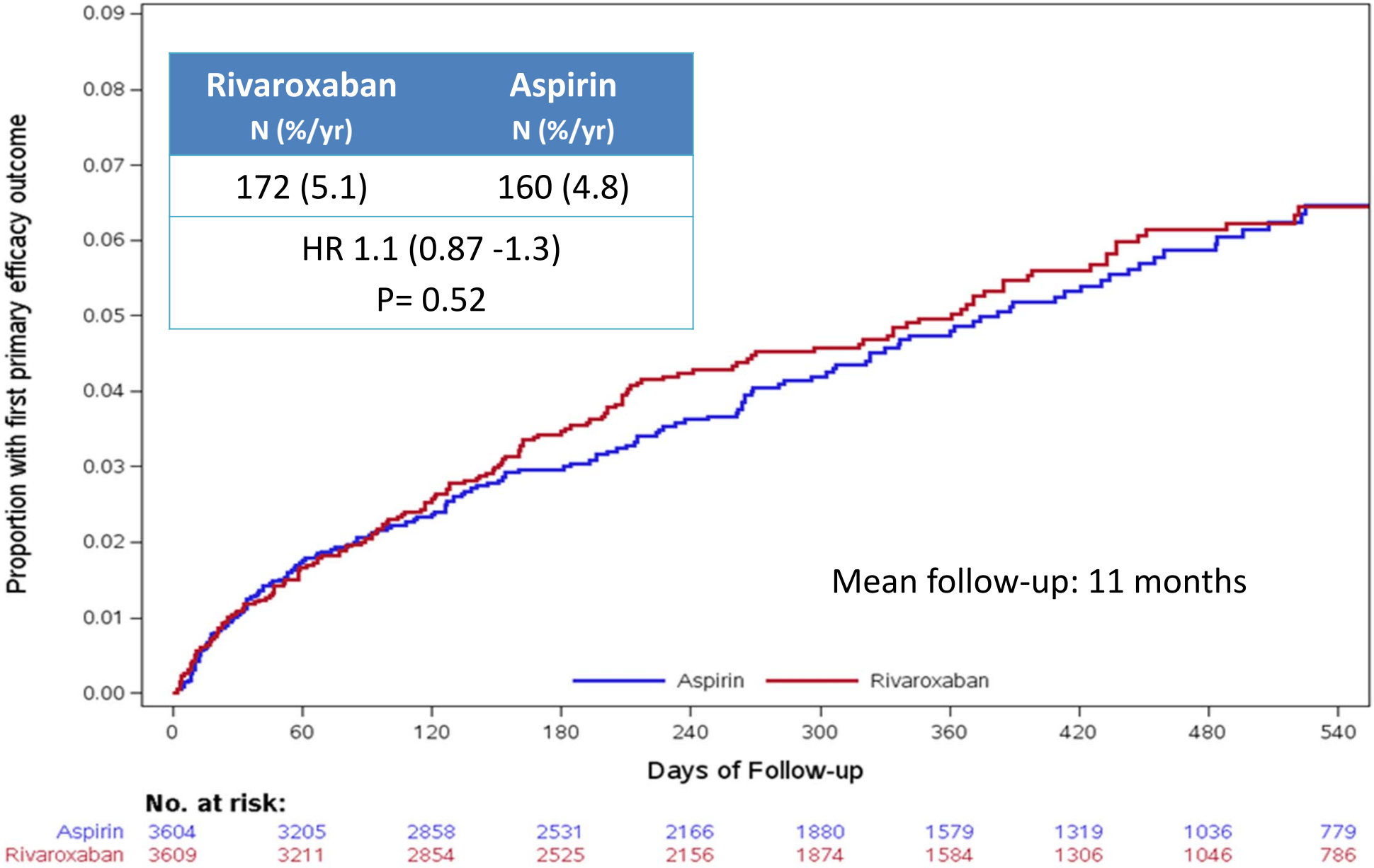
"In the absence of offsetting benefit, and little chance of showing benefit if the study were completed, there is a clear risk of excess bleeding."

Baseline Characteristics

	Rivaroxaban (N=3609)	ASA (N=3604)
Age, years (mean)	66.9	66.9
Male sex	62 %	61%
Systolic Blood Pressure, mmHg (mean ± s.d.)	135.1 ± 17.0	134.9 ± 16.6
Statin use after randomization	78 %	77 %
Hypertension	77 %	78 %
Diabetes mellitus	25 %	25 %
Current tobacco use	21%	20%
Prior stroke or TIA	17 %	18 %
Geographic region • U.S.A. and Canada • Latin America • Europe • East Asia	 13 % 10% 59 % 19 %	 13 % 10 % 58 % 19 %
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)
Intravenous tPA use	17 %	18 %
Time from qualifying stroke to randomization	38.0 d	36.0 d
Intracranial vascular imaging (any type)	78 %	78 %
Cardiac rhythm monitoring ≥48 hours	34 %	34 %

Figure 1a. Kaplan-Meier curves for time to first primary efficacy outcome

Rivaroxaban N (%/yr)	Aspirin N (%/yr)
172 (5.1)	160 (4.8)
HR 1.1 (0.87 -1.3) P= 0.52	



No. at risk:

Aspirin	3604	3205	2858	2531	2166	1880	1579	1319	1036	779
Rivaroxaban	3609	3211	2854	2525	2156	1874	1584	1306	1046	786

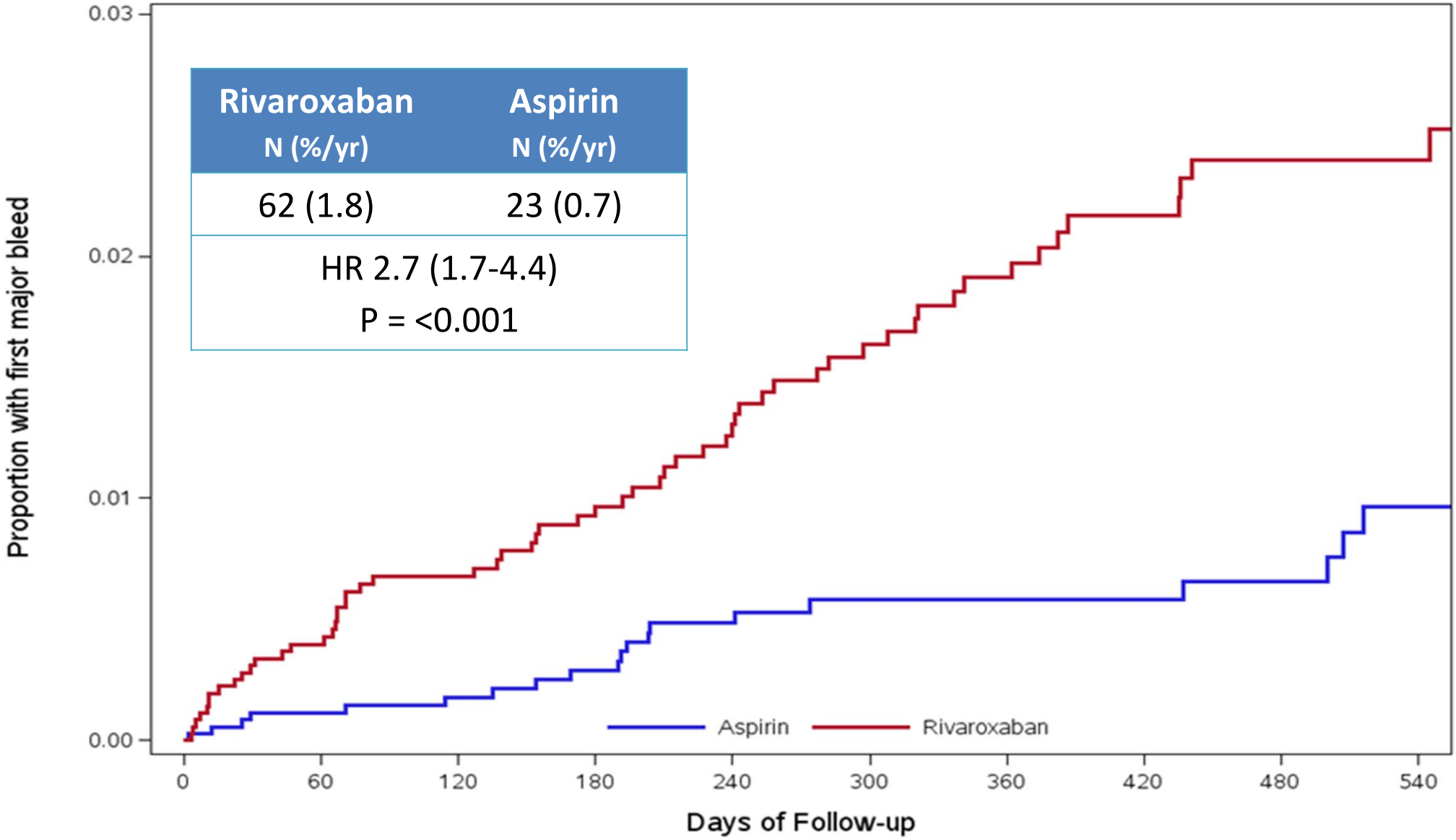
NAVIGATE ESUS

Efficacy Outcomes

	Rivaroxaban N=3609 n (%/year)	ASA N=3604 n (%/year)	HR (95% CI)	p-value
Primary outcome (all recurrent stroke or systemic embolism)	172 (5.1)	160 (4.8)	1.1 (0.87-1.3)	0.52
Individual components included in the primary outcome				
All recurrent stroke (ischemic, hemorrhagic, undefined)	171 (5.1)	158 (4.7)	1.1 (0.87-1.3)	0.48
Ischemic stroke	158 (4.7)	156 (4.7)	1.0 (0.81-1.3)	0.92
Hemorrhagic stroke	13 (0.4)	2 (0.1)	6.5 (1.5-28)	0.01

Figure 1b. Kaplan-Meier curves for time to first major bleed

Rivaroxaban N (%/yr)	Aspirin N (%/yr)
62 (1.8)	23 (0.7)
HR 2.7 (1.7-4.4) P = <0.001	



No. at risk:

Aspirin	3604	3254	2918	2597	2231	1939	1637	1371	1083	822
Rivaroxaban	3609	3249	2906	2582	2206	1911	1615	1342	1071	807

NAVIGATE ESUS

Safety Outcomes

	Rivaroxaban N=3609 n (%/year)	ASA N=3604 n (%/year)	HR (95% CI)	p-value
Primary safety outcome (ISTH major bleeding)	62 (1.8)	23 (0.7)	2.7 (1.7-4.4)	0.0001
Secondary safety outcomes				
Life-threatening/fatal bleeding	35 (1.0)	15 (0.4)	2.3 (1.3-4.3)	0.006
Clinically-relevant non-major bleeding	118 (3.5)	79 (2.3)	1.5 (1.1-2.0)	0.005
Symptomatic intracranial hemorrhage	20 (0.6)	5 (0.1)	4.0 (1.5-10.7)	0.005
- intracerebral hemorrhage	12 (0.3)	3 (0.1)	4.0 (1.1-14.2)	0.03
- subarachnoid hemorrhage	5 (0.1)	1 (0.0)	5.0 (0.59-43)	0.10
- subdural/epidural hematoma	3 (0.1)	2 (0.1)	1.5(0.25-9.0)	0.65

What rates of ISTH major hemorrhage are anticipated in NAVIGATE ESUS?

(presented to the DMC in March 2016)

- **Rivaroxaban**: Based on RCTs involving older patients with atrial fibrillation, most taking 20mg/d, the major hemorrhage risk was 3% per year. In NAVIGATE ESUS, a lower dose (15mg/d) is tested in younger patients. Estimate **about 2%/yr**. (Vazquez FJ et al. *Thromb Res* 2016; 138: 1-6)

  Observed: 1.8%/yr

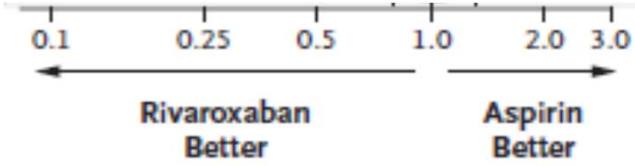
- **Aspirin**: The major hemorrhage rate in RCTs involving secondary prevention of stroke is **about 1%/yr.** (Haris M et al. *Am J Cardiol* 2009; 103: 1107-12)

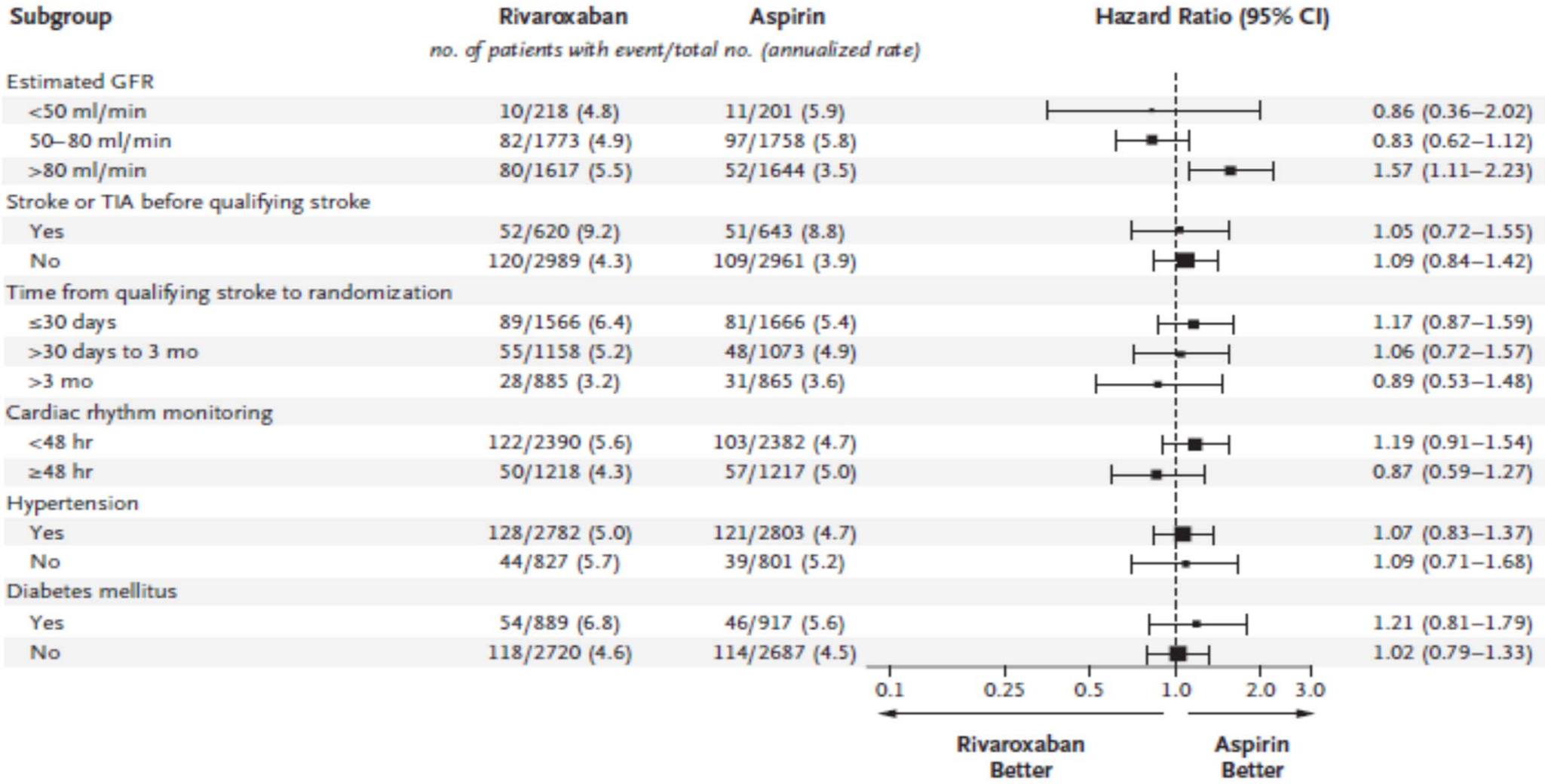
  Observed: 0.7%/yr

- Anticipated **intracerebral hemorrhage rate** with aspirin: 0.20%/yr.

  Observed ICH rate: 0.03%/yr (1/3600 pts x 11 months)

Subgroup	Rivaroxaban	Aspirin	Hazard Ratio (95% CI)
	no. of patients with event/total no. (annualized rate)		
Overall	172/3609 (5.1)	160/3604 (4.8)	1.07 (0.87–1.33)
Age			
<60 yr	43/861 (5.4)	25/855 (3.1)	1.73 (1.06–2.83)
60–75 yr	90/2019 (4.8)	93/1993 (5.1)	0.94 (0.71–1.26)
>75 yr	39/729 (5.7)	42/756 (5.8)	0.97 (0.63–1.51)
Sex			
Male	122/2232 (5.8)	102/2204 (4.9)	1.17 (0.90–1.53)
Female	50/1377 (4.0)	58/1400 (4.5)	0.89 (0.61–1.29)
Race			
White only	106/2612 (4.4)	114/2604 (4.7)	0.93 (0.71–1.21)
Black only	2/51 (3.9)	4/60 (7.9)	0.51 (0.09–2.83)
Asian only	57/716 (8.3)	34/698 (5.0)	1.65 (1.08–2.52)
Other	7/230 (3.5)	8/242 (3.9)	0.91 (0.33–2.51)
Geographic region			
United States and Canada	27/461 (6.4)	15/457 (3.5)	1.82 (0.97–3.42)
Latin America	12/372 (4.2)	10/374 (3.5)	1.23 (0.53–2.85)
Western Europe	56/1541 (3.7)	80/1540 (5.4)	0.69 (0.49–0.97)
Eastern Europe	24/560 (4.9)	22/558 (4.4)	1.10 (0.61–1.96)
East Asia	53/675 (8.1)	33/675 (5.0)	1.61 (1.04–2.49)




Subgroup
Rivaroxaban
Aspirin
Hazard Ratio (95% CI)
no. of patients with event/total no. (annualized rate)
Estimated GFR
<50 ml/min 10/218 (4.8) 11/201 (5.9) 0.86 (0.36–2.02)
50–80 ml/min 82/1773 (4.9) 97/1758 (5.8) 0.83 (0.62–1.12)
>80 ml/min 80/1617 (5.5) 52/1644 (3.5) 1.57 (1.11–2.23)
Stroke or TIA before qualifying stroke
Yes 52/620 (9.2) 51/643 (8.8) 1.05 (0.72–1.55)
No 120/2989 (4.3) 109/2961 (3.9) 1.09 (0.84–1.42)
Time from qualifying stroke to randomization
≤30 days 89/1566 (6.4) 81/1666 (5.4) 1.17 (0.87–1.59)
>30 days to 3 mo 55/1158 (5.2) 48/1073 (4.9) 1.06 (0.72–1.57)
>3 mo 28/885 (3.2) 31/865 (3.6) 0.89 (0.53–1.48)
Cardiac rhythm monitoring
<48 hr 122/2390 (5.6) 103/2382 (4.7) 1.19 (0.91–1.54)
≥48 hr 50/1218 (4.3) 57/1217 (5.0) 0.87 (0.59–1.27)
Hypertension
Yes 128/2782 (5.0) 121/2803 (4.7) 1.07 (0.83–1.37)
No 44/827 (5.7) 39/801 (5.2) 1.09 (0.71–1.68)
Diabetes mellitus
Yes 54/889 (6.8) 46/917 (5.6) 1.21 (0.81–1.79)
No 118/2720 (4.6) 114/2687 (4.5) 1.02 (0.79–1.33)
0.1
0.25
0.5
1.0
2.0
3.0
Rivaroxaban Better
Aspirin Better

NAVIGATE ESUS Main Results- I

- Rigorously-conducted, hypothesis-testing phase III international randomized trial.
- No reduction in recurrent stroke by rivaroxaban 15 mg daily vs. aspirin, and major bleeding was increased.
- Stopped early with 74% of planned primary events, but adequate power to exclude >13% benefit by rivaroxaban.
- High rate of recurrent stroke (~5%/yr) with either treatment.

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NAVIGATE ESUS Main Results - II

- "A beautiful hypothesis slain by ugly facts."*
- Atrial fib identified in 3%; while under-detected, unlikely to be frequent because results were negative.
- Why was NAVIGATE ESUS negative?
  - Did ESUS criteria define embolic strokes?
  - Heterogeneous embolic sources with different composition of emboli did not respond better to factor Xa inhibition?
- Ongoing randomized trials testing alternative anticoagulants will clarify whether the ESUS construct has value beyond identifying cryptogenic stroke patients with high risk of stroke recurrence.

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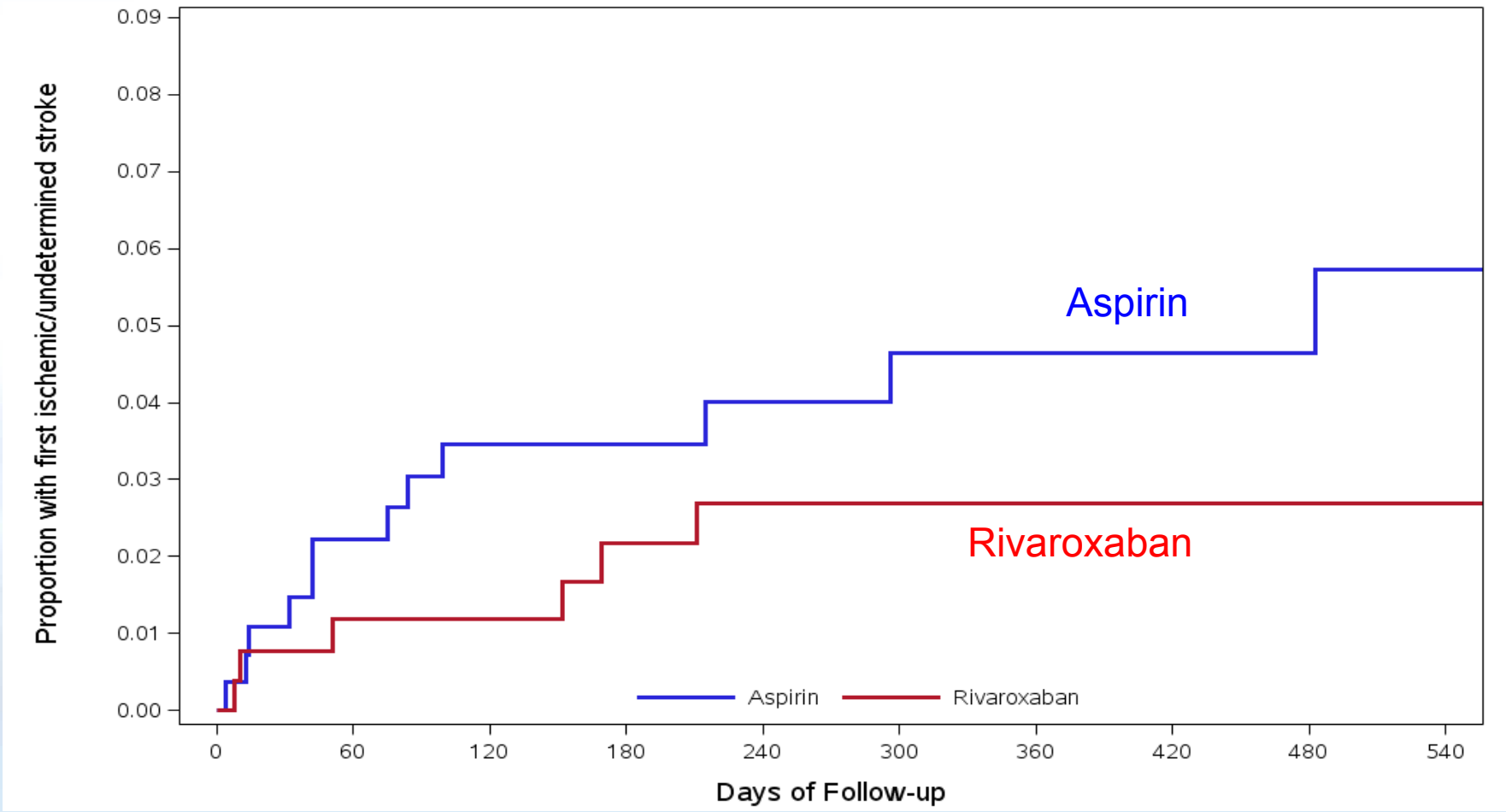
* Adapted from Thomas Huxley; address to British Association for Advancement of Science (1870).

Why Did NAVIGATE Fail?

- Four D's equals one F
  - Design—Is the ESUS concept dumb?
  - Drug—Wrong drug, wrong dose, need for dual agent (aspirin)?
  - Doctors—Enrolled the wrong patients?
  - DSMB—Did they abort too soon?

NAVIGATE: Rivaroxaban vs. Aspirin with PFO



PFO present: HR 0.54 (0.22-1.36)

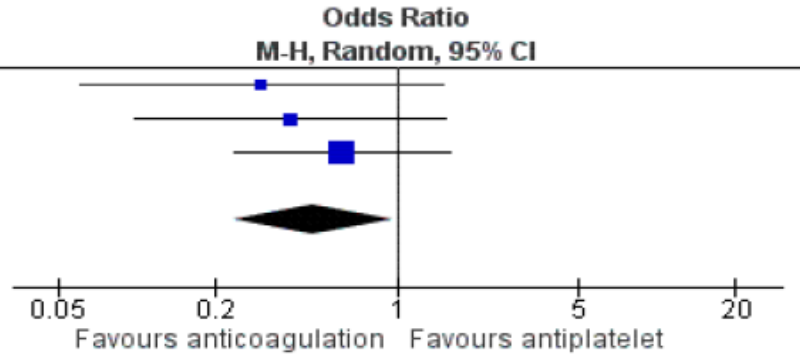
NAVIGATE ESUS

Meta-analysis: Anticoagulation vs. Antiplatelet

Study or Subgroup	Anticoagulation Events	Anticoagulation Total	Antiplatelet Events	Antiplatelet Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PICSS 2002	2	42	8	56	19.2%	0.30 [0.06, 1.49]	2002
CLOSE 2017	3	187	7	174	26.4%	0.39 [0.10, 1.53]	2017
NAVIGATE 2018	7	182	12	197	54.3%	0.62 [0.24, 1.60]	2018
Total (95% CI)		**411**		**427**	**100.0%**	**0.48 [0.24, 0.96]**	
Total events	12		27				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.69$, $df = 2$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 2.07$ ($P = 0.04$)



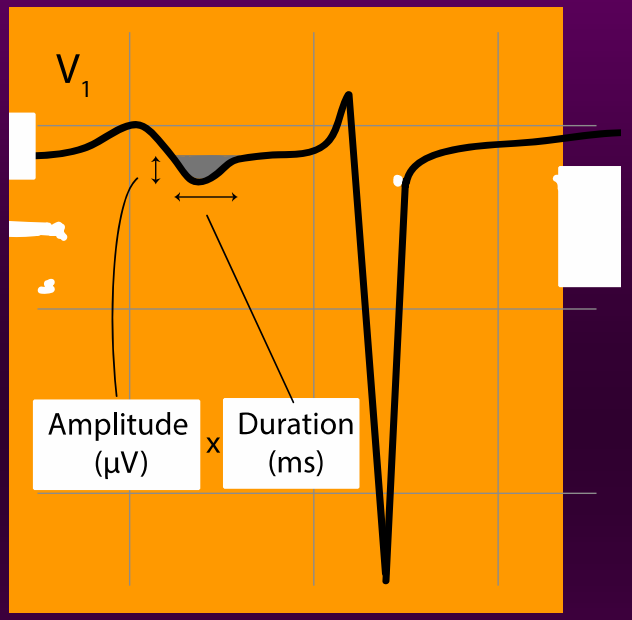
OR 0.48 (0.24-0.96); p=0.04

No evidence of heterogeneity

NAVIGATE ESUS

ARCADIA Hypothesis

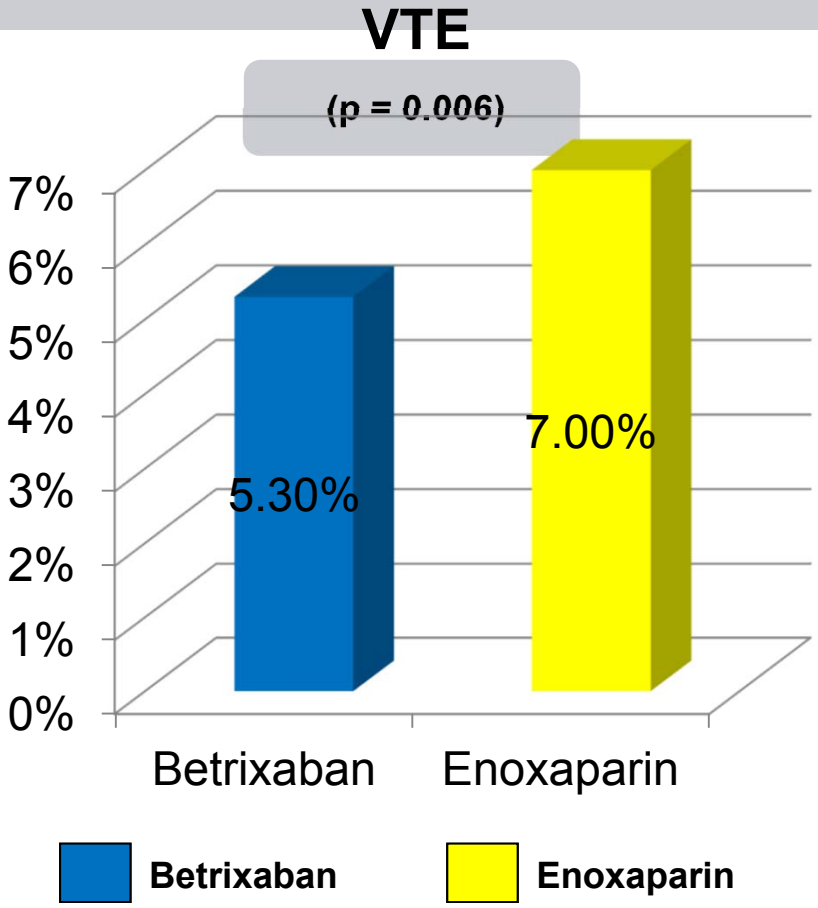
- **Atrial cardiopathy can cause thromboembolism even in the absence of AF**
  - AF is a common manifestation of atrial cardiopathy but is not necessary to cause thromboembolism
  - Other atrial dysrhythmias associated with stroke even wihtout AF:
    - Frequent PACs <> 2-fold higher risk of stroke
  - Enlarged left atrium potential source of embolism
  - Large p wave negative terminal force indicator of left atrial stress



Kamel et al, *Stroke*, 2016

APEX—Betrixaban FXa Inhibitor

Patients hospitalized with an **acute medical illness (heart failure, infection, stroke)** randomized to oral betrixaban for 35-42 days (n=3,759) vs.
subcutaneous enoxaparin for 10 days (n=3,754)



Results

- Significant reduction in composite of symptomatic and asymptomatic VTE
- Major bleeding: 0.7% versus 0.6% (p=0.55)

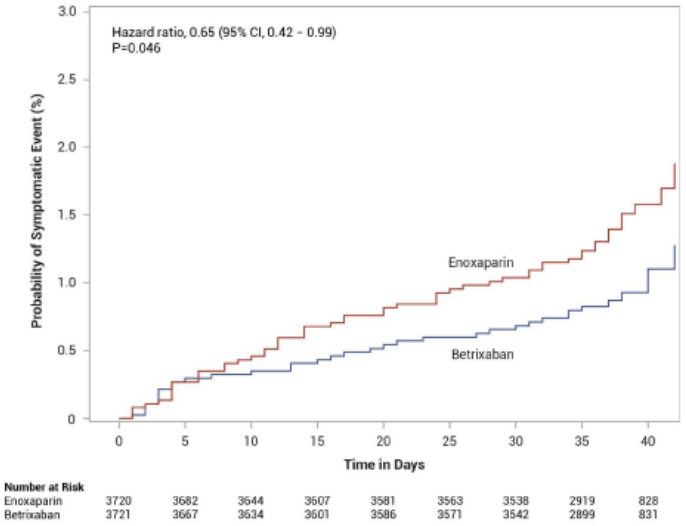
Conclusions

- Betrixaban superior to enoxaparin in preventing thrombotic complications
- Bleeding was similar between the groups
- Role in stroke prevention intriguing

Cohen AT, et al. N Engl J Med 2016;375:534-44

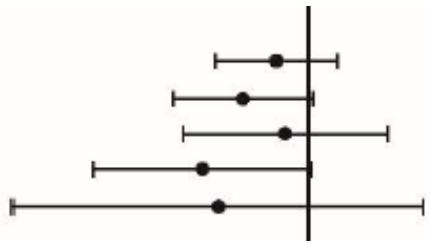
Betrixaban--Broad Applications?

Figure S4. Kaplan-Meier Curve for Symptomatic Events (prespecified analysis)



Time to first symptomatic event in the full second secondary efficacy outcome population.

Reason for Hospital Admission				
Acute decompensated HF	2909	83/1481	69/1428	0.85 (0.62, 1.16)
Acute infection	1737	69/854	49/883	0.72 (0.50, 1.02)
Acute respiratory failure	728	29/375	24/353	0.89 (0.53, 1.49)
Acute ischemic stroke	716	33/363	18/353	0.58 (0.34, 1.02)
Acute rheumatic disorders	195	9/101	5/94	0.63 (0.22, 1.78)

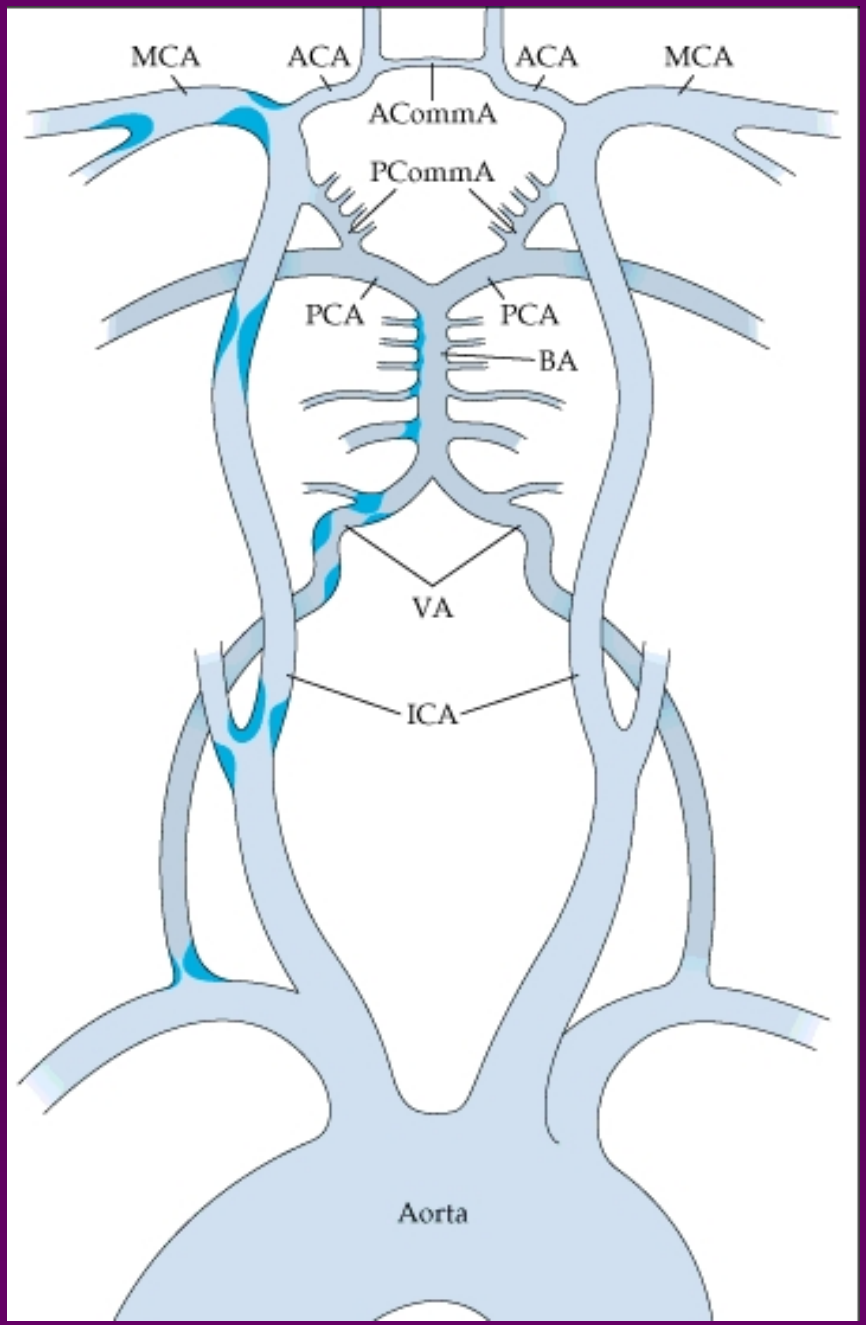


Also 47% relative reduction in new ischemic stroke!

RR 0.53 (0.30-0.94)

Large Vessel Disease

- Aortic arch
- Carotid artery (extracranial)
- Vertebral artery (extracranial)
- Intracranial arteries (carotid siphon, MCA, ACA, PCA, Vertebral, Basilar)

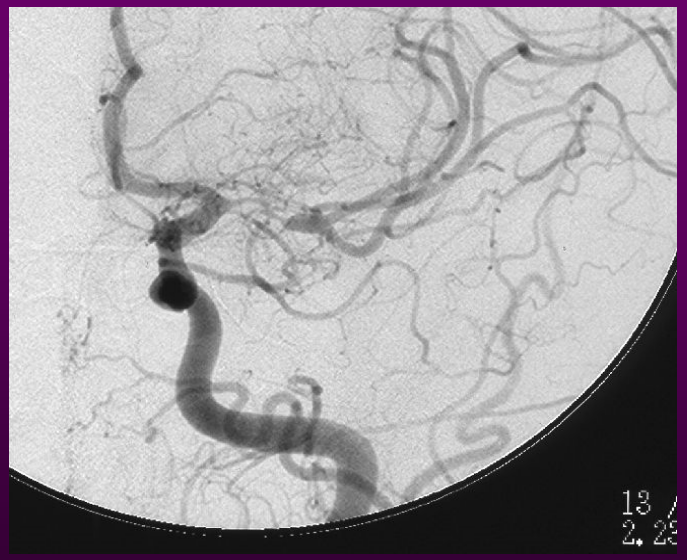


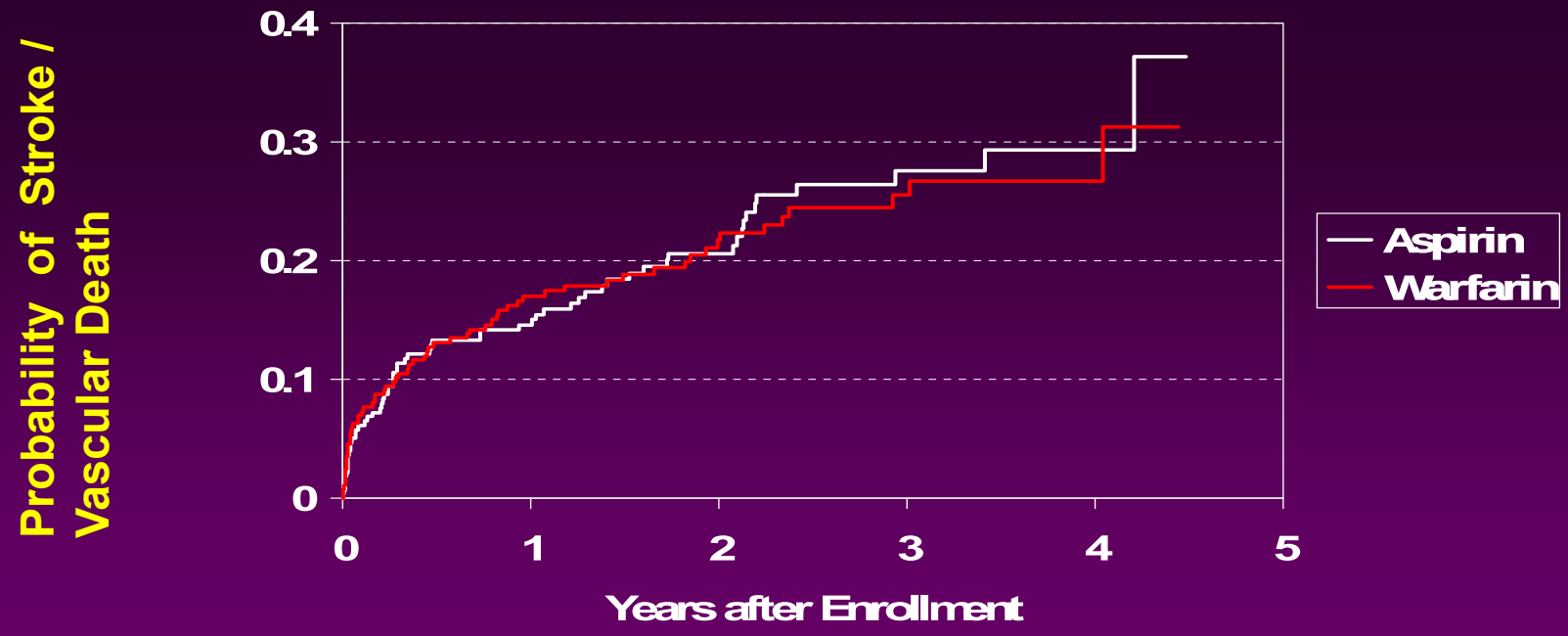
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

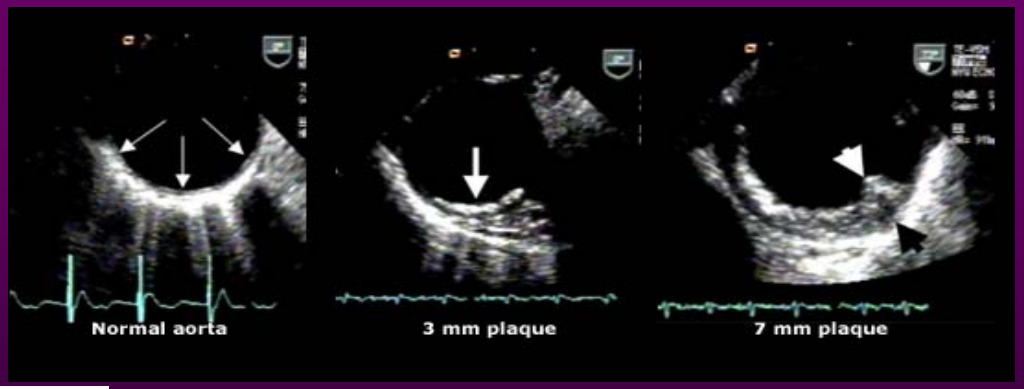
Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

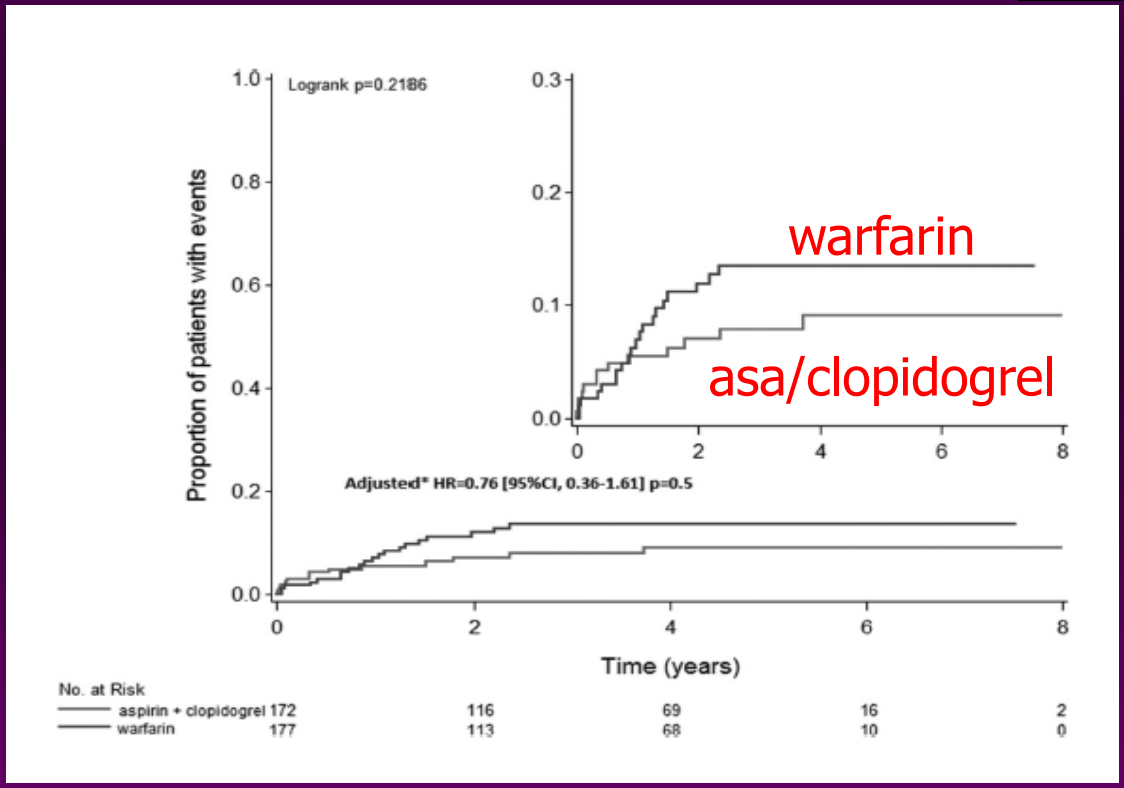
Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Harriet Howlett-Smith, R.N., Barney J. Stern, M.D., Vicki S. Hertzberg, Ph.D., Michael R. Frankel, M.D., Steven R. Levine, M.D., Seemant Chaturvedi, M.D., Scott E. Kasner, M.D., Curtis G. Benesch, M.D., Cathy A. Sila, M.D., Tudor G. Jovin, M.D., and Jose G. Romano, M.D., for the Warfarin–Aspirin Symptomatic Intracranial Disease Trial Investigators*





ARCH Trial





- 7.6% of ASA/clopidogrel vs. 11.3% warfarin
- OR 0.76 (0.36-1.61), p=0.50 → Inconclusive
- More vascular death with warfarin

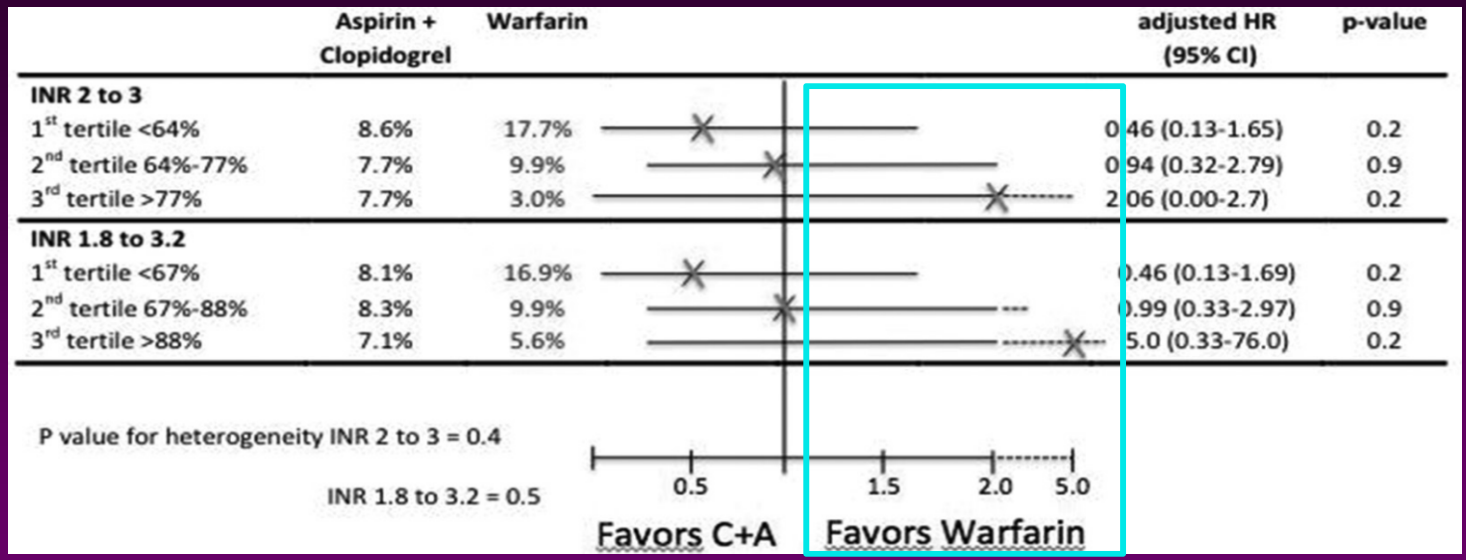
Anticoagulation For Large Artery Disease?

Intracranial stenosis (WASID)

Aortic arch atheroma (ARCH)

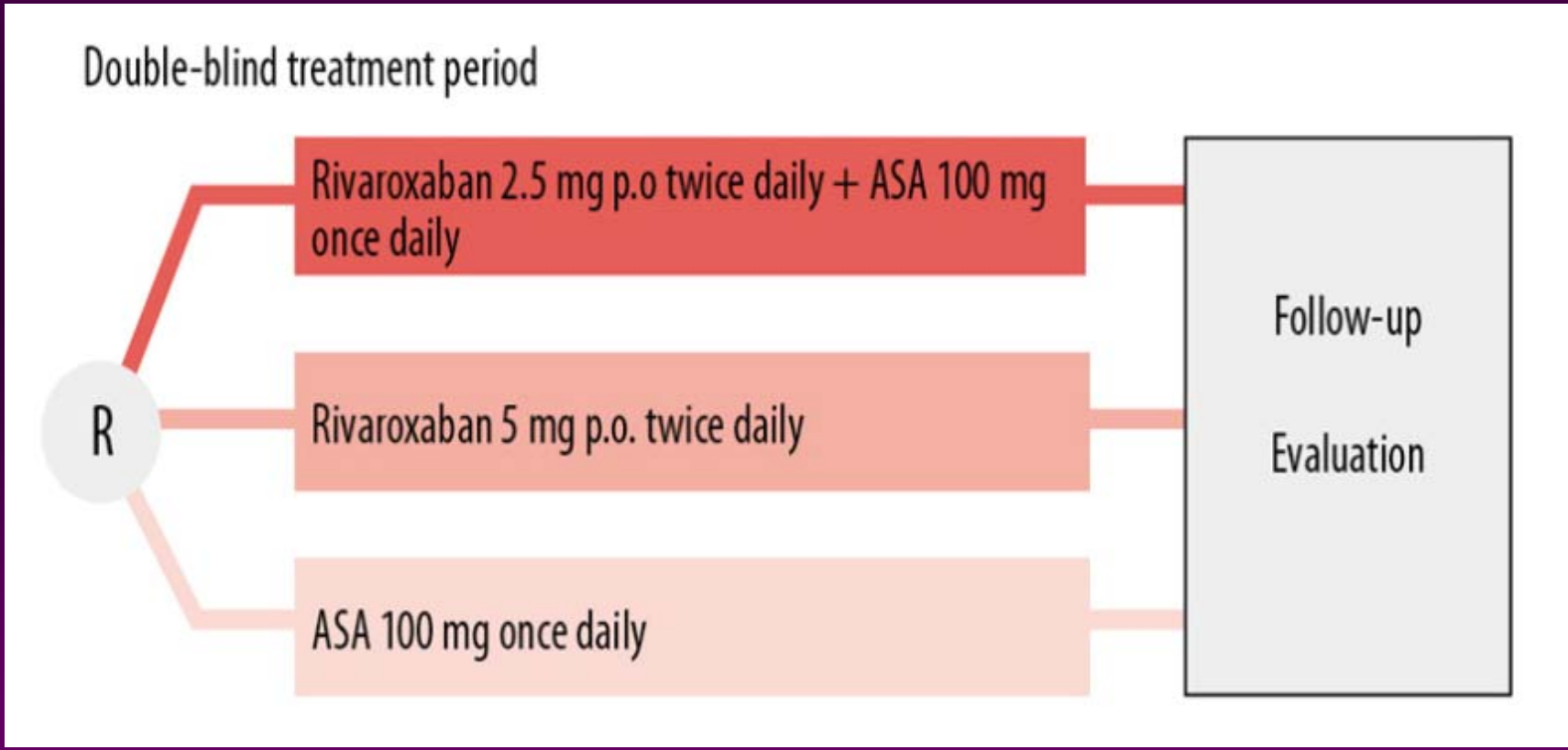
Table 4. Post Hoc Analysis of On-Treatment, INR-Specific Rates of Major Hemorrhage, Ischemic Stroke, and Major Cardiac Events among Patients Randomly Assigned to Receive Warfarin.*

INR Category†	No. of Patient-yr‡	Major Hemorrhage		Ischemic Stroke		Major Cardiac Event§	
		No. of Events	No. of Events per 100 Patient-yr (95% CI)	No. of Events	No. of Events per 100 Patient-yr (95% CI)	No. of Events	No. of Events per 100 Patient-yr (95% CI)
<2.0	92.5	1	1.1 (0.03–6.0)	23	24.9 (15.8–37.3)	10	10.8 (5.2–19.9)
2.0–3.0	256.9	9	3.5 (1.6–6.6)	13	5.1 (2.7–8.7)	1	0.4 (0.01–2.2)
3.1–4.4	52.6	8	15.2 (6.6–30.0)	3	5.7 (1.2–16.7)	3	5.7 (1.2–16.7)
≥4.5	4.9	6	123.3 (45.3–268.4)	1	20.6 (0.5–114.5)	0	0 (0–61.6)

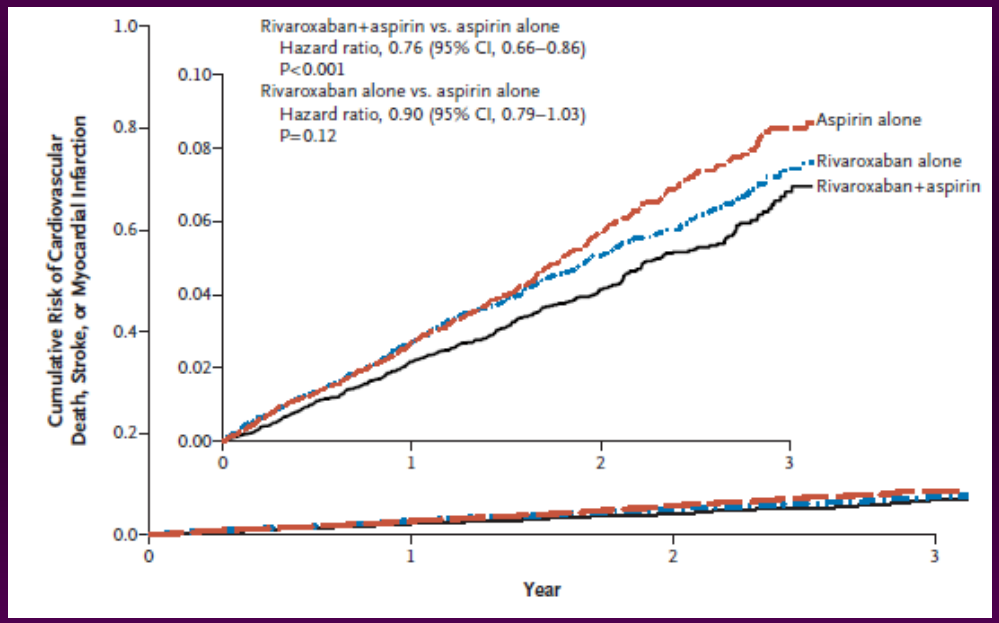


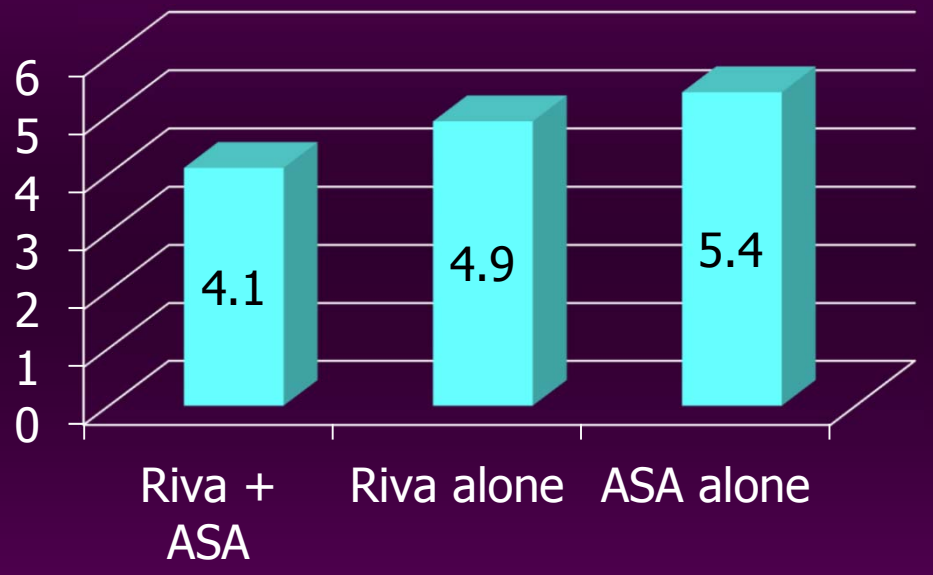
Anticoagulation for Large Artery Disease?
COMPASS: Rivaroxaban, Aspirin, or Both:

Prevention of MI, Stroke, or Cardiovascular Death in Patients with CAD or PAD (included carotid disease)



COMPASS Primary Outcome
CV death, stroke, or MI





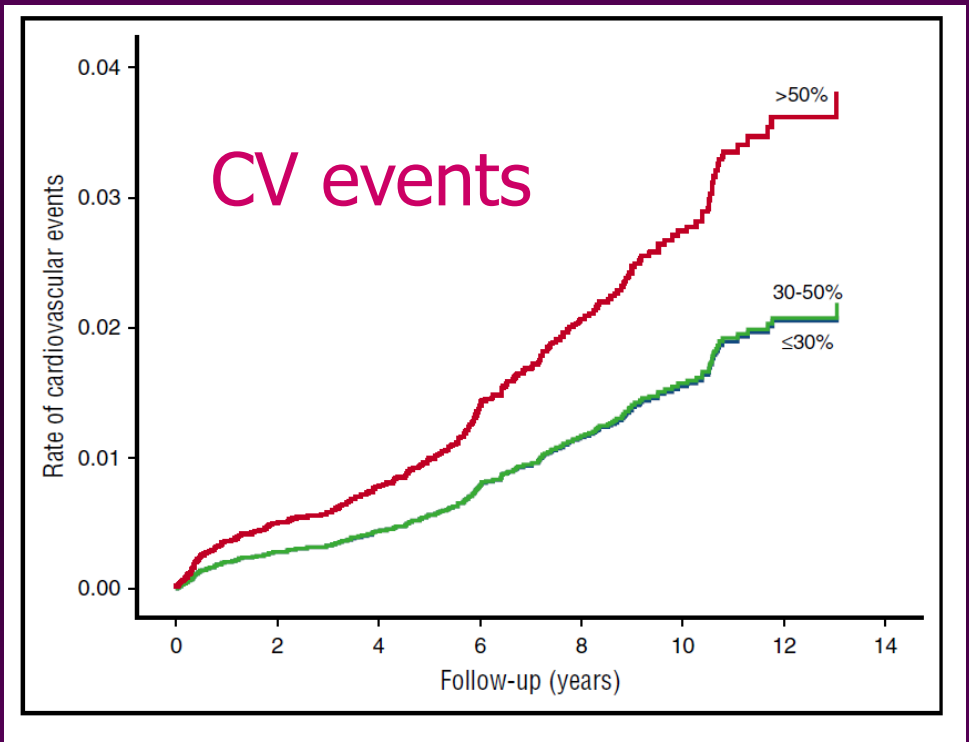
Combination HR 0.76 (0.66-0.86) vs. ASA alone

Secondary: Ischemic stroke HR HR 0.51 (0.38-0.68)!

Is this *PRIMARY* prevention for stroke?

Newer than NOAC

- Factor XIa inhibition
  - Small molecule and antibody strategies
- Why is XI different?
  - Mutants
    - Rare in general population but 0.2%-9% in some groups
    - No or minimal bleeding but elevated PTT
    - Low risk of cardiovascular and thromboembolic events



Cardiovascular events HR 0.57 (0.35-0.93)
VTE 0.26 (0.08-0.64)

Short Term Risk after TIA / Minor Stroke

ABCD² score	Patients (%)	% risk at 2 days
0-3	1628 (34%)	1.0%
4-5	2169 (45%)	4.1%
6-7	1012 (21%)	8.1%

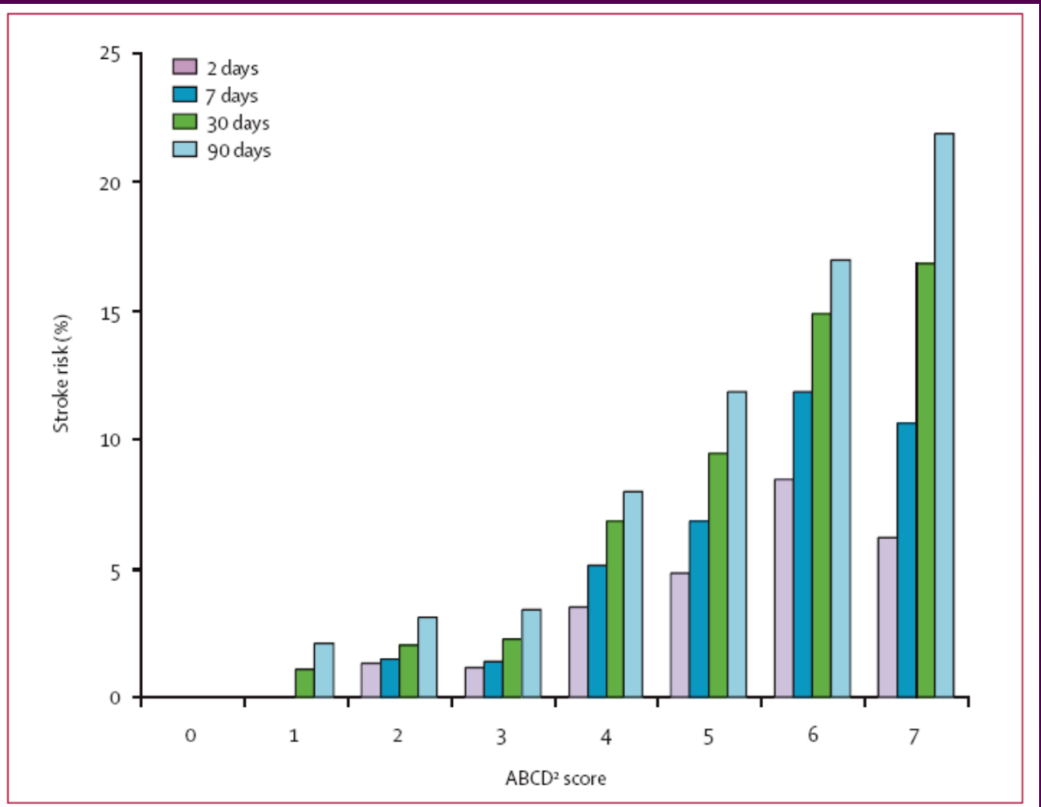
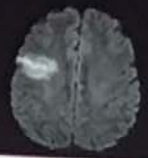
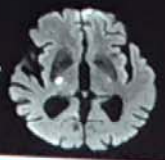
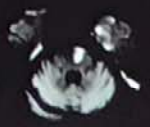
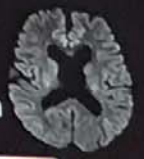


Figure: Short-term risk of stroke by ABCD² score in six groups combined (n=4799)

DATAS II Protocol

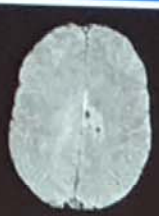
ESUS  Lacunar  Posterior Circulation  No Lesion 

Key Exclusion Criteria:
1. DWI volume <25 ml
2. No OAC indication
3. No revascularization procedure planned

300 Patients, NIHSS 0-9, MRI, Randomized <72 h from Onset

Dabigatran 150/110 mg BID x 30 days

Day 30: MRI and clinical assessment

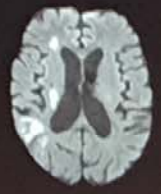
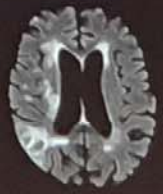
SWI 

Hemorrhagic Transformation
(Primary Endpoint)

Day 90: Clinical Assessment

ASA 81 mg OD x 30 days

Day 30: MRI and clinical assessment

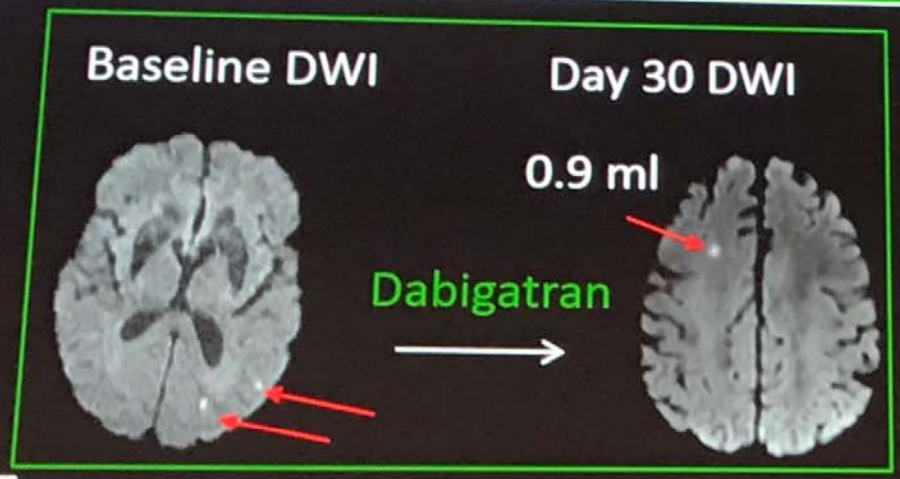
DWI  FLAIR 

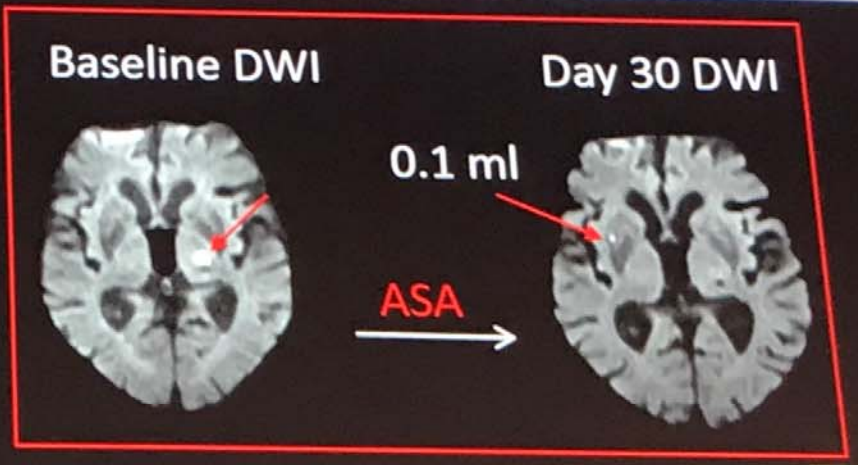
Recurrent Infarction

Day 90: Clinical Assessment

Secondary Outcome: Recurrent Infarcts

Intention To Treat	Dabigatran (142)	ASA (142)	Relative Risk (95% CI)
Recurrent Infarct on Day 30 MRI n (Proportion)	9 (6.3%)	14 (9.9%)	0.64 (0.29, 1.44)





Primary Outcome (Safety)

DATAS II

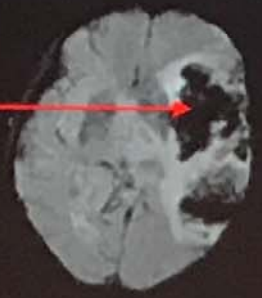
Symptomatic HT:

1. >30% of the infarcted area on DWI (PH2)
2. ≥4 point increase NIHSS
3. <5 weeks of randomization

On Treatment	Dabigatran (151)	ASA (150)	Relative Risk (95% CI)
Symptomatic Hemorrhagic Transformation	0	0	N/A
Parenchymal Hemorrhage	0	0	N/A

PH2

(SWI MRI)



Dabigatran did not increase the rate of symptomatic Hemorrhagic Transformation relative to ASA.

University of Alberta

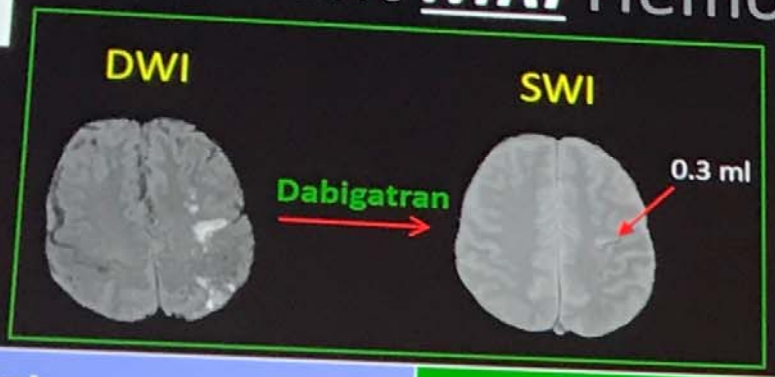
Population Health Research

Health Through Knowledge

PHR

DATAS II

Incident ***MRI*** Hemorrhagic Infarction Type 1



On Treatment	Dabigatran (141)	ASA (142)	Relative Risk (95% CI)
Hemorrhagic Infarction (%)	11 (7.8%)	5 (3.5%)	2.22 (0.79, 6.21)
Hemorrhage Volume (ml ± SD)	0.22 ± 0.11	0.34 ± 0.28	0.12 (-0.08, 0.32)

UNIVERSITY OF ALBERTA

Population Health Research
Health Through Kn
PHR

Anticoagulation for Stroke Prevention 2018

- Anticoagulation for AF √
- No anticoagulation for ESUS
  - Atrial cardiopathy a new target? Enroll in ARCADIA!
- Low dose anticoag + ASA for CAD and PAD including asymptomatic carotid disease but not stroke
- Evolving landscape
  - Acute therapy, hospitalized patients, large vessel disease, factor XI inhibitors, …