The Emerging Role of DOACs in *Stable* CAD and PAD

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Disclosures

Grant Support/Drugs

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Grant Support/Devices

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- Medtronic - Boston Scientific
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- V-Wave Medical - Svelte

Consulting/Advisory Boards

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- Janssen Pharmaceuticals - Heartflow

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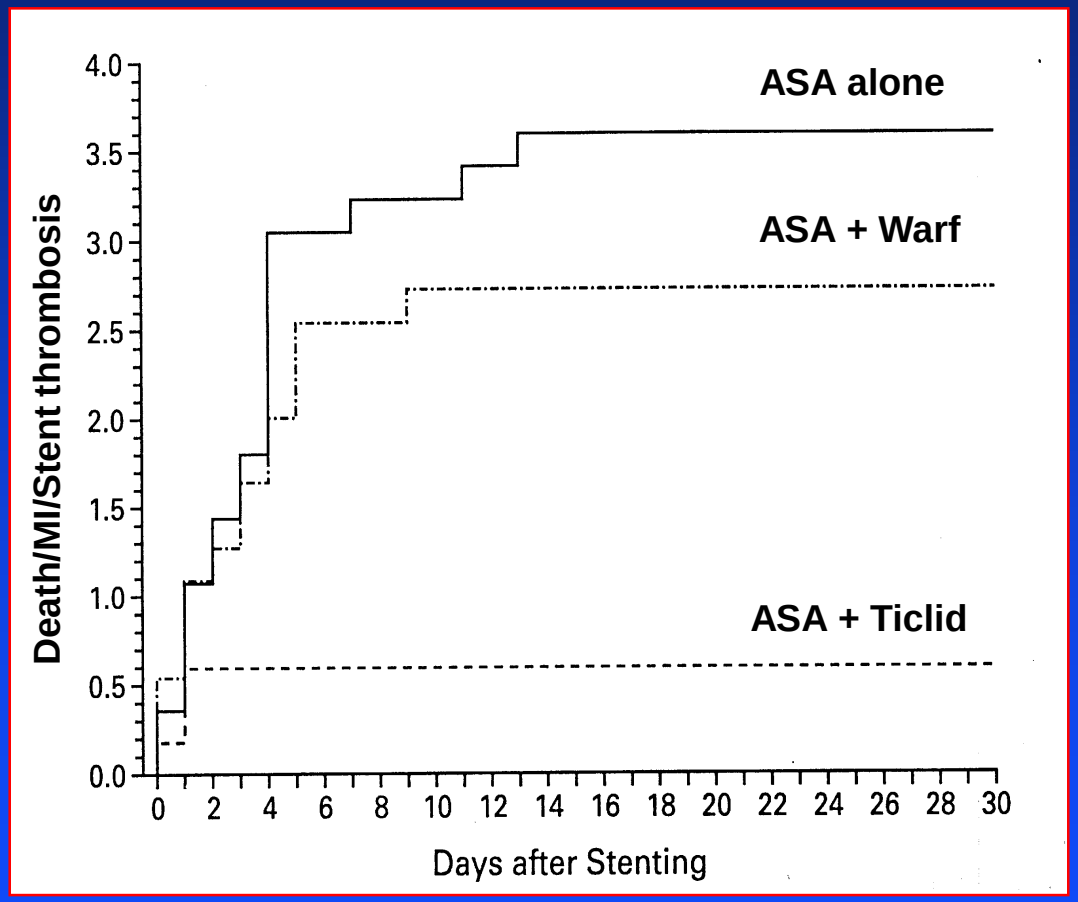
Rationale for Thrombin Inhibition

- Despite aggressive secondary prevention, patients with atherosclerotic cardiovascular disease continue to experience recurrent events at a rate of 5-10%/year
- Previous studies have demonstrated that vitamin K antagonists, either alone or in combination with ASA can lead to modest further reductions in coronary event rates but with unacceptable increases in bleeding including ICH and fatal bleeding

Coronary Stenting: Improved Outcomes with Improved Antiplatelet Therapy



STARS Trial

- 1650 pts with "optimal" stent result
- Significant reduction in stent thrombosis with ASA + Ticlid (p=0.001)
- Possible benefit with warfarin as well

Leon MB et al. NEJM 1998;339:1665-71

Rationale for Thrombin Inhibition (2)

- Recently, several direct acting oral anticoagulants have been introduced and have shown generally similar efficacy to warfarin for pts with thrombotic conditions (AF, DVT/PE) with an improved safety profile
- In the ATLAS/TIMI-51 trial, rivaroxaban (a direct factor Xa inhibitor) was shown to reduce major adverse cardiovascular events including CV mortality in patients with stabilized ACS
- The COMPASS trial was designed to determine whether rivaroxaban, either alone or in combination with low dose ASA, can provide greater protection from recurrent CV events in patients with stable CAD or PAD

COMPASS Trial Design

Stable CAD or PAD (n=27,395)

Study Flow

- Study planned to accrue 2200 primary outcome events
- At first interim look (50% of total events), DSMB recommended early termination of trial for overwhelming efficacy in RIVA + ASA arm
- Median treatment duration 23 months

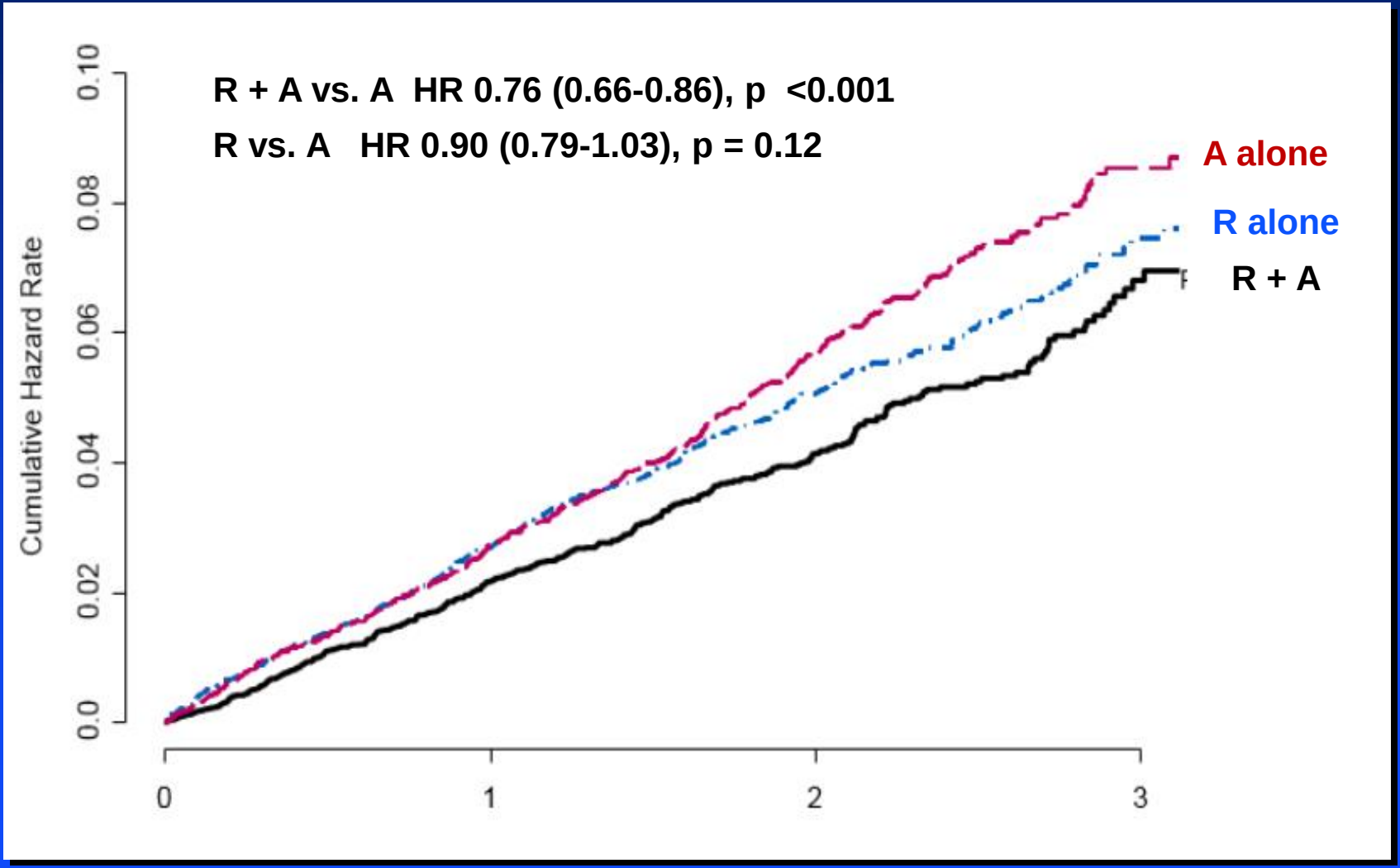
Safety Endpoint: ISTH major bleeding (similar to BARC 3)

Patient Population

	RIVA + ASA	RIVA	ASA
Age	68 ± 8 yrs	68 ± 8 yrs	68 ± 8 yrs
Male sex	78%	78%	78%
H/O CAD	91%	91%	91%
H/O PAD	27%	27%	27%
Diabetes	38%	38%	38%
Smoking	21%	21%	22%
Prior MI	62%	62%	63%
Prior Stroke	4%	4%	4%

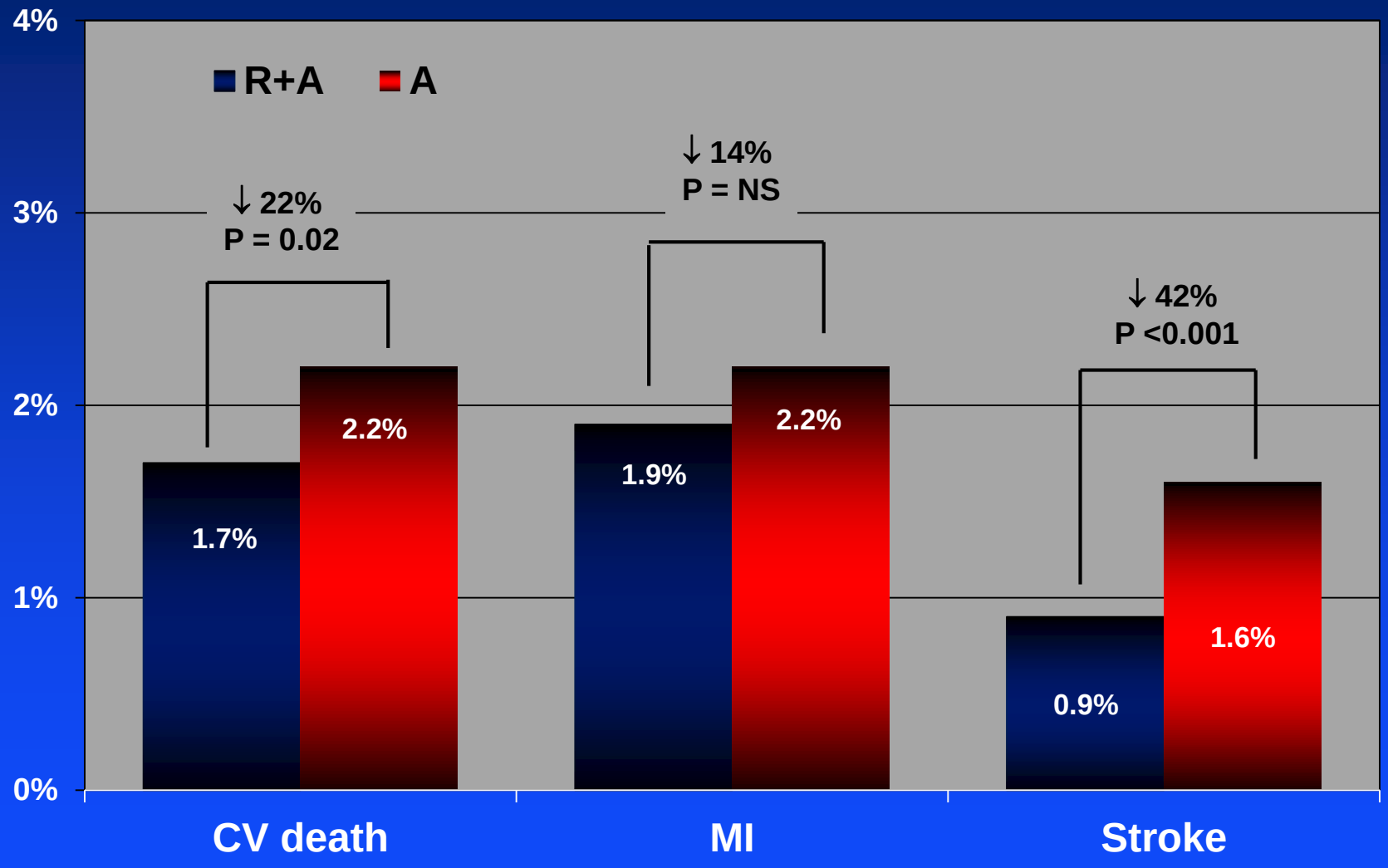
P = NS for all comparisons

Primary Endpoint: CV Death, MI, Stroke



Eikelboom JW, et al. NEJM 2017; 377: 1319-30

Endpoint Components



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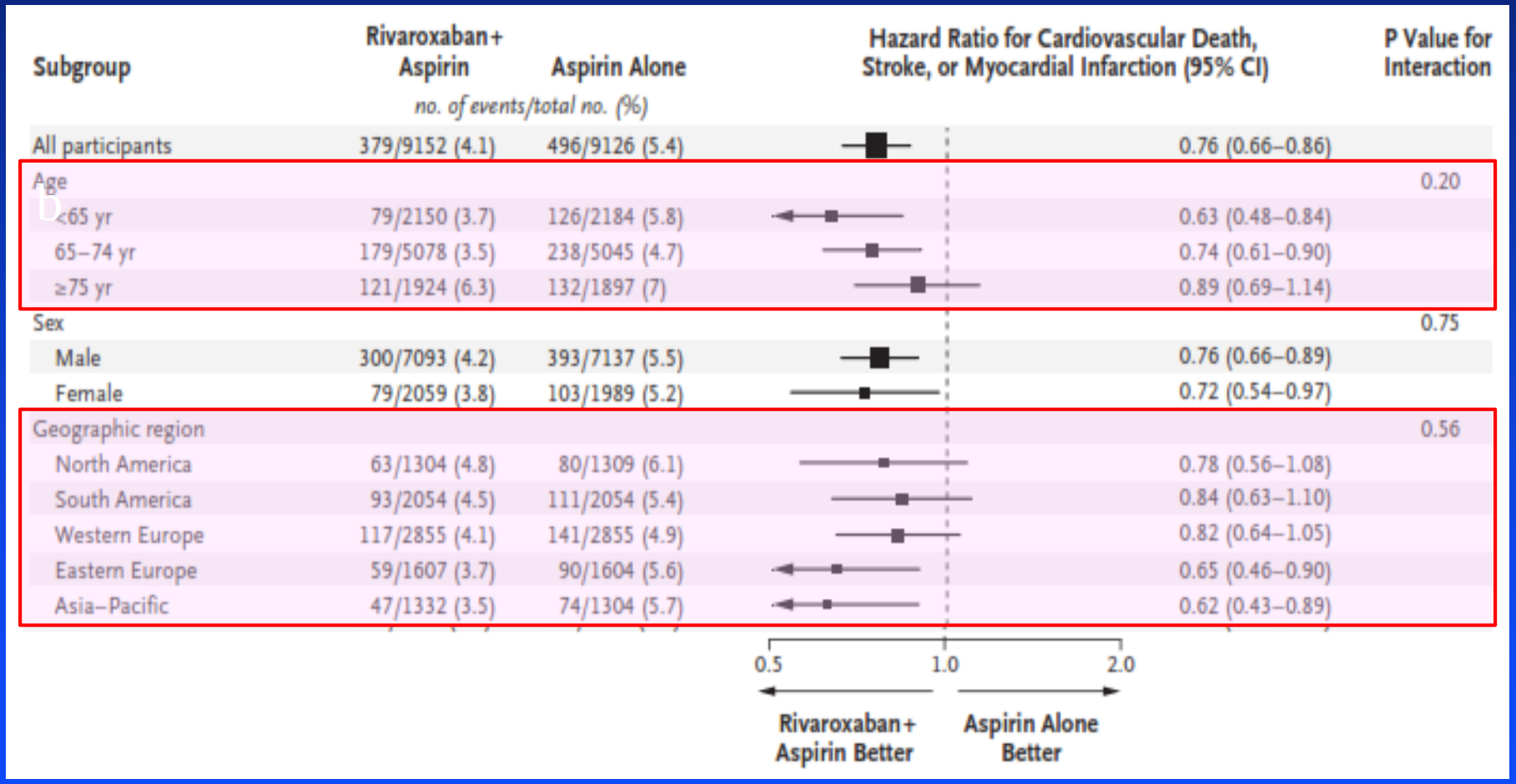
Subgroup Analyses



Subgroup	Rivaroxaban + Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All participants	379/9152 (4.1)	496/9126 (5.4)	0.76 (0.66–0.86)	
Age				0.20
<65 yr	79/2150 (3.7)	126/2184 (5.8)	0.63 (0.48–0.84)	
65–74 yr	179/5078 (3.5)	238/5045 (4.7)	0.74 (0.61–0.90)	
≥75 yr	121/1924 (6.3)	132/1897 (7)	0.89 (0.69–1.14)	
Sex				0.75
Male	300/7093 (4.2)	393/7137 (5.5)	0.76 (0.66–0.89)	
Female	79/2059 (3.8)	103/1989 (5.2)	0.72 (0.54–0.97)	
Geographic region				0.56
North America	63/1304 (4.8)	80/1309 (6.1)	0.78 (0.56–1.08)	
South America	93/2054 (4.5)	111/2054 (5.4)	0.84 (0.63–1.10)	
Western Europe	117/2855 (4.1)	141/2855 (4.9)	0.82 (0.64–1.05)	
Eastern Europe	59/1607 (3.7)	90/1604 (5.6)	0.65 (0.46–0.90)	
Asia–Pacific	47/1332 (3.5)	74/1304 (5.7)	0.62 (0.43–0.89)	

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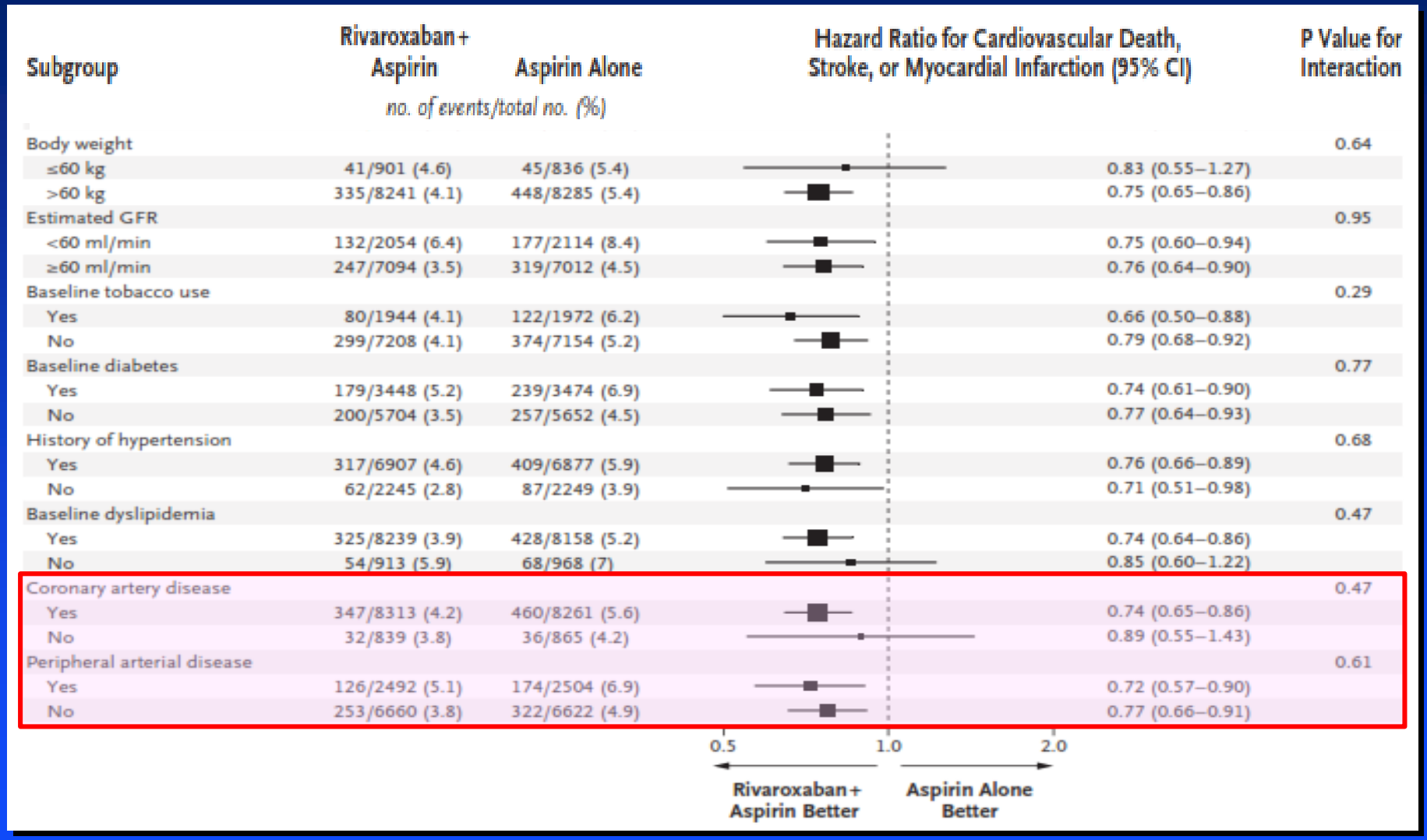
Subgroup Analyses (cont)



Subgroup	Rivaroxaban + Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Body weight				0.64
≤60 kg	41/901 (4.6)	45/836 (5.4)	0.83 (0.55–1.27)	
>60 kg	335/8241 (4.1)	448/8285 (5.4)	0.75 (0.65–0.86)	
Estimated GFR				0.95
<60 ml/min	132/2054 (6.4)	177/2114 (8.4)	0.75 (0.60–0.94)	
≥60 ml/min	247/7094 (3.5)	319/7012 (4.5)	0.76 (0.64–0.90)	
Baseline tobacco use				0.29
Yes	80/1944 (4.1)	122/1972 (6.2)	0.66 (0.50–0.88)	
No	299/7208 (4.1)	374/7154 (5.2)	0.79 (0.68–0.92)	
Baseline diabetes				0.77
Yes	179/3448 (5.2)	239/3474 (6.9)	0.74 (0.61–0.90)	
No	200/5704 (3.5)	257/5652 (4.5)	0.77 (0.64–0.93)	
History of hypertension				0.68
Yes	317/6907 (4.6)	409/6877 (5.9)	0.76 (0.66–0.89)	
No	62/2245 (2.8)	87/2249 (3.9)	0.71 (0.51–0.98)	
Baseline dyslipidemia				0.47
Yes	325/8239 (3.9)	428/8158 (5.2)	0.74 (0.64–0.86)	
No	54/913 (5.9)	68/968 (7)	0.85 (0.60–1.22)	
Coronary artery disease				0.47
Yes	347/8313 (4.2)	460/8261 (5.6)	0.74 (0.65–0.86)	
No	32/839 (3.8)	36/865 (4.2)	0.89 (0.55–1.43)	
Peripheral arterial disease				0.61
Yes	126/2492 (5.1)	174/2504 (6.9)	0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)	0.77 (0.66–0.91)	

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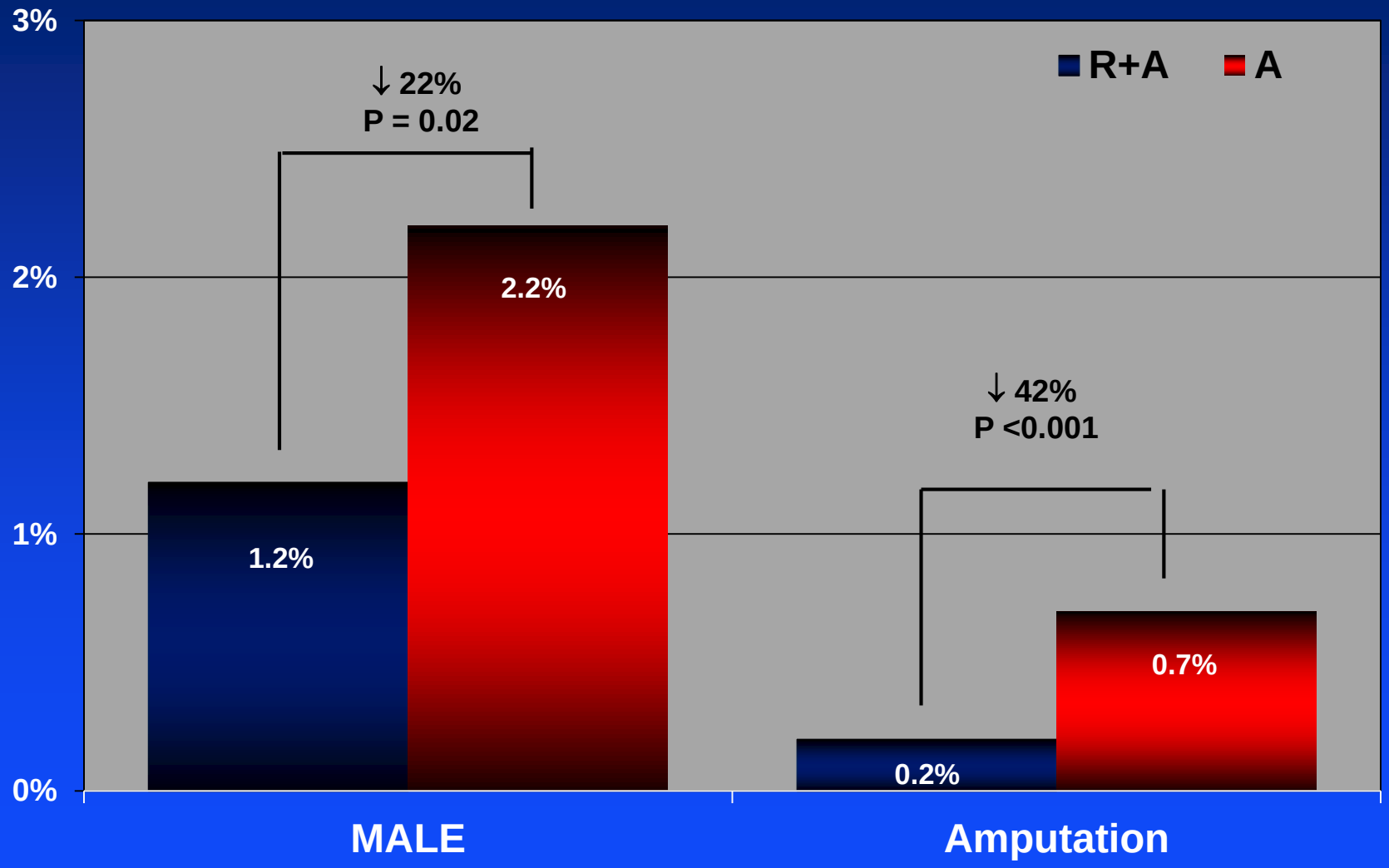
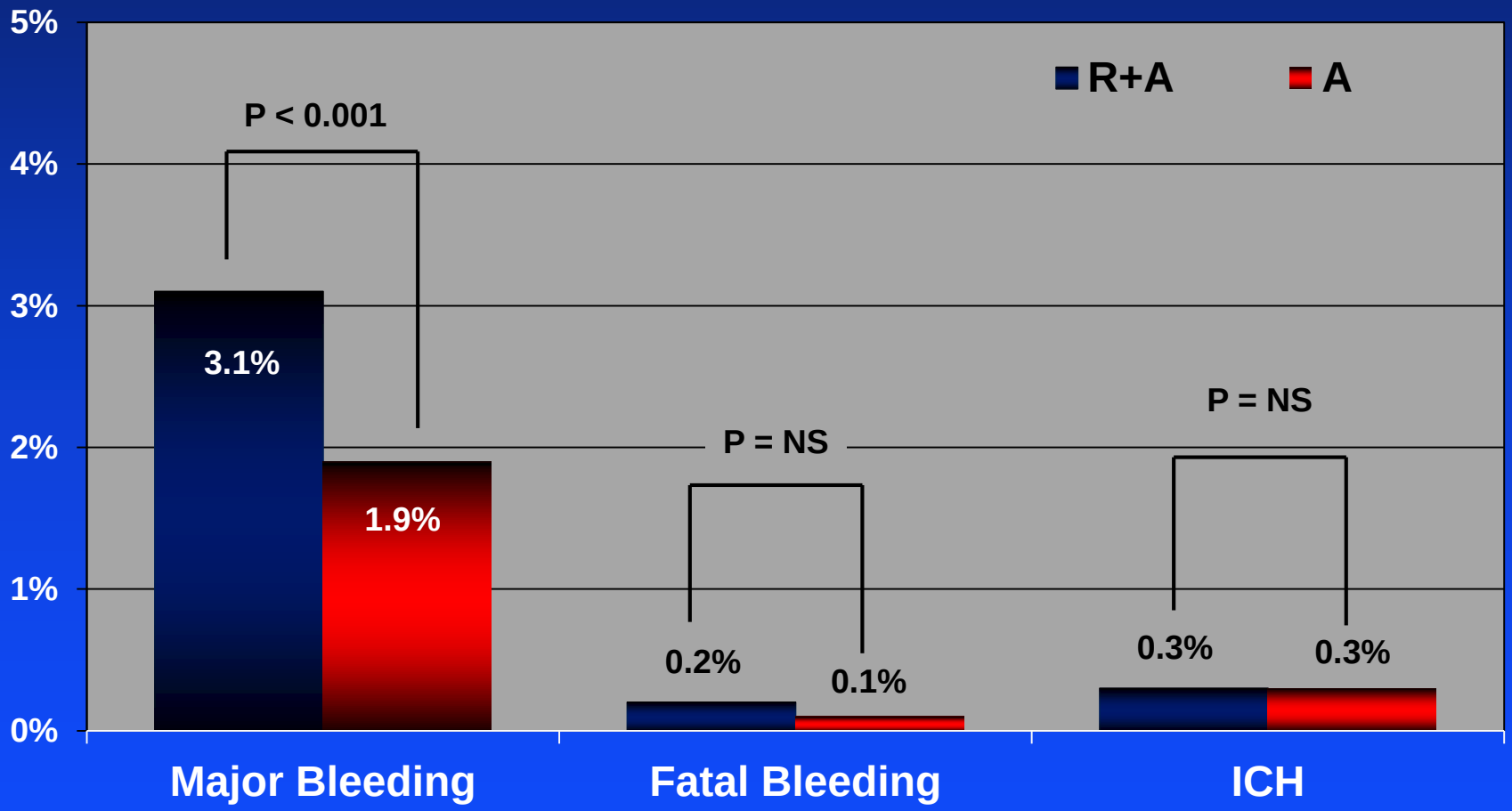
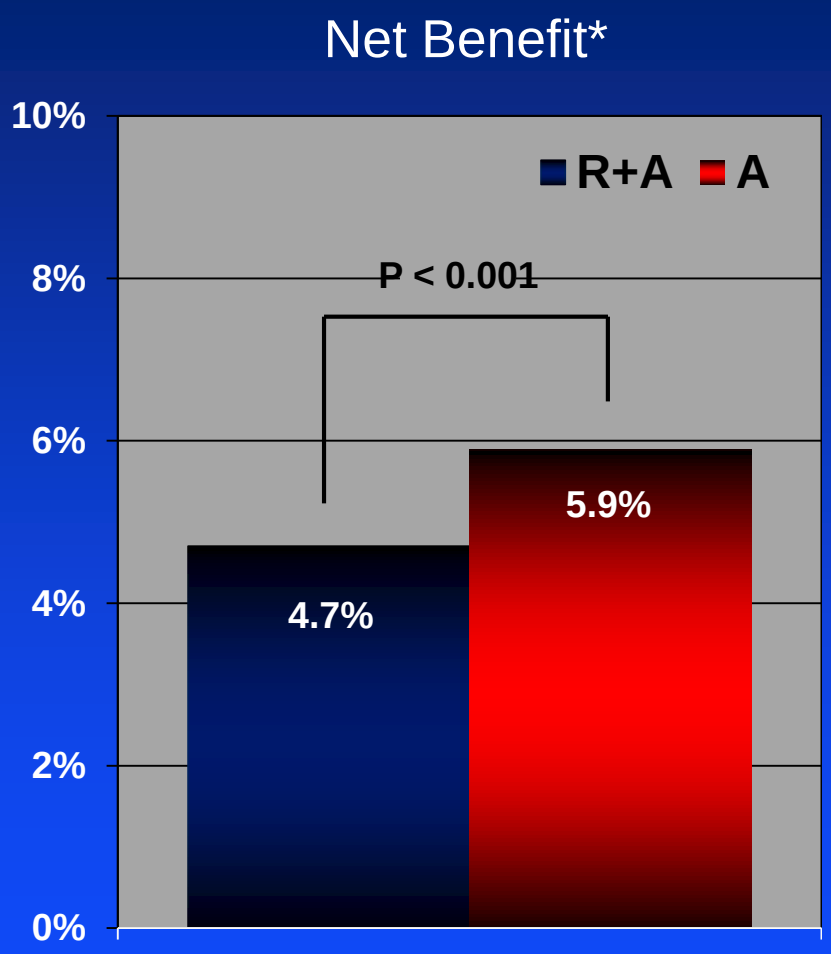
PAD Subset: Limb-Related Outcomes

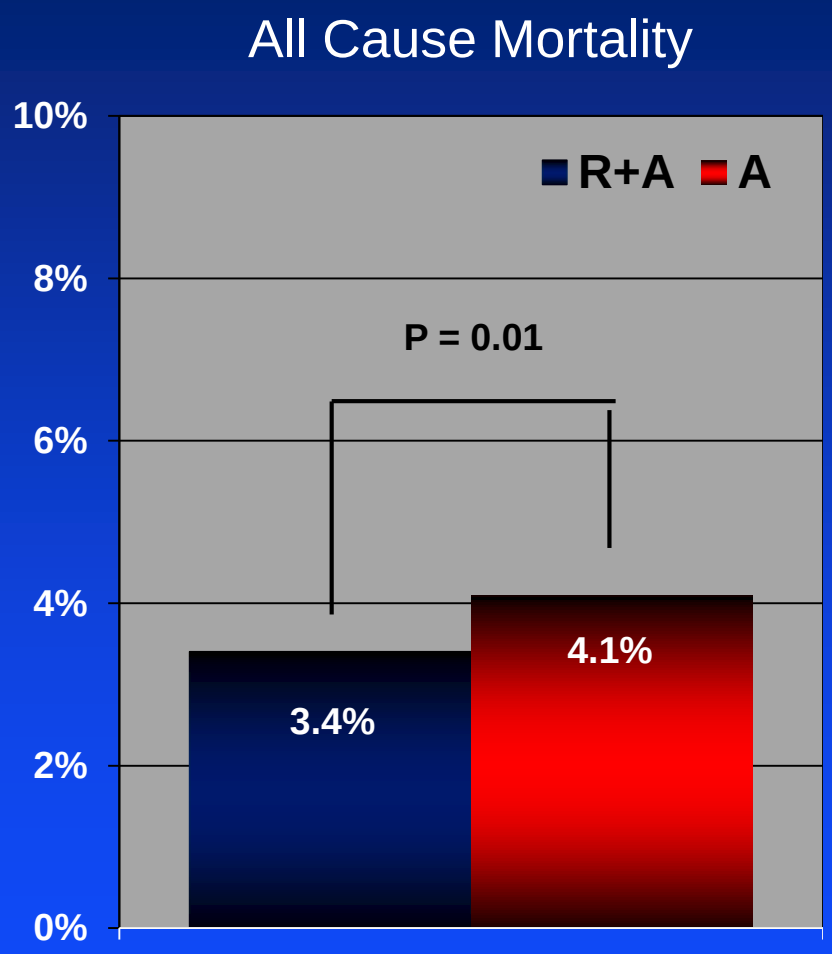


Safety Endpoints



Balance of Safety/Efficacy





Net Benefit Endpoint: Composite of CV death, MI, stroke, fatal bleeding, or bleeding into critical organ

DOAC vs. P2Y12 Inhibition

Trial	Therapy*	CVD, MI, or Stroke	Bleeding	All-Cause Mort.	Net Benefit
CHARISMA (est. CVD)	Clopidogrel	↓	↑	↔	↔

* All trials performed on background low-dose ASA

DOAC vs. P2Y12 Inhibition

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CHARISMA (est. CVD)	Clopidogrel	↓	↑	↔	↔
PEGASUS (prior MI)	Ticagrelor	↓	↑	↔	↔

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DOAC vs. P2Y12 Inhibition

Trial	Therapy*	CVD, MI, or Stroke	Bleeding	All-Cause Mort.	Net Benefit
CHARISMA (est. CVD)	Clopidogrel	↓	↑	↔	↔
PEGASUS (prior MI)	Ticagrelor	↓	↑	↔	↔
COMPASS (CAD/PAD)	RIVA	↓	↑	↓	↑

* All trials performed on background low-dose ASA

Should COMPASS Change Practice?

- Among pts with established CAD or PAD, the addition of very low dose rivaroxaban (2.5 mg bid) to low dose ASA led to significant reductions in cardiovascular events, driven mainly by reductions in CV death and stroke
- Although bleeding risk was also increased, the majority of bleeding was non-fatal, and net benefit calculations continued to favor treatment
- When coupled with the significant reduction in all-cause mortality, these findings suggest the addition of rivaroxaban to low-dose ASA should be strongly considered for such patients– especially those with involvement of multiple vascular beds