Pharmacologic Agents to Prevent Stroke in Non-Valvular Atrial Fibrillation and PFO

Gregg W. Stone, MD

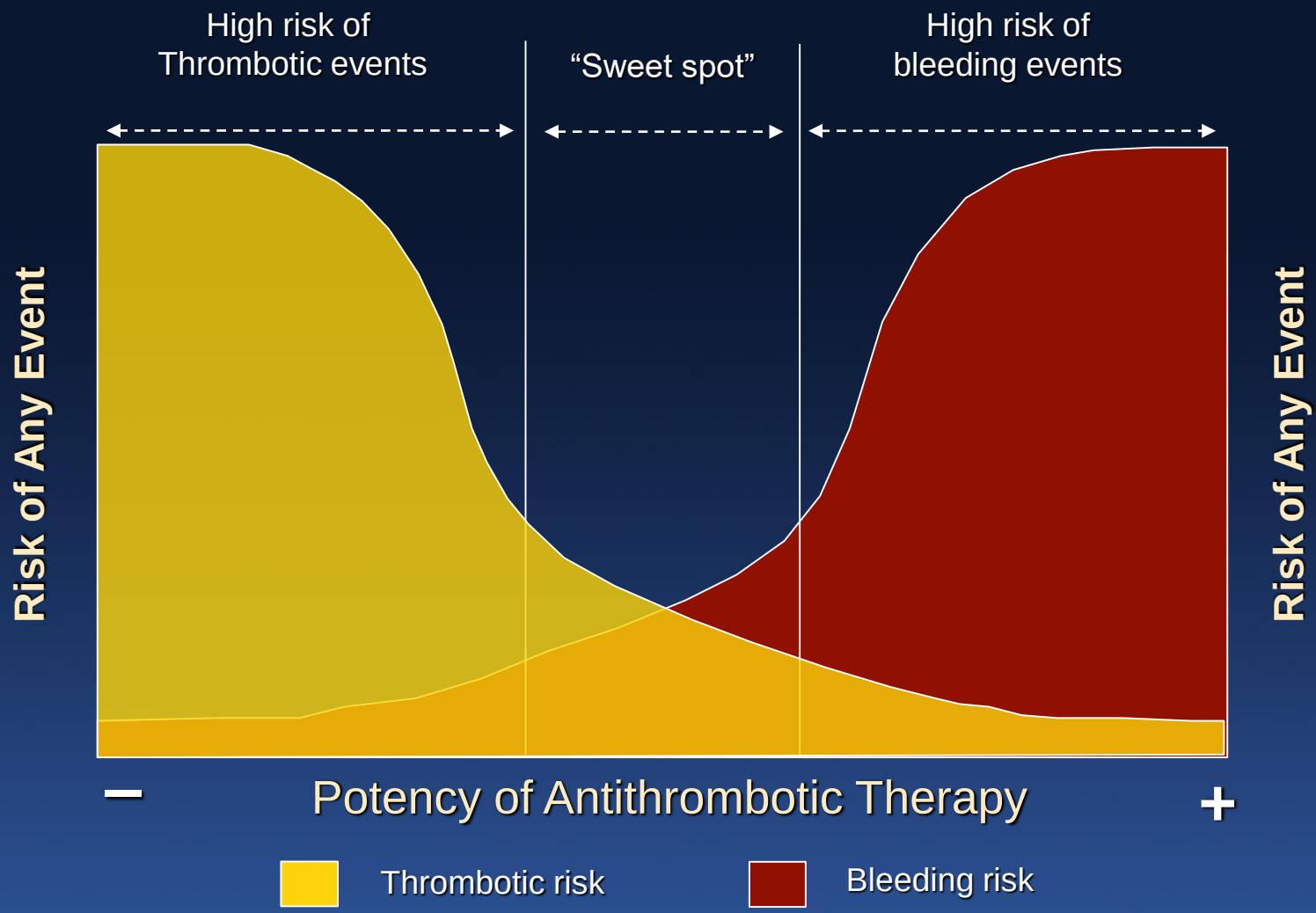
Columbia University Medical Center

The Cardiovascular Research Foundation

Disclosures

- None

Anticoagulation: Balancing Risks



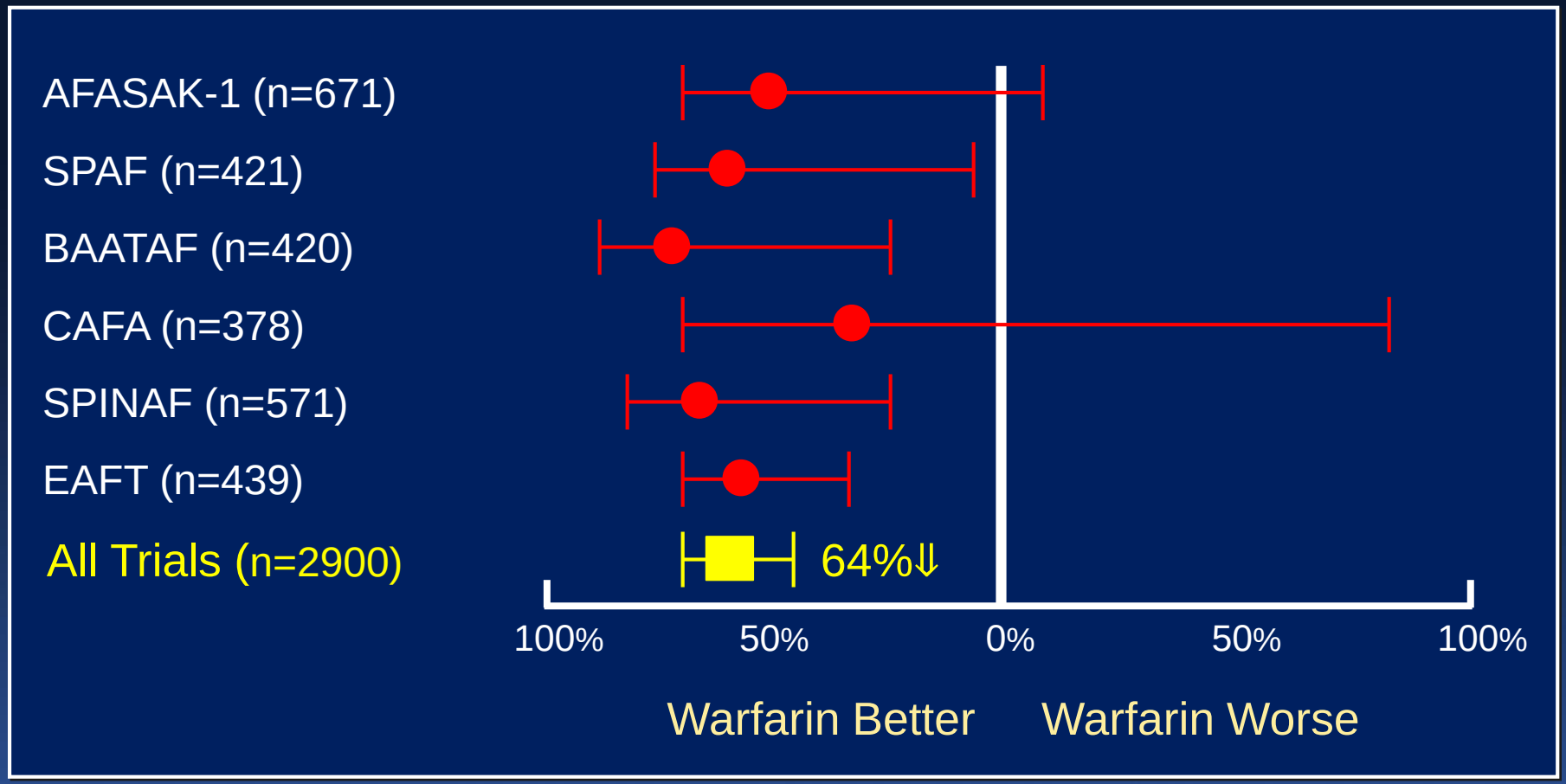
Adapted from: Ferreiro JL et al. Thromb Haemost. 2010;103:1-8

Non-valvular atrial fibrillation

Warfarin vs. Antiplatelet Rx

Stroke Prevention in NVAF

6 Randomized Trials of Warfarin vs. Placebo



Meta-analysis of antiplatelet agents and warfarin in NVAF: Stroke

29 RCTs with 28,044 pts, including:

Warfarin vs placebo or no treatment: 6 RCTs, 2,900 pts
Antiplatelet agents vs placebo or no treatment : 8 RCTs, 4,876 pts
Warfarin vs antiplatelet agents: 12 RCTs, 12,963 pts

Comparison	All-cause stroke			
A vs B	A) rate/yr	B) rate/yr	RRR (95%CI)	Absolute ↓/yr
Warfarin vs. placebo or no treatment	2.2%	6.0%	64% (49 to 74)	1° prev: 2.7 2° prev: 8.4
Aspirin vs. placebo	6.9%	8.8%	22% (2 to 39)	1° prev: 1.9 2° prev: 2.5
Aspirin vs. no treatment	5.2%	6.3%	19% (-1 to 35)	1° prev: 0.8 2° prev: 2.5
Warfarin vs. antiplatelet agents	2.1%	3.5%	39% (22 to 52)	1° prev: 0.9 2° prev: -

Hart RG et al. Ann Intern Med. 2007;146:857-867

Meta-analysis of antiplatelet agents and warfarin in NVAF: Mortality

29 RCTs with 28,044 pts, including:

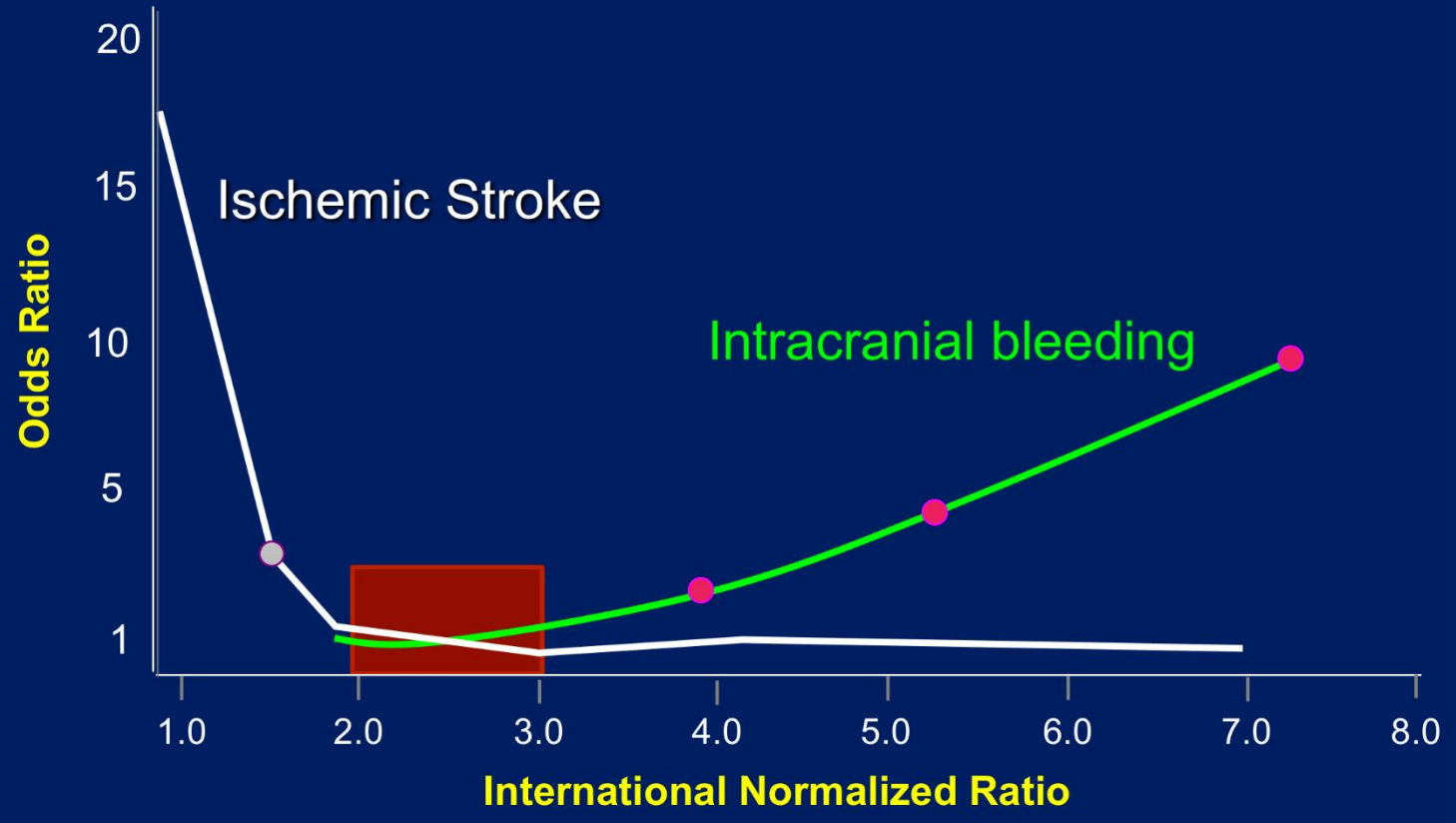
Warfarin vs placebo or no treatment: 6 RCTs, 2,900 pts
Antiplatelet agents vs placebo or no treatment : 8 RCTs, 4,876 pts
Warfarin vs antiplatelet agents: 12 RCTs, 12,963 pts

Comparison	Mortality			
A vs B	A) # deaths	B) # deaths	RRR (95%CI)	Absolute ↓/yr
Warfarin vs. placebo or no treatment (6 trials, 2900 pts)	110	143	26% (3 to 43)	1.6%
Aspirin vs. placebo (5 trials, 3762 pts)	184	204	14% (-7 to 31)	0.5%
Warfarin vs. aspirin (8 trials, 3647 pts)	117	128	9% (-19 to 30)	0.5%

Hart RG et al. Ann Intern Med. 2007;146:857-867

Limitations of Warfarin

1. Lowest risk of stroke and bleeding is achieved by maximizing the time in the optimum therapeutic range (TTR), with an INR of 2.0 – 3.0



Fang MC et al. Ann Intern Med 2004;141:745
Hylek EM et al. N Engl J Med 1996;335:540

Limitations of Warfarin

1. Lowest risk of stroke and bleeding is achieved by maximizing the time in the optimum therapeutic range (TTR), with an INR of 2.0 – 3.0
   - There are large variations in TTR between individuals, sites, and countries, which affects patient outcomes
2. Genetic variability in metabolism (VKORC1 and CYP2C9)
3. Multiple interactions with foods and drugs

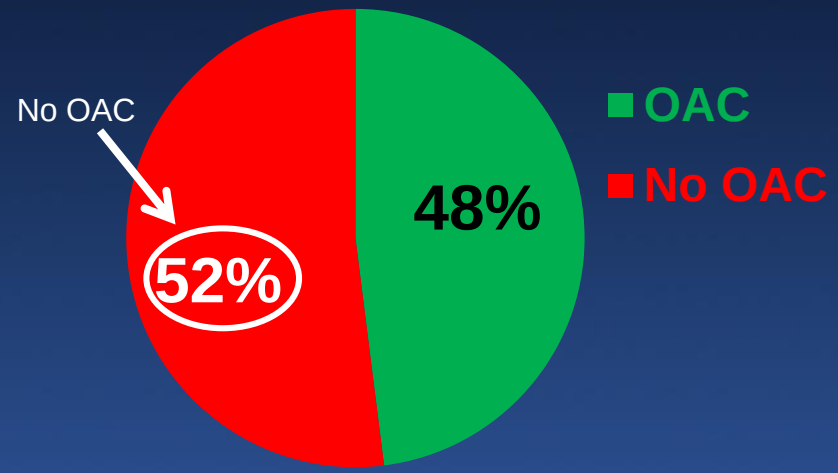
   → Requires regular lab-guided dose adjustments
4. Delayed onset and offset
5. Rates of bleeding and discontinuation are high

"Shocking Level" of OAC Undertreatment in AF Patients at High Risk for Stroke

US PINNACLE Registry (N=429,417 outpts with AF*)

*Treated by cardiovascular specialists

Most AF patients at high risk of stroke do not receive OAC therapy!



"HCPs may be more reluctant to prescribe anticoagulation in sicker patients due to concerns regarding bleeding risk."

- >2000 strokes/year could have been prevented if OAC therapy was used

Hsu JC et al. JAMA Cardiol. 2016 Mar 16. [Epub ahead of print]

Non-valvular atrial fibrillation
NOACs vs. Warfarin

New Agents for Atrial Fibrillation

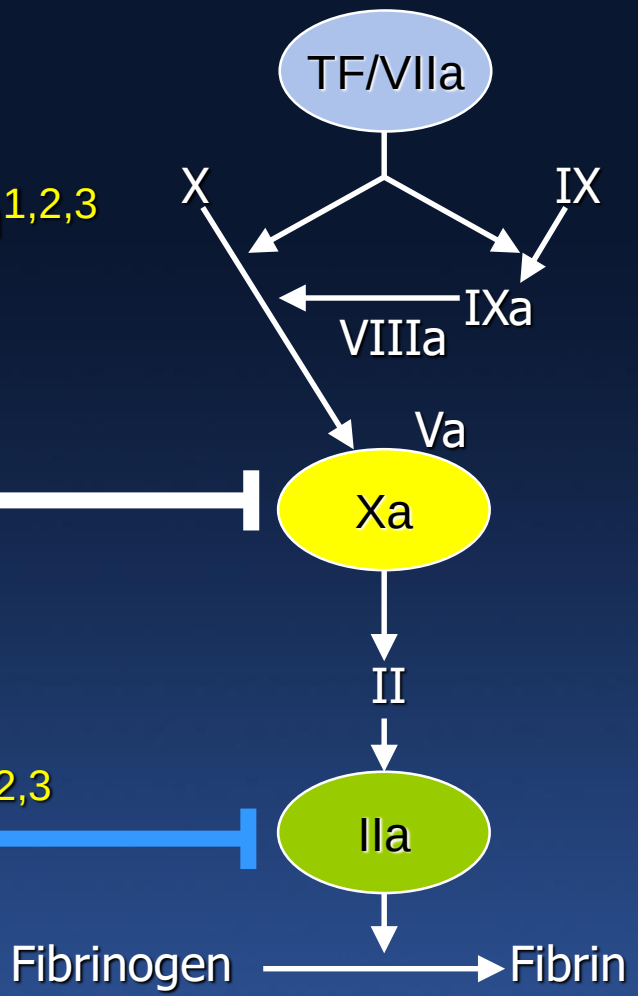
Oral direct inhibitors

Xa inhibitors

- Rivaroxaban[1,2,3]
- Apixaban[1]
- Edoxaban[1,2]
- Betrixaban[3]
- Darexaban
- Letaxaban

IIa inhibitors

- Dabigatran[1,2,3]
- AZD 0837



[1]Approved for stroke prevention in NVAF
[2]Approved for VTE treatment
[3]Approved for VTE prophylaxis

Characteristics of New Oral Anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
$T_{1/2}$	12-17 hrs	5-9 hrs (young) 11-13 hrs (old)	9-14 hrs	10-14 hrs
Regimen	BID	QD, BID	BID	QD
Peak to trough	2	12 (QD)	3-5	~3
Renal excretion	80%	35%	27%	50%
Potential for drug interactions	P-GP inhibitor	P-GP inhibitor and CYP3A4 substrate	P-GP inhibitor and CYP3A4 substrate	P-GP inhibitor; min CYP3A4 substrate

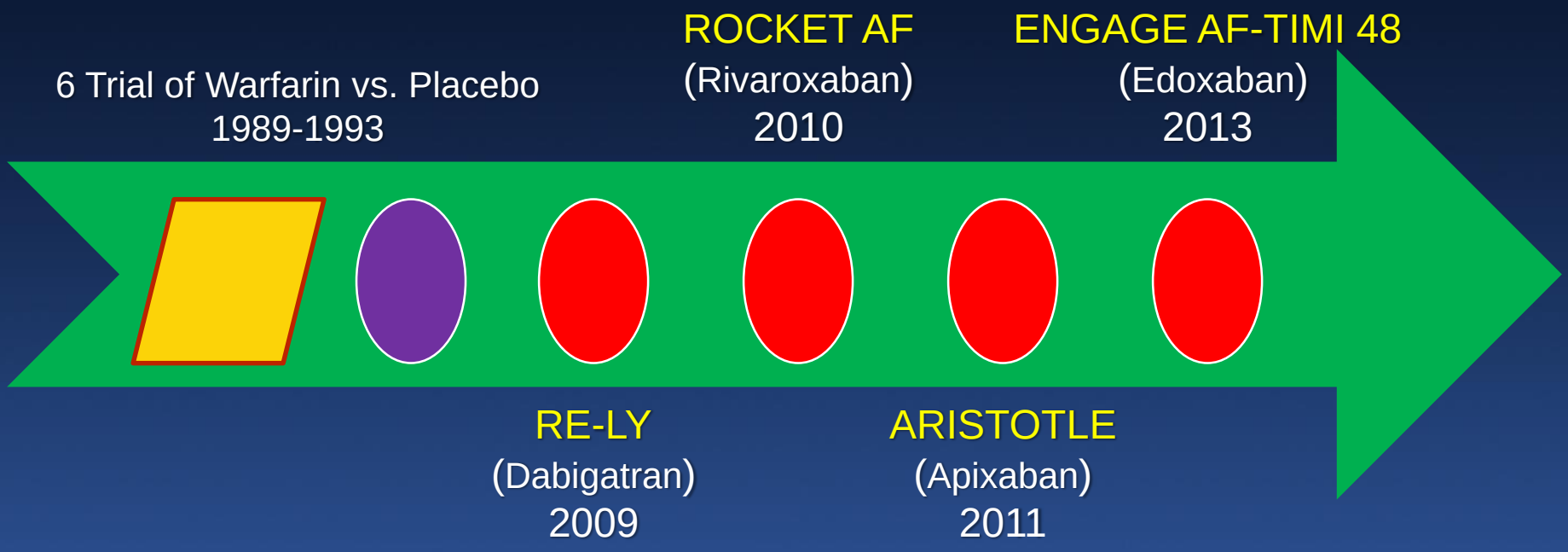
P-GP = P-glycoprotein (interactions with digoxin, verapamil, diltiazem, quinidine, amiodarone, dronedarone, atorvastatin, erythromycin, etc.)

Usman MH et al.: Curr Treat CV Med. 2008;10:388-397
Piccini JP et al. Curr Opin Cardiol. 2010;25(4):312-320

Pivotal Warfarin and NOAC Trials of Stroke Prevention in NVAF

Warfarin vs. Placebo
2,900 patients

NOACs vs. Warfarin
71,683 patients



New Oral Anticoagulants
Phase III AF Trials

	RE-LY (n=18,113)	ROCKET-AF (n=14,264)	ARISTOTLE (n=18,201)	ENGAGE AF-TIMI 48 (n=21,105)
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg)	150, 110	20 (15*)	5 (2.5*)	60, 30 (30*, 15*)
Frequency	BID	QD	BID	QD
N	18,113	14,266	18,206	21,105
Design	Open-label†	Double-blind	Double-blind	Double-blind
AF criteria	AF x 1 <6 mos	AF x 2 (≥1 in <30d)	AF or AFl x 2 <12 mos	AF x 1 <12 mos
VKA naive	50%	38%	43%	41%
Follow-up (yrs)	2.0	1.9	1.8	2.8

*In pts with ↓drug clearance; †dabi dose concealed, but no sham INR monitoring

New Oral Anticoagulants
Phase III AF Trials

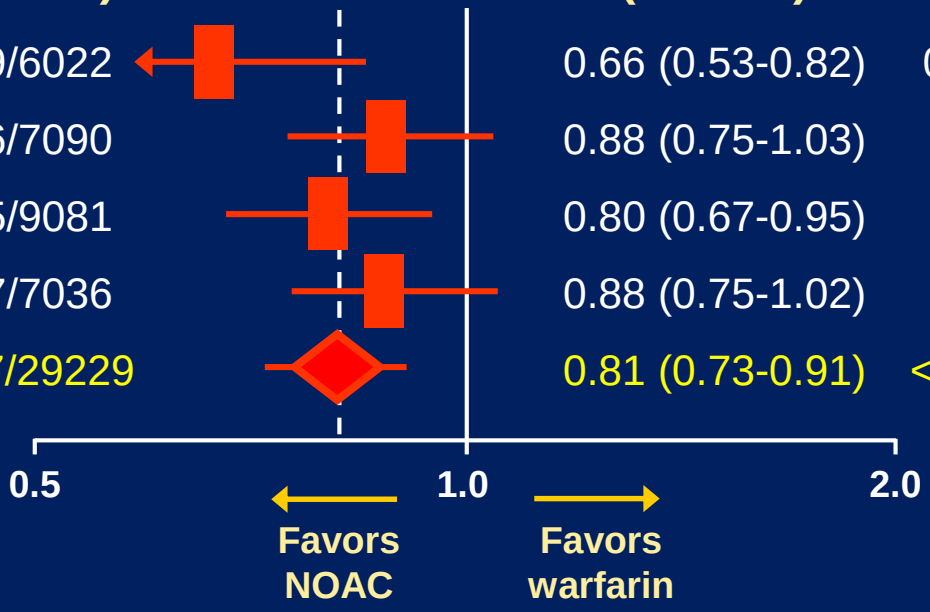
	Re-LY (dabigatran)	ROCKET-AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF (edoxaban)
Age, yrs	71.5 mean	73 median	70 median	72 median
Female	37%	40%	35%	38%
Hypertension	79%	91%	87%	94%
Diabetes	23%	40%	25%	36%
Heart failure	32%	62%	35%	57%
Prior stroke/TIA	20%	55%	20%	28%
$CHADS_2$ mean	2.2	3.5	2.1	2.8
- 0-1	32%	-	34%	<1%
- 2	35%	13%	36%	77%
- ≥3	33%	87%	30%	23%
TTR, median	66%	58%	66%	68%

NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Primary efficacy: Stroke or systemic embolization

	NOAC (events)	Warfarin (events)	RR (95% CI)	*P*
RE-LY	134/6076	199/6022	0.66 (0.53-0.82)	0.0001
ROCKET-AF†	269/7081	306/7090	0.88 (0.75-1.03)	0.12
ARISTOTLE‡	212/9120	265/9081	0.80 (0.67-0.95)	0.012
ENGAGE AF-TIMI 48	296/7035	337/7036	0.88 (0.75-1.02)	0.10
Combined (random)	911/29312 (3.1% vs. 3.8%)	1107/29229	0.81 (0.73-0.91)	<0.0001



Heterogeneity: I^2=47%; p=0.13

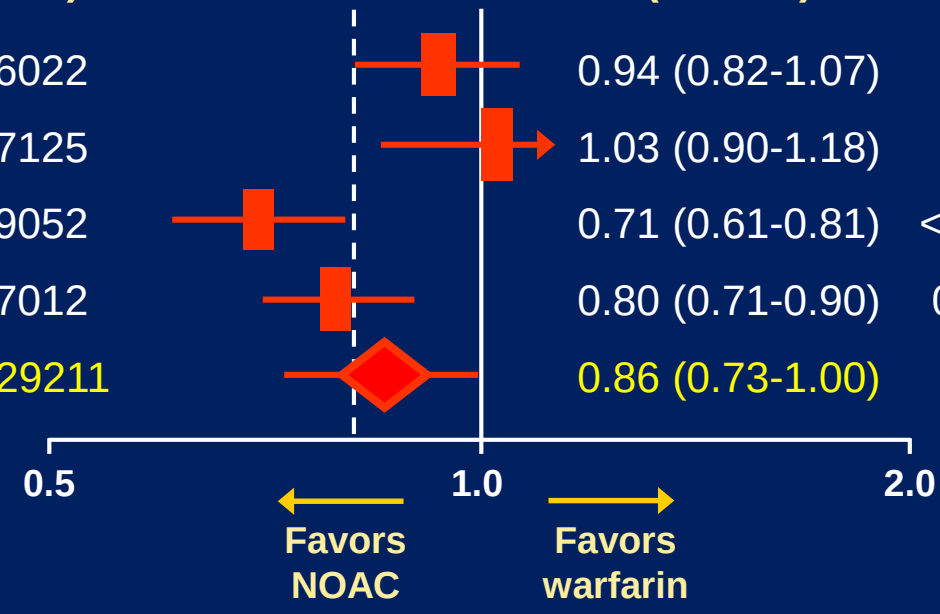
Dabigatran 150 mg bid. †Rivaroxaban 20 mg qd. ‡Apixaban 5 mg bid. §Edoxaban 60 mg qd.

NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Primary safety: Major bleeding

	NOAC (events)	Warfarin (events)	RR (95% CI)	*P*
RE-LY	375/6076	397/6022	0.94 (0.82-1.07)	0.34
ROCKET-AF†	395/7111	386/7125	1.03 (0.90-1.18)	0.72
ARISTOTLE‡	327/9088	462/9052	0.71 (0.61-0.81)	<0.0001
ENGAGE AF-TIMI 48	444/7012	557/7012	0.80 (0.71-0.90)	0.0002
Combined (random)	1541/29287 (5.3% vs. 6.2%)	1802/29211	0.86 (0.73-1.00)	0.06



Heterogeneity: I^2=83%; p=0.001.

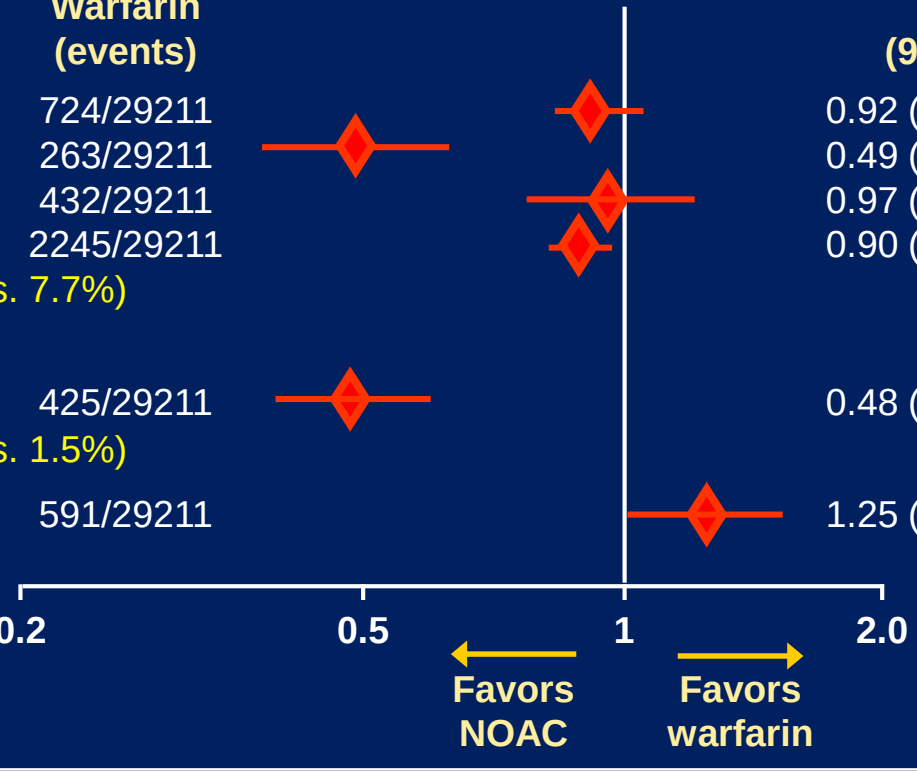
*Dabigatran 150 mg bid. †Rivaroxaban 20 mg qd. ‡Apixaban 5 mg bid. §Edoxaban 60 mg qd.

NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Secondary efficacy and safety outcomes

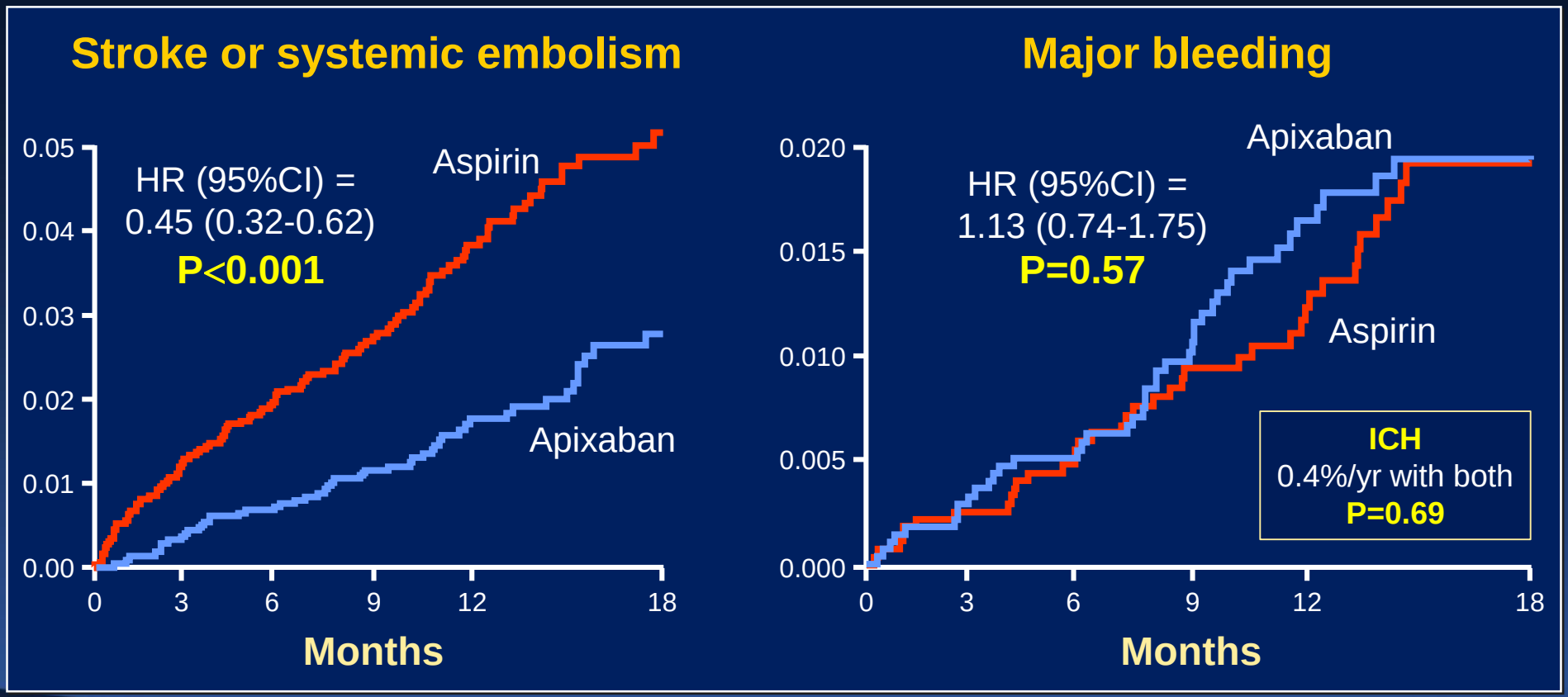
	NOAC (events)	Warfarin (events)	RR (95% CI)	*P*
Efficacy				
Ischemic stroke	665/29292	724/29211	0.92 (0.83-1.02)	0.10
Hemorrhagic stroke	130/29292	263/29211	0.49 (0.38-0.64)	<0.0001
MI	413/29292	432/29211	0.97 (0.78-1.20)	0.77
All-cause mortality	2022/29292 (6.9% vs. 7.7%)	2245/29211	0.90 (0.85-0.95)	0.0003
Safety				
Intracranial hemorrhage	204/29287 (0.7% vs. 1.5%)	425/29211	0.48 (0.39-0.59)	<0.0001
Gastrointestinal bleeding	751/29287	591/29211	1.25 (1.01-1.55)	0.04



Heterogeneity: ischemic stroke I^2=32%, p=0.22; hemorrhagic stroke I^2=34%, p=0.21; MI I^2=48%, p=0.13; all-cause mortality I^2=0%, p=0.81; ICH I^2=32%, p=0.22; GIB I^2=74%, p=0.009.

AVERROES: Apixaban vs Aspirin in 5,599 Pts with Nonvalvular AF and ≥1 Additional Risk Factor for Stroke Unsuitable for Warfarin by Physician or Pt Preference

Apixaban dose was 5 mg bid in 94% of pts; 2.5 mg bid was used in pts with ≥2 of the following criteria: age ≥80 yrs, weight ≤60 kg, or s.cr. ≥1.5 mg/dL



Current (2014) ACC/AHA/HRS Guidelines for Anticoagulation

Oral anticoagulants are recommended with in pts with prior stroke, TIA, or CHA2DS2-VASc score ≥2. Options include:

Warfarin
Dabigatran, rivaroxaban or apixiban

I	A
I	B

Direct thrombin or factor Xa inhibitor is recommended if unable to maintain therapeutic INR

I	C

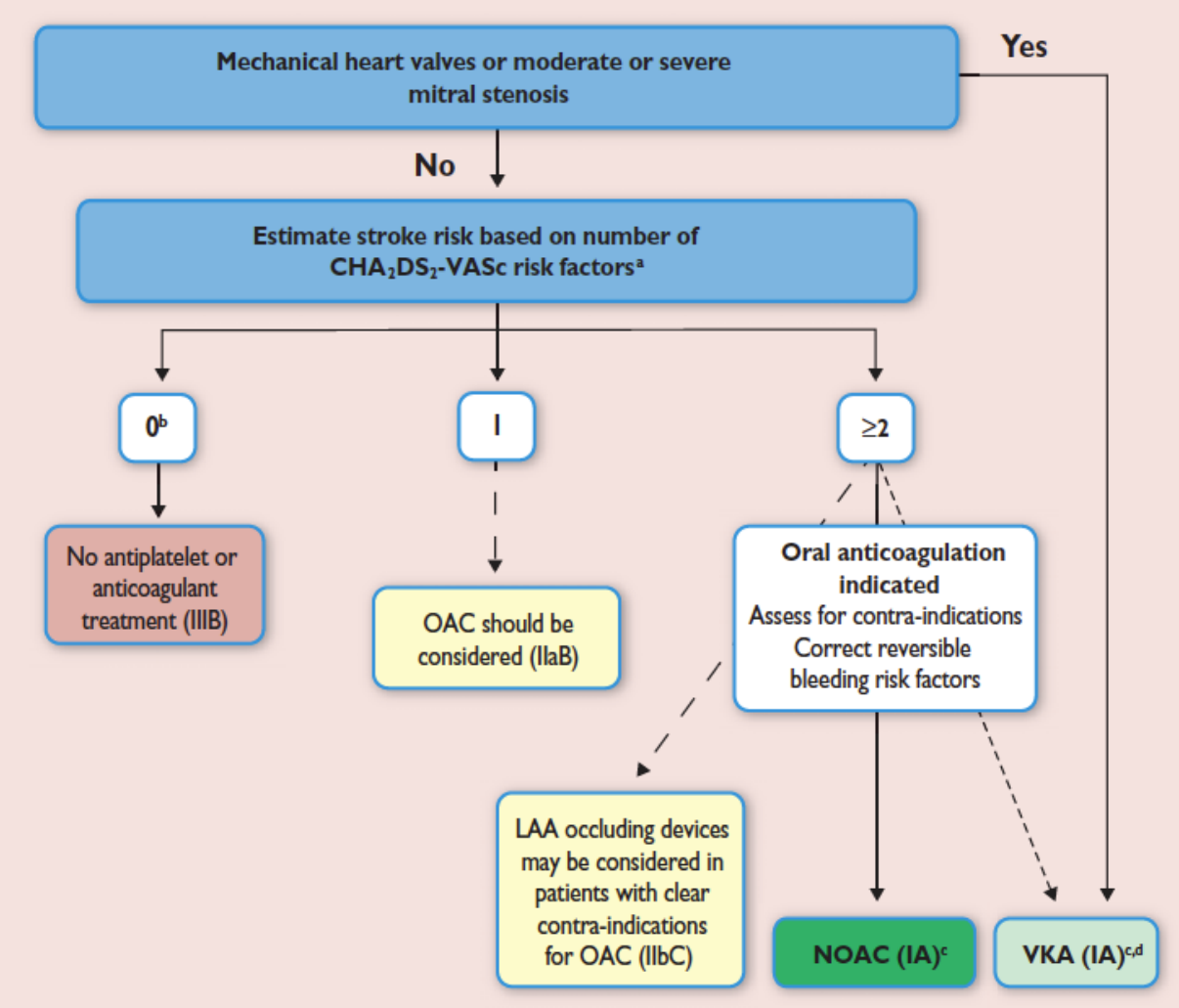
Warfarin is recommended for mechanical heart valves, with target INR intensity based on type and location of prosthesis

I	B

Dabigatran should not be used with a mechanical heart valve

III: Harm	B

Current (2016) ESC Guidelines for OAC



a. CHF, HTN, age ≥75 yrs (2 pts), age 65-74 yrs, DM, prior CVA/TIA/embolus (2 pts), vascular ds., female

b. Includes women without other stroke risk factors

c. IIaB for women with only 1 additional stroke risk factor

d. IB for pts with mechanical heart valves or mitral stenosis

When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.

I | A

Atrial fibrillation + PCI or ACS

Dual vs. Triple Therapy

The Clinical Challenge of Patients with NVAF Undergoing PCI (or w/ACS)

10-15% of pts undergoing PCI (or with ACS) have NVAF

OAC for stroke prevention

DAPT for ST prevention

→ Triple therapy ←

↓

Bleeding

Connolly S et al. Lancet. 2006;367:1903-12

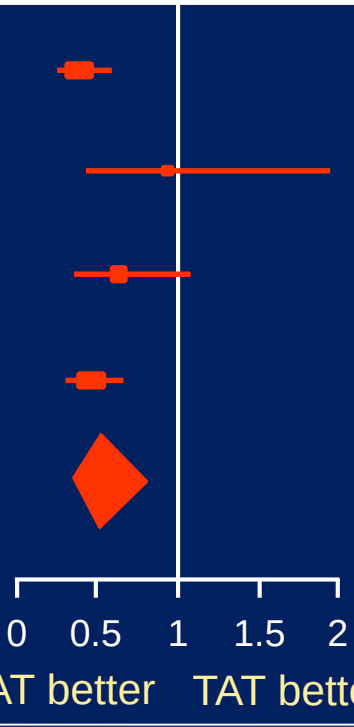
Meta-analysis of TAPT vs. DAPT after PCI in pts indicated for OAC

5,317 pts in 4 RCTs with mean FU 9-14 months

WOEST (W/A/C vs. W/C), ISAR-TRIPLE (W/A/Cx6mo vs. W/A/Cx6wk),
PIONEER AF-PCI (W/A/C vs. R 15/C), RE-DUAL PCI (W/A/C vs. Dabi 110 or 150/C)

TIMI major/minor bleeding

Study	Hazard Ratio (95% CrI)	DAT Arm	TAT Arm
WOEST	0.40 (0.27, 0.59)	39/279	89/284
ISAR TRIPLE (landmark analysis)	0.95 (0.46, 1.97)	14/307	15/307
PIONEER-AF-PCI	0.64 (0.38, 1.09)	21/696	33/697
RE-DUAL PCI (total)	0.47 (0.33, 0.67)	56/1744	69/981
Overall	0.53 (0.36, 0.85)	130/3026	206/2269
I^2=42.9%, P_{het}=0.16		4.3% vs. 9.0%	



Meta-analysis of TAPT vs. DAPT after PCI in pts indicated for OAC

5,317 pts in 4 RCTs with mean FU 9-14 months

WOEST (W/A/C vs. W/C), ISAR-TRIPLE (W/A/Cx6mo vs. W/A/Cx6wk),
PIONEER AF-PCI (W/A/C vs. R 15/C), RE-DUAL PCI (W/A/C vs. Dabi 110 or 150/C)

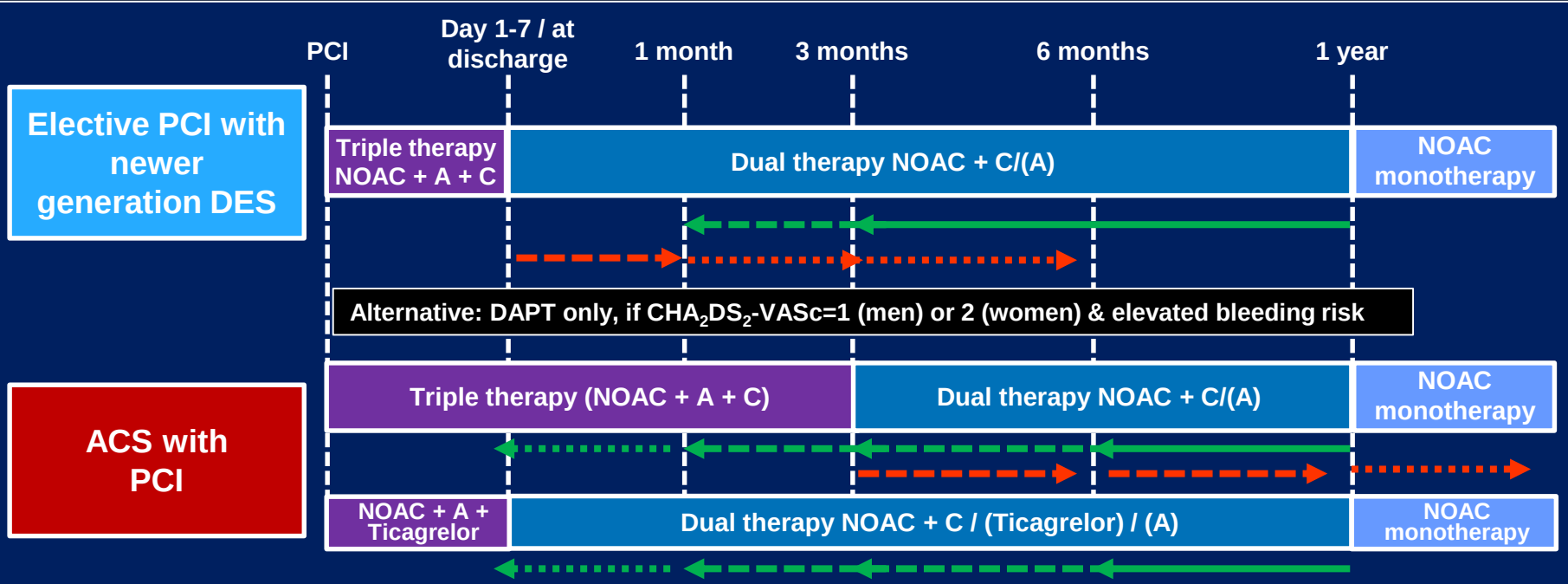
MACE (trial-defined)

Study	Hazard Ratio (95% CrI)	DAT Arm	TAT Arm
WOEST	0.60 (0.38, 0.94)	31/279	50/284
ISAR TRIPLE (landmark analysis)	0.40 (0.13, 1.24)	4/307	10/307
PIONEER-AF-PCI	1.08 (0.69, 1.69)	41/694	36/695
RE-DUAL PCI (total)	1.04 (0.84, 1.29)	239/1744	131/981
Overall	0.85 (0.48, 1.29)	315/3024	227/2267

I^2=52.4%, P_{het}=0.06

10.4% vs. 10.0%

Antiplatelet and OAC Considerations after PCI in SIHD and ACS



Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE <140 if ACS)

Factors to lengthen combination therapy

- First generation DES
- High atherothrombotic risk (per scores as above; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis, etc.) and low bleeding risk

Pharmacologic Therapy to Prevent Recurrent Cryptogenic Stroke with PFO

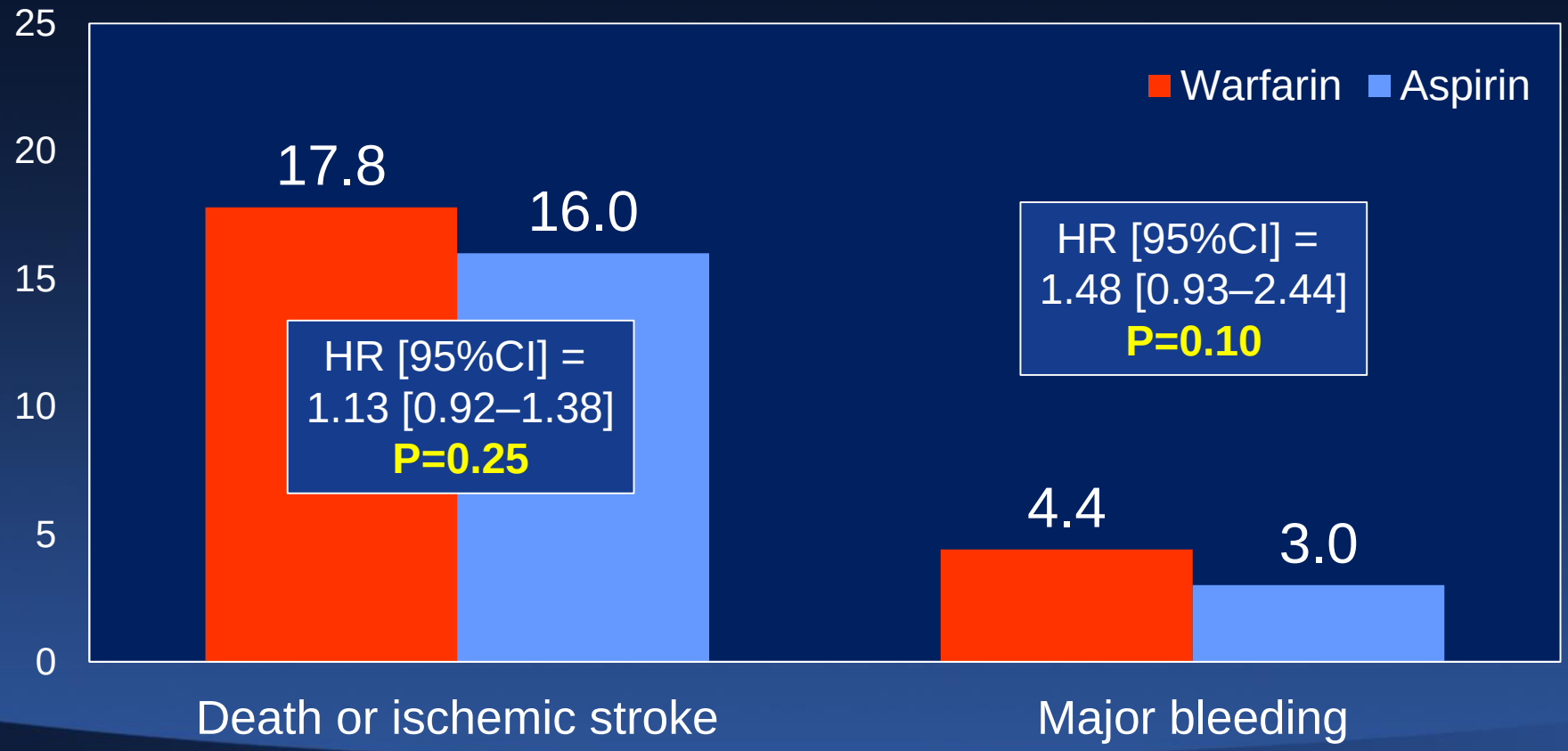
Chronic Oral Anticoagulation vs. Antiplatelet Therapy

OAC vs. APT for Recurrent Stroke

WARRS

Warfarin (mean INR 2.1) vs. ASA 325 mg qd
N=2206; Mean FU 2 years

Two-year event rates (%)



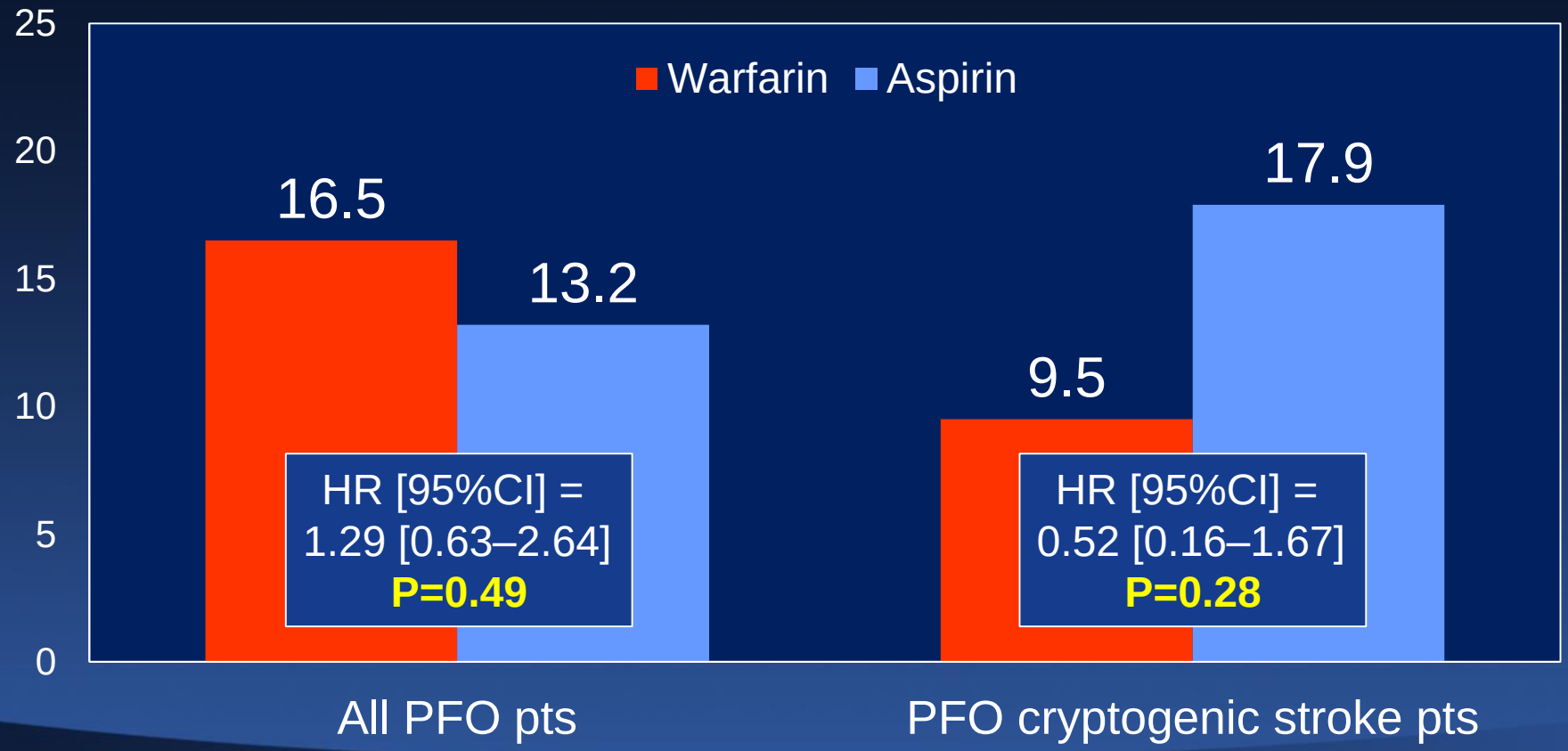
Mohr JP et al. NEJM 2001;345:1444-51

OAC vs. APT for Recurrent Stroke

PICSS (WARRS substudy)

Warfarin (mean INR 2.1) vs. ASA 325 mg qd; N=203/630 pts (33.8%) who underwent TEE had PFO; 98 pts had cryptogenic stroke

Two-year death or ischemic stroke (%)



OAC vs. APT Rx in cryptogenic stroke with PFO: TAcTiCS

Individual pt data meta-analysis of 12 studies

2,385 pts (804 warfarin and 1581 APT), 227 events (stroke/TIA/death)

Recurrent Stroke, TIA or Death

- Adjusted study estimate
- Unadjusted study estimate

Study name	Events/OAC	Events/APT	HR (95% CI)
Toronto	2/26	10/63	1.29 (0.22, 7.68)
			0.60 (0.13, 2.79)
Tufts	2/49	2/46	1.59 (0.21, 12.08)
			0.85 (0.12, 6.16)
PICSS	7/42	13/56	0.66 (0.24, 1.85)
			0.72 (0.29, 1.81)
Schuchlenz	7/47	24/66	0.32 (0.13, 0.80)
			0.46 (0.19, 1.09)
Sapienza	5/35	4/80	1.43 (0.32, 6.37)
			2.05 (0.58, 7.30)
FORI	4/24	7/93	1.69 (0.39, 7.28)
			2.74 (0.78, 9.95)
Bern Pub	16/79	17/67	0.76 (0.36, 1.60)
			0.80 (0.41, 1.58)
PC Trial	1/64	10/141	0.20 (0.03, 1.61)
			0.22 (0.03, 1.72)
CODICIA	4/82	15/212	0.42 (0.13, 1.30)
			0.58 (0.19, 1.73)
German	12/135	21/161	1.34 (0.63, 2.84)
			0.95 (0.46, 1.97)
CLOSURE	8/114	19/265	0.77 (0.28, 2.11)
			0.98 (0.43, 2.23)
RESPECT	3/106	14/332	0.67 (0.17, 2.68)
			0.60 (0.17, 2.13)
Meta-analysis estimates			**0.76 (0.52, 1.12)**
			0.82 (0.59, 1.14)

8.8% vs. 9.9%

HR [95%CI] (log scale)

0.05 0.1 0.25 0.5 1.0 2.0 5.0 10.0

Favors OAC Favors APT

Kent DM et al *EHJ* 201536: 2381-9

Cardiovascular Research Foundation

OAC vs. APT Rx in cryptogenic stroke with PFO: TAcTiCS

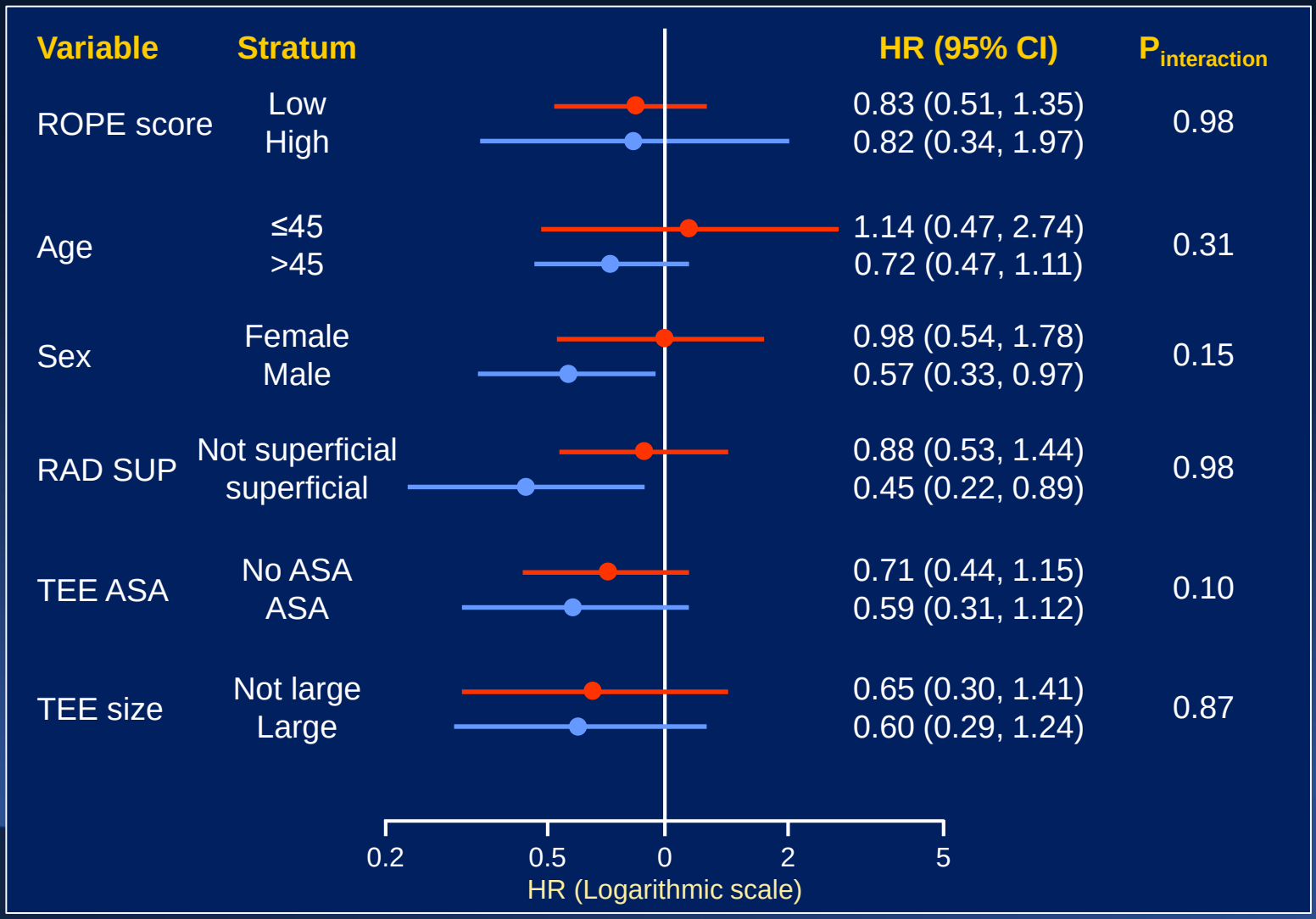
Individual pt data meta-analysis of 12 studies

2,385 pts (804 warfarin and 1581 APT), 227 events (stroke/TIA/death)

Subgroups

Recurrent Stroke, TIA or Death

- Adjusted study estimate
- Unadjusted study estimate



Kent DM et al *EHJ* 201536: 2381-9

Cardiovascular Research Foundation

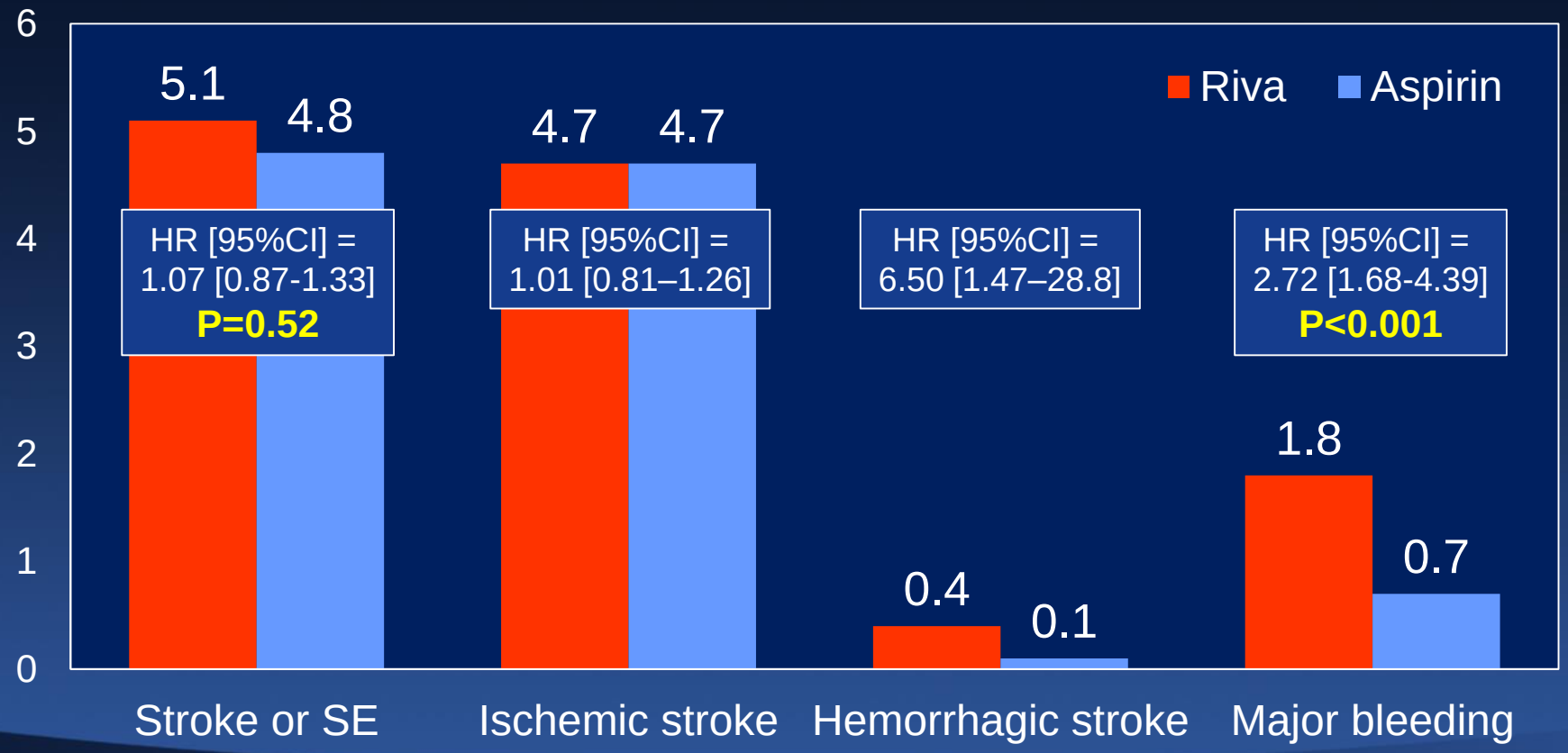
OAC vs. APT for Cryptogenic Stroke

NAVIGATE ESUS

Rivaroxaban 15 mg qd vs. ASA 100 mg qd

N=7213; 534 (7.4%) with documented PFO; Median FU 11 mo

Annualized event rate (%)



Cardiovascular Research Foundation

Hart RG et al. NEJM 2018:on-line

Columbia University Medical Center
NewYork-Presbyterian

Conclusions
Warfarin and NOACs in NVAF and PFO

- Warfarin and NOACs are markedly effective at reducing ischemic stroke in NVAF, but increase major bleeding (including intracranial hemorrhage [ICH])
- Compared to warfarin, NOACs reduce major bleeding (especially ICH) and possibly mortality, do not require monitoring and have fewer drug/food interactions, but are more expensive
  - NOACs have emerged as the preferred first-line therapy for many pts with NVAF
- Pts with NVAF and PCI/ACS are a high-risk cohort
  - Standard of care (OAC + APT) in these pts is evolving
- There is no clear pharmacologic gold-standard for PFO