



a COMPASS towards a new era of vascular protection?



Marco Alings, MD PhD FESC

Department of Cardiology, Amphia Ziekenhuis, Breda
U-TRIAL, University Medical Center Utrecht
Julius Clinical, Zeist

Disclosures

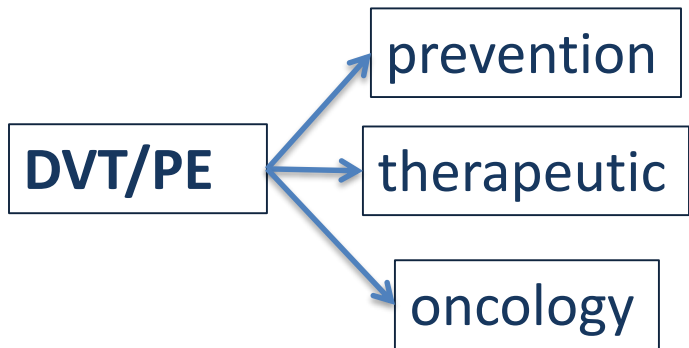
Advisory boards:

Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Milestone, Pfizer, Roche Diagnostics, Sanofi

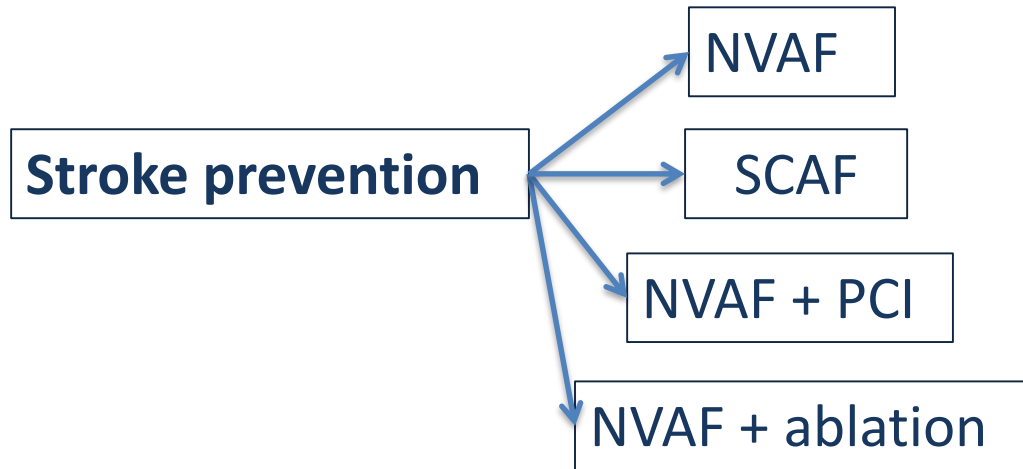
National coordinator:

COMPASS

NOAC: trials / therapeutic areas

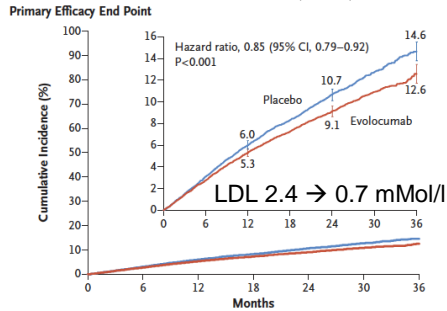
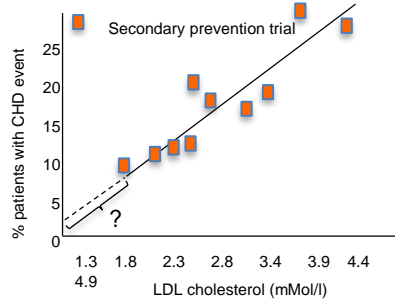


~~Mechanical valves~~



Vascular prevention

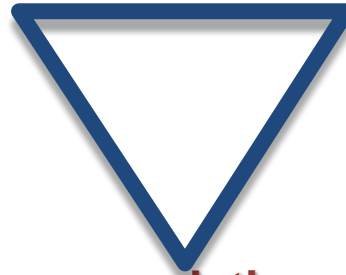
Vascular protection



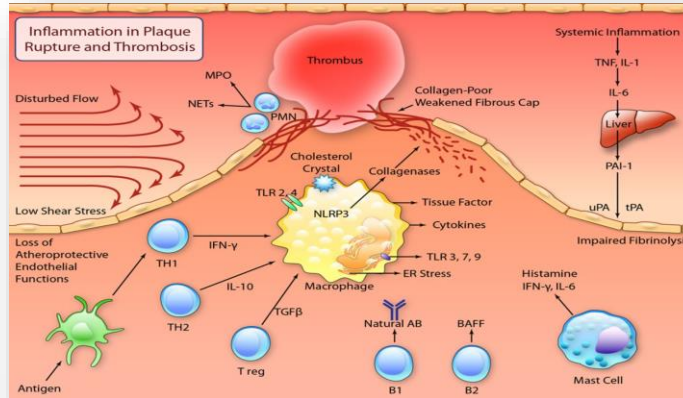
N Engl J Med 2017;376:1713-22

← Lipids-LDL

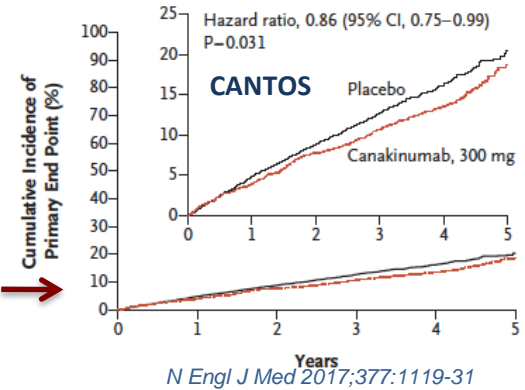
inflammation →



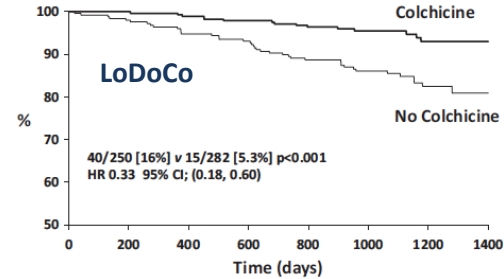
coagulation



Primary End Point with Canakinumab, 300 mg, vs. Placebo



N Engl J Med 2017;377:1119-31



Secondary prevention in cardiovascular diseases

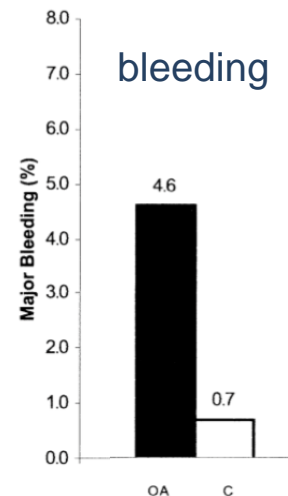
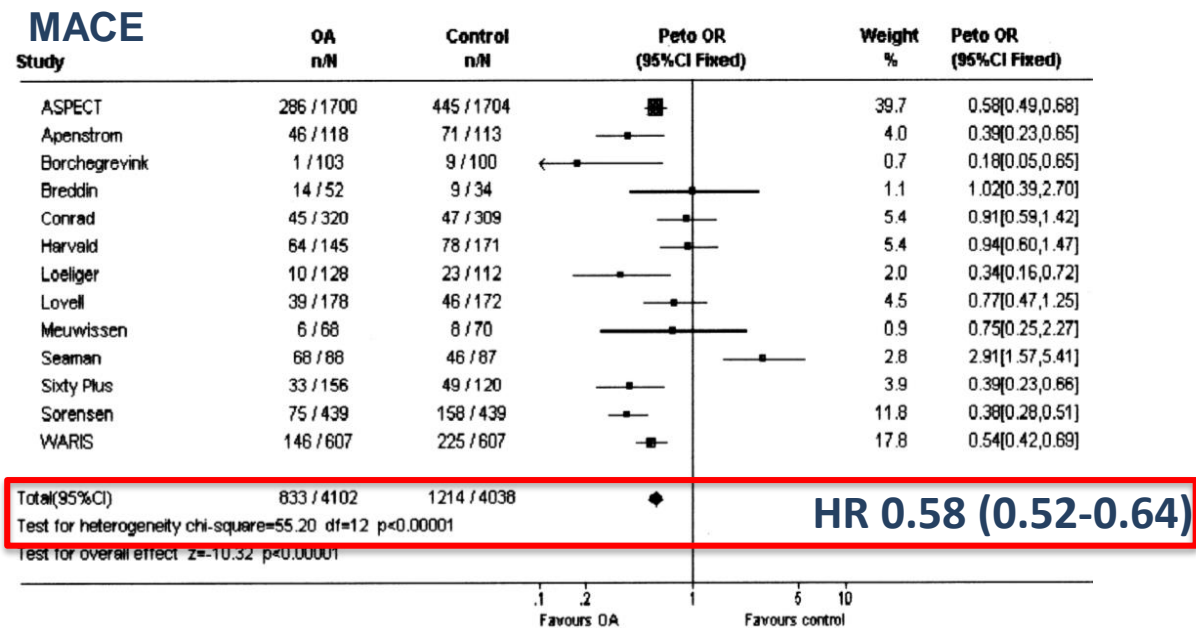
Outcome	Lipid lowering (1 mmol/L) ^{1,2}	BP Lowering (10 mm Hg) ³	ACE (HOPE) ⁴	Aspirin ⁵
MACE	21% HR 0.78; 0.69 - 0.89	20% HR 0.80; 0.77 - 0.83	22% 14.0% vs 17.8% HR 0.78; 0.70 - 0.86	18% 0.28% vs 0.34% HR 0.82; 0.75 - 0.90
Mortality	9%	13%	16%	9%
Stroke	15%	27%	32%	19%
MI	24%	17%	20%	20%

- despite secondary prevention therapies, 9 to 18% of patients with cardiovascular disease have recurrent events each year⁶

1. Collins R, et al. Lancet 2016;388:2532-61; 2. CTT Collaboration. Lancet 2015;385:1397-1405; 3. Ettehad D, et al. Lancet 2016;387:957-67;
4. Yusuf S, et al. N Engl J Med 2000;342:145-53; 5. ATT Collaboration. Lancet 2009;373:1849-60; 6. Bhat et al, JAMA 2010; 304: 1350-7

Alternatives to aspirin: Vit K antagonists

- Meta-analysis, 20,000 patients: Vit K antagonist (INR >2.8) significantly reduced MACE but increased bleeding (including ICH)



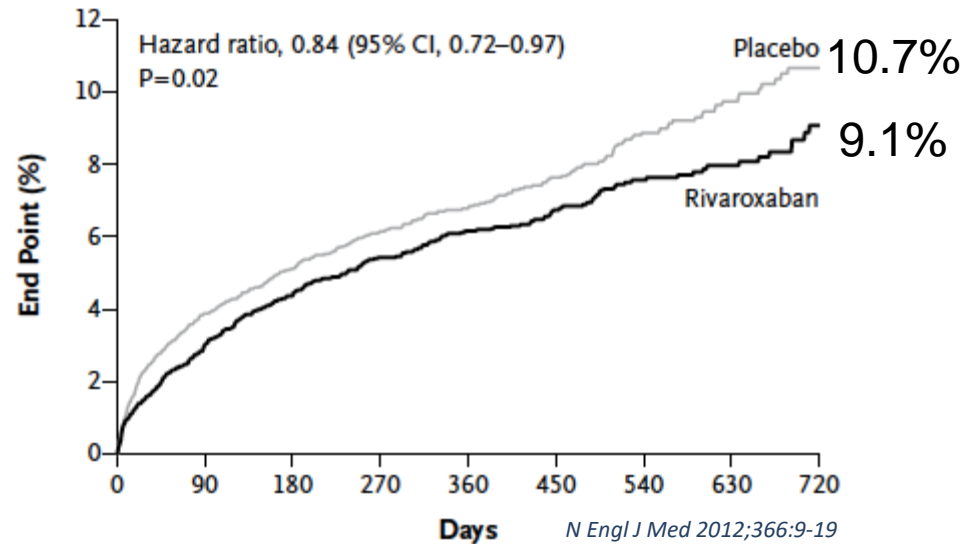
HR 4.5 (3.5-6.0)

Anand SS, J Am Coll Cardiol 2003; 41: Suppl S:62S-69S

ATLAS-TIMI 51

- 15,526 patients with a recent ACS → rivaroxaban 2.5 mg or 5 mg 2dd or placebo
- Primary: CV death, myocardial infarction, or stroke:
 - 8.9% vs 10.7% (HR 0.84; (0.74 - 0.96); $p = 0.008$)
 - 2.5-mg dose: 9.1% vs 10.7%, $p = 0.02$
 - 5-mg dose 8.8% vs. 10.7%, $p = 0.03$
- major bleeding (not related to CABG):
 - 2.1% vs. 0.6%, (HR 3.96; 2.46-6.38); $p < 0.001$
 - fatal bleeding: 0.3% vs. 0.2%, $p = 0.66$

A Primary Efficacy End Point, 2.5 mg Twice Daily



COMPASS

Hypothesis:

is rivaroxaban alone or combination of riva + with aspirin more effective than aspirin alone in preventing recurrent cardiovascular events, with acceptable safety, in patients with stable atherosclerotic vascular disease

Primary endpoint:

CV death, stroke, myocardial infarction

Secondary endpoint:

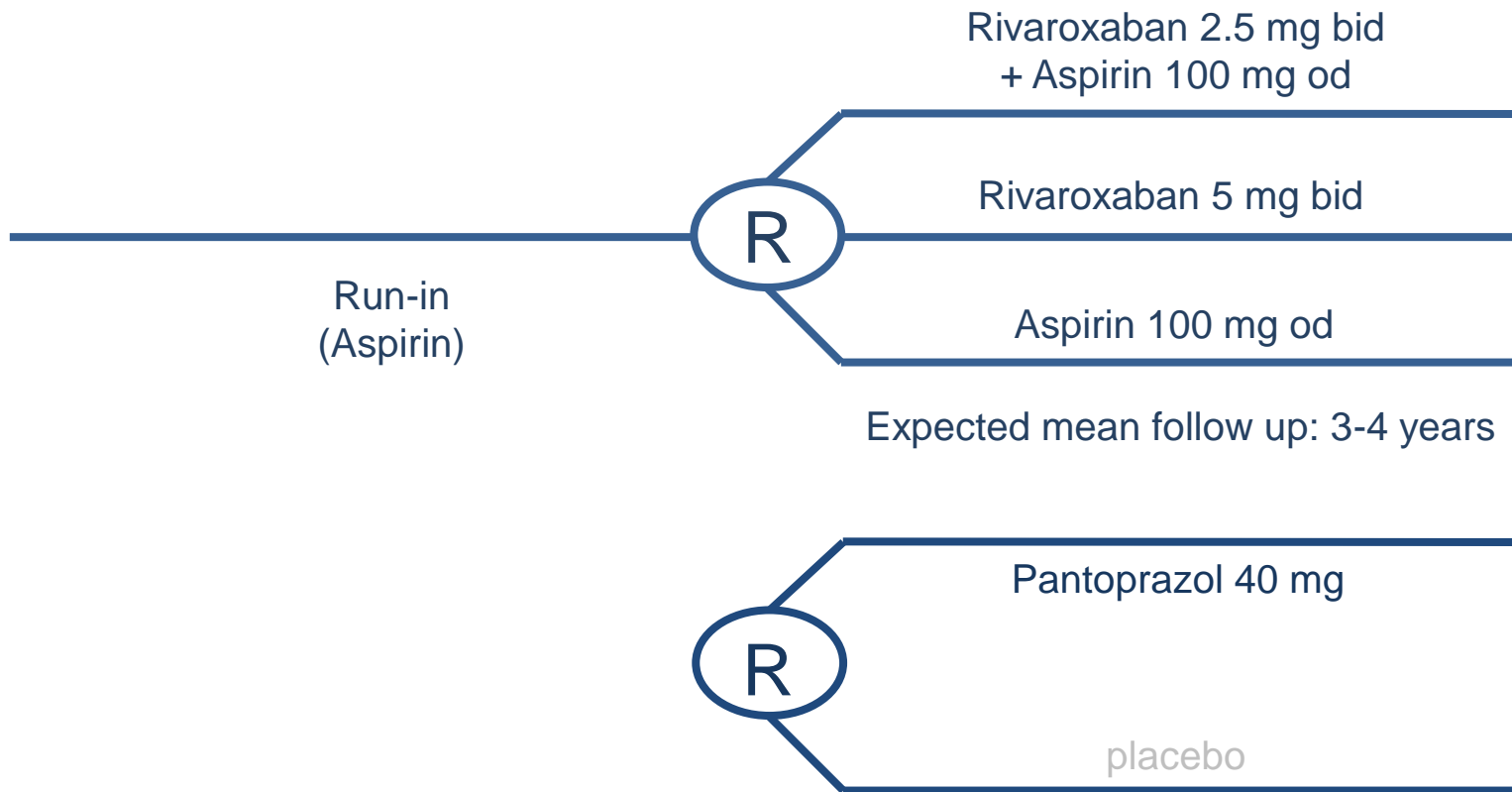
CHD death, i-stroke, MI, acute limb ischemia

Safety outcome: major bleeding (ISTH modification)

fatal; symptomatic into critical organ; leading to hospitalization (including ER visit)

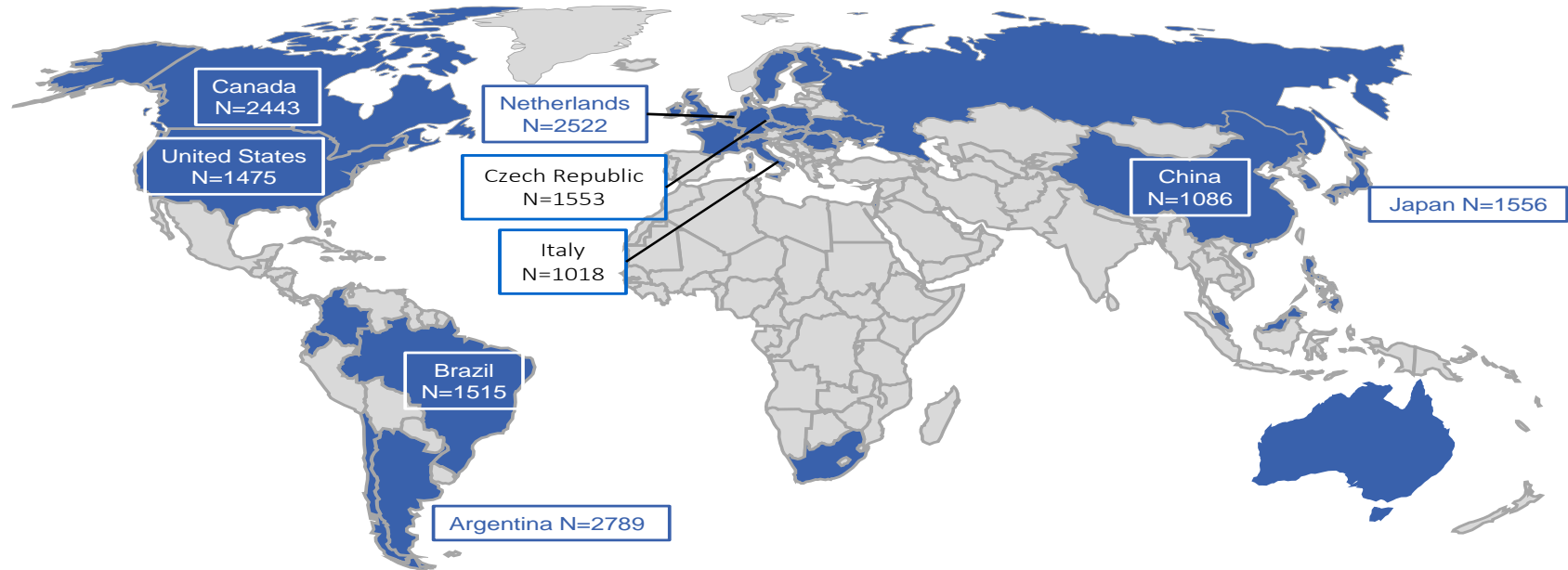
N Engl J Med 2017; 377(14):1319-1330

COMPASS



COMPASS

n=27,395; 602 sites; 33 countries; mean follow-up 23 months

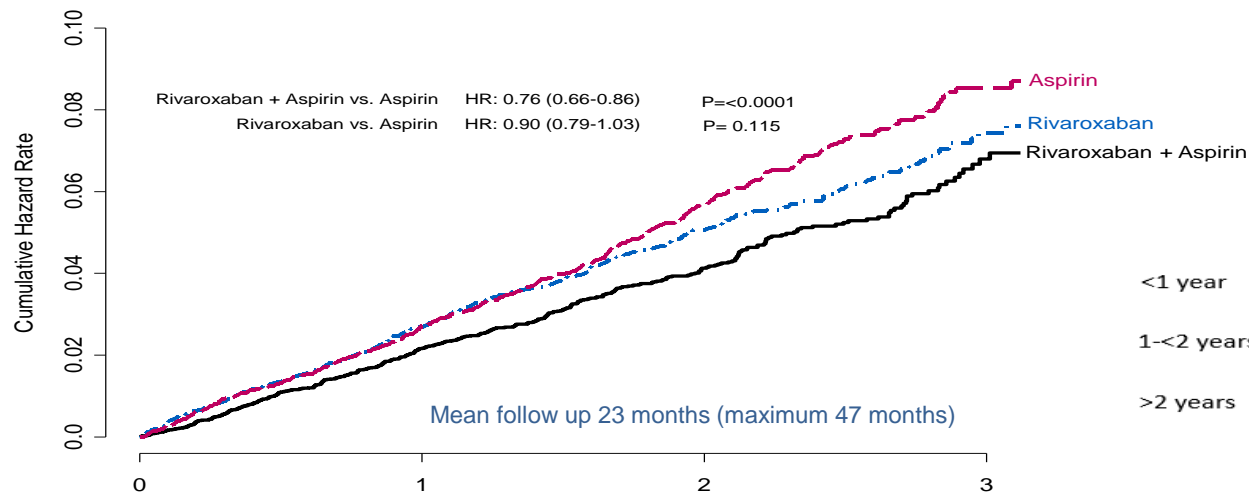


COMPASS: baseline characteristics

	Rivaroxaban + ASA N=9,152	Rivaroxaban N=9,117	Aspirin N=9,126
Age, yr	68	68	68
Female	22%	22%	22%
SBP/DBP, mmHg	136/77	136/78	136/78
Cholesterol, mmol/L	4.2	4.2	4.2
CAD	91%	90%	90%
PAD	27%	27%	27%
Diabetes	38%	38%	38%
Lipid-lowering	90%	90%	89%
ACE-I/ARB	71%	72%	71%
PPI (non study)	36%	36%	36%

COMPASS primary endpoint: CV death, stroke, MI

	R + A (n = 9,152)	Riva (n = 9,117)	Aspirin (n = 9,126)	Riva + ASA vs. ASA HR (95% CI)		Riva vs. ASA HR (95% CI)	
CV death, stroke, MI	379 (4.1%)	448 (4.9%)	496 (5.4%)	0.76 (0.66-0.86)	<0.0001	0.90 (0.79-1.03)	0.11



N Engl J Med. 2017;377(14):1319-1330



CV death, stroke, MI

	Riva + Aspirin		Aspirin	HR (95% CI)	
<1 year	2.1%	vs	2.7%	0.79	(0.66-0.96)
1-<2 years	1.6%	vs	2.3%	0.68	(0.54-0.85)
>2 years	1.6%	vs	1.9%	0.82	(0.58-1.15)

0.5 1.0 2.0
 Riva/Aspirin better Aspirin better

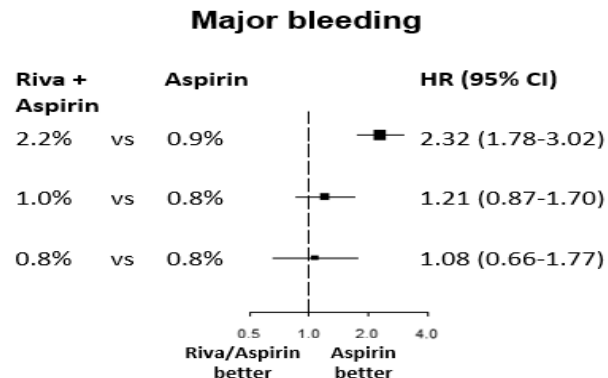
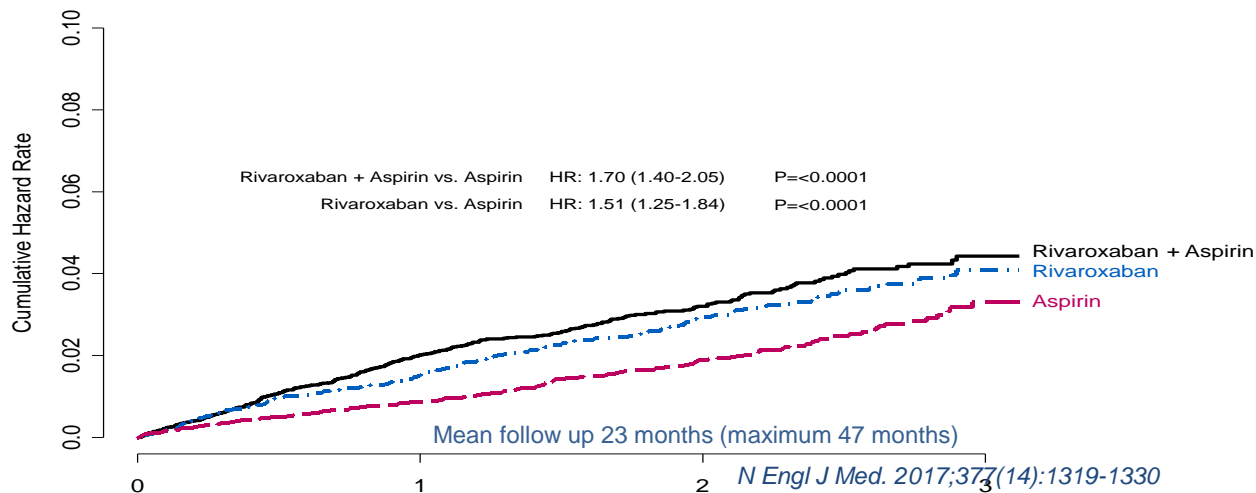
COMPASS components primary endpoint

	R + A (n = 9,152)	Aspirin (n = 9,126)	Riva + ASA vs. ASA HR (95% CI)	
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	<0.02
stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
<i>ischemic</i>	64 (0.7%)	125 (1.4%)	0.51 (0.38-0.69)	<0.0001
<i>hemorrhagic</i>	5 (<0.1%)	14 (<0.1%)	0.35 (0.13-0.99)	0.04
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

N Engl J Med. 2017;377(14):1319-1330

COMPASS: major bleeding

	R + A (n = 9,152)	Riva (n = 9,117)	Aspirin (n = 9,126)	Riva + ASA vs. ASA HR (95% CI)		Riva vs. ASA HR (95% CI)	
Major bleed	288 (3.1%)	252 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001



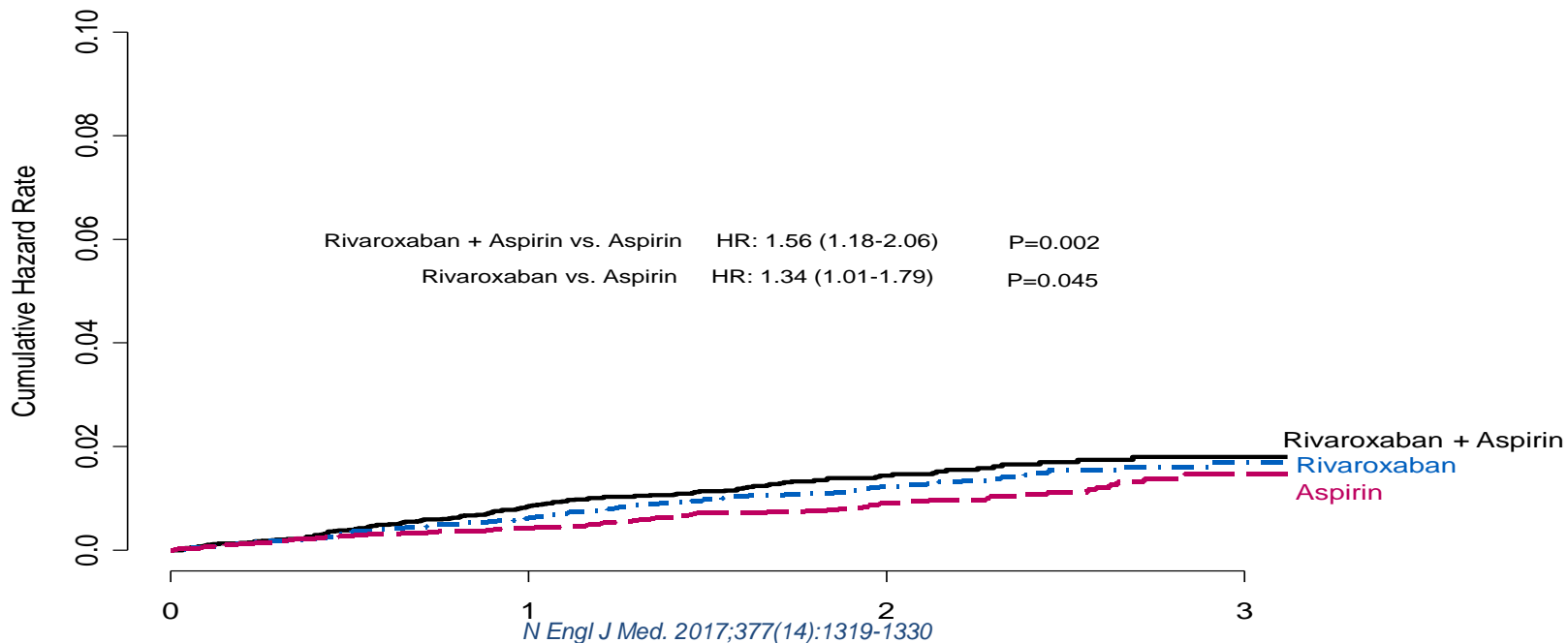
COMPASS: components major bleeding

	R + A (n = 9,152)	Aspirin (n = 9,126)	Riva + ASA vs. ASA HR (95% CI)	
Major bleed	288 (3.1%)	170 (1.9%)	0.78 (0.64-0.96)	$p < 0.02$
<i>fatal</i>	15 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	$p = 0.32$
<i>Non fatal ICH</i>	21 (0.2%)	19 (0.2%)	1.101 (0.59-2.04)	$p = 0.77$
<i>Critical site</i>	42 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	$p = 0.14$
<i>other</i>	210 (2.3%)	112 (1.2%)	1.88 (1.49-2.36)	$p < 0.0001$
<i>GI bleed</i>	140 (1.5%)	65 (0.7%)	2.15 (1.60-2.89)	< 0.0001

N Engl J Med. 2017;377(14):1319-1330

COMPASS: major bleeds excluding serious bleeds

- Major bleed, not fatal or in critical organ or requiring two units transfusion



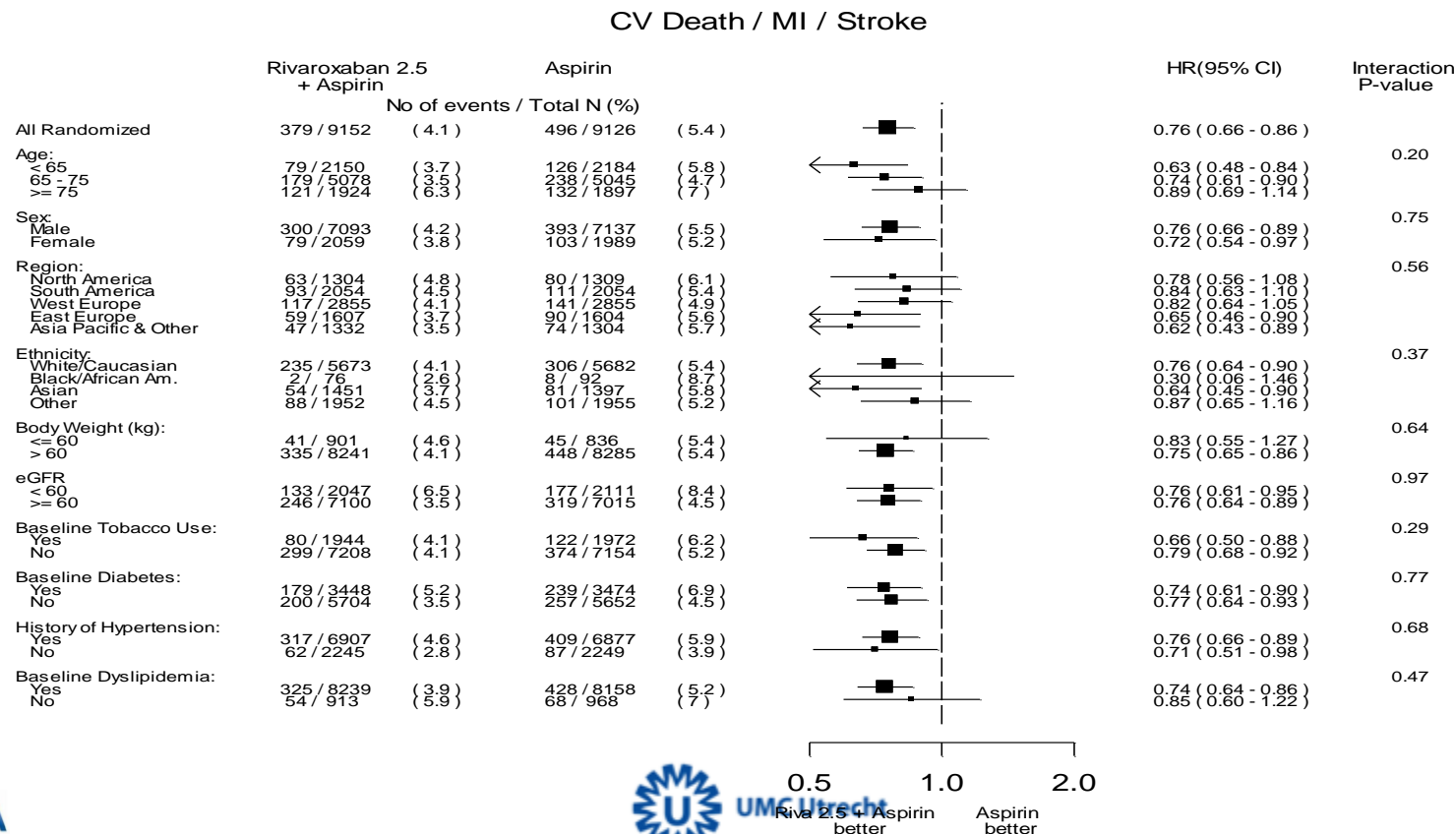
COMPASS net clinical benefit

composite net-clinical-benefit outcome of:

- cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ

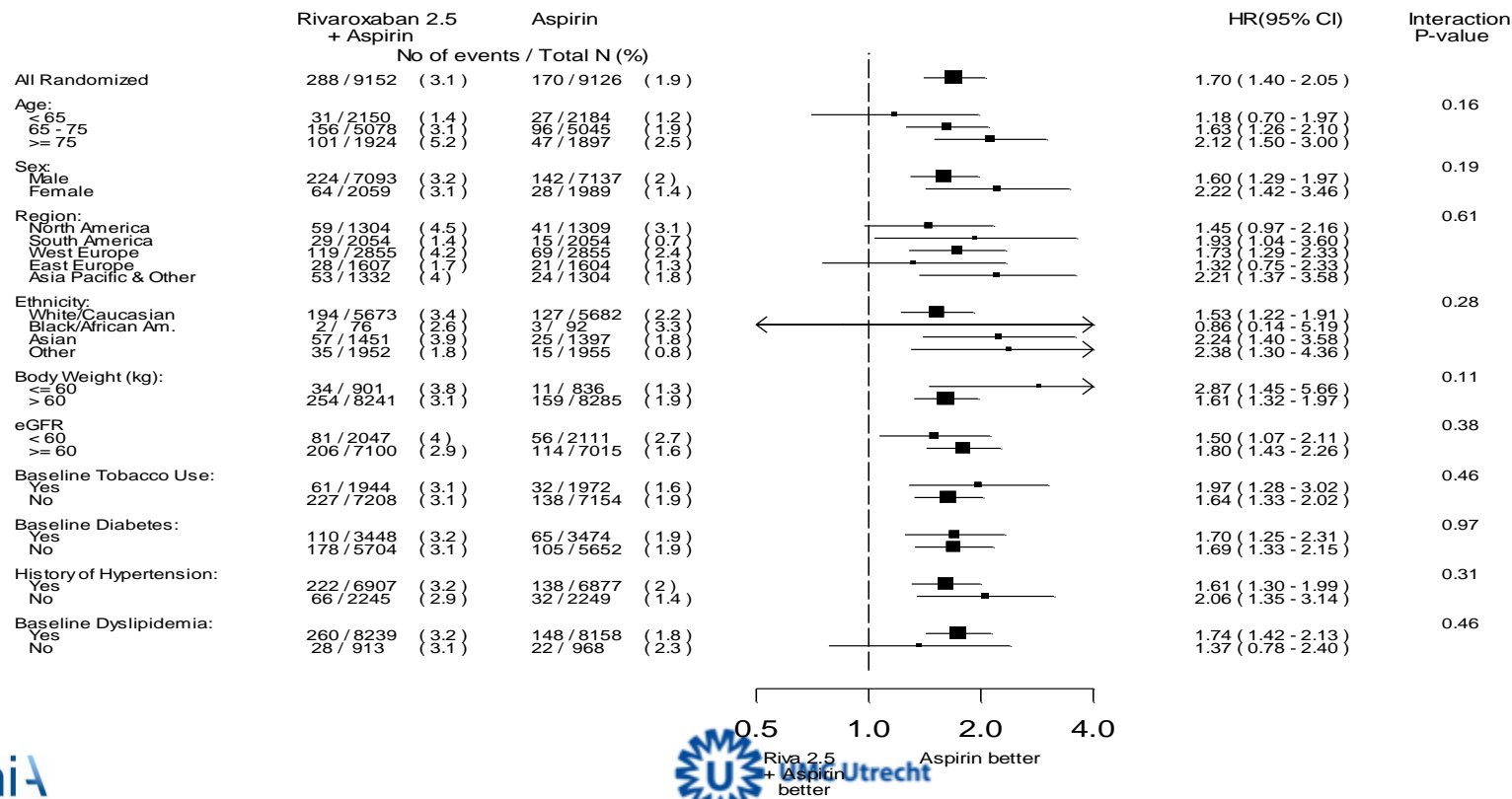
	R + A (n = 9,152)	Aspirin (n =9,126)	Riva + ASA vs. ASA HR (95% CI)	
Net clinical benefit	431 (4.7%)	534 (5.8%)	0.80 (0.70-0.91)	<0.001

COMPASS subgroups: primary outcome



COMPASS subgroups: major bleeding

Major Bleeding



COMPASS: patients with peripheral artery disease

- n = 7470 (symptomatic: n = 6048; CAD + ABI <0.90; n = 1422)
- Primary Outcome: MACE (CV death, stroke, or MI)
- Major Adverse Limb Events (MALE):
 - limb ischemia leading to intervention (PTA, bypass surgery, amputation, thrombolysis)
 - Major Amputation above forefoot

Outcome	R + A N=2,492	A N=2,504	Rivaroxaban + aspirin vs. aspirin	
	N (%)	N (%)	HR (95% CI)	p
MACE	126 (5%)	174 (7%)	0.72 (0.57-0.90)	0.0047
MALE or amputation	32 (1%)	60 (2%)	0.54 (0.35-0.82)	0.0037
Major bleeding	77 (3%)	48 (2%)	1.61 (1.12-2.31)	0.0089
Net clinical benefit	140 (6%)	185 (7%)	0.75 (0.60-0.94)	0.011

COMPASS: conclusion

In patients with stable vascular disease, receiving secondary prevention therapy, compared to aspirin alone, low dose rivaroxaban PLUS aspirin:

Outcome	all	PAD	Riva + aspirin vs. aspirin
MACE	-24% (4.1% vs 5.4%)	-28% (5% vs 7%)	
MALE or amputation	-	-46% (1% vs 2%)	
Major bleeding	+70% (3.1% vs 1.9%)	+61% (3% vs 2%)	mainly GI bleeds No increase in fatal, critical organ or ICB
Net clinical benefit	-20% (4.7% vs 5.9%)	-25% (6% vs 7%)	

COMPASS in context

Outcome	Lipid lowering (1 mmol/L) ^{1,2}	BP Lowering (10 mm Hg) ³	ACE (HOPE) ⁴	Aspirin ⁵	COMPASS Riva + aspirin
MACE	21%	20%	22%	18%	24%
Mortality	9%	13%	16%	9%	18%
Stroke	15%	27%	32%	19%	42%
MI	24%	17%	20%	20%	14%
MALE					46%

COMPASS: in context antithrombotics for 2^o prevention

Outcome	CAPRIE Clopidogrel	CHARISMA Clopidogrel + aspirin	PEGASUS Tica 90 + aspirin	COMPASS Rivaroxaban + aspirin
MACE	7%	7%	15%	24%
Mortality	2%	1%	0%	18%
Stroke	-	21%*	18%	42%
MI	-	6%*	19%	14%
Major Bleeds	-33%	-25%-62%	-169%	-70%

COMPASS: discussion

- What are costs related to rivaroxaban for “vascular protection”?
- In which patient to start rivaroxaban for secondary prevention?
- What explains the 49% reduction in ischemic stroke?
 - In AF goats, nadroparin attenuates atrial fibrosis and the complexity of the AF substrate. Inhibition of coagulation may prevent the development of a substrate for AF¹