Background

- Aspirin is most widely used preventive treatment but produces only a 19% RRR during the long term.

- Warfarin (±ASA) is more effective than ASA but increases bleeding, including intracranial hemorrhage.

- Rivaroxaban is safer than warfarin and reduces mortality in patients with recent acute coronary syndrome.

Objectives

To determine in stable CV disease, whether:

- Rivaroxaban 2.5 mg bid + aspirin 100 mg od, or
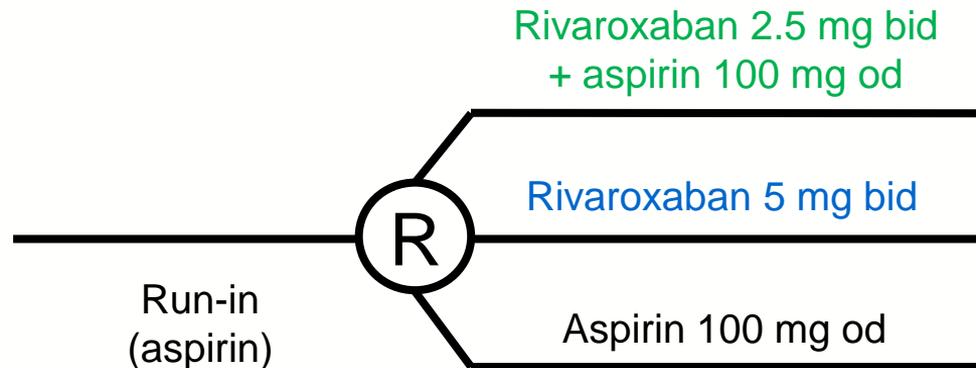
- Rivaroxaban 5 mg bid

reduces CV death, stroke or MI compared with ASA 100 mg

And whether:

- Pantoprazole compared with placebo reduces upper GI events (ongoing)

COMPASS design

Stable CAD or PAD
2,200 with a primary outcome event

Rivaroxaban 2.5 mg bid
+ aspirin 100 mg od

Rivaroxaban 5 mg bid

R

Aspirin 100 mg od

Run-in
(aspirin)

Expected follow up
3-4 years

Primary: CV death, stroke, MI

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
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)	0.12

Primary: CV death, stroke, MI

Rivaroxaban + Aspirin vs. Aspirin   HR: 0.76, 95% CI 0.66-0.86, P=<0.0001

Rivaroxaban vs. Aspirin   HR: 0.90, 95% CI 0.79-1.03, P= 0.12

No. at Risk				
Rivaroxaban + Aspirin	9152	7904	3912	658
Rivaroxaban	9117	7824	3862	670
Aspirin	9126	7808	3860	669
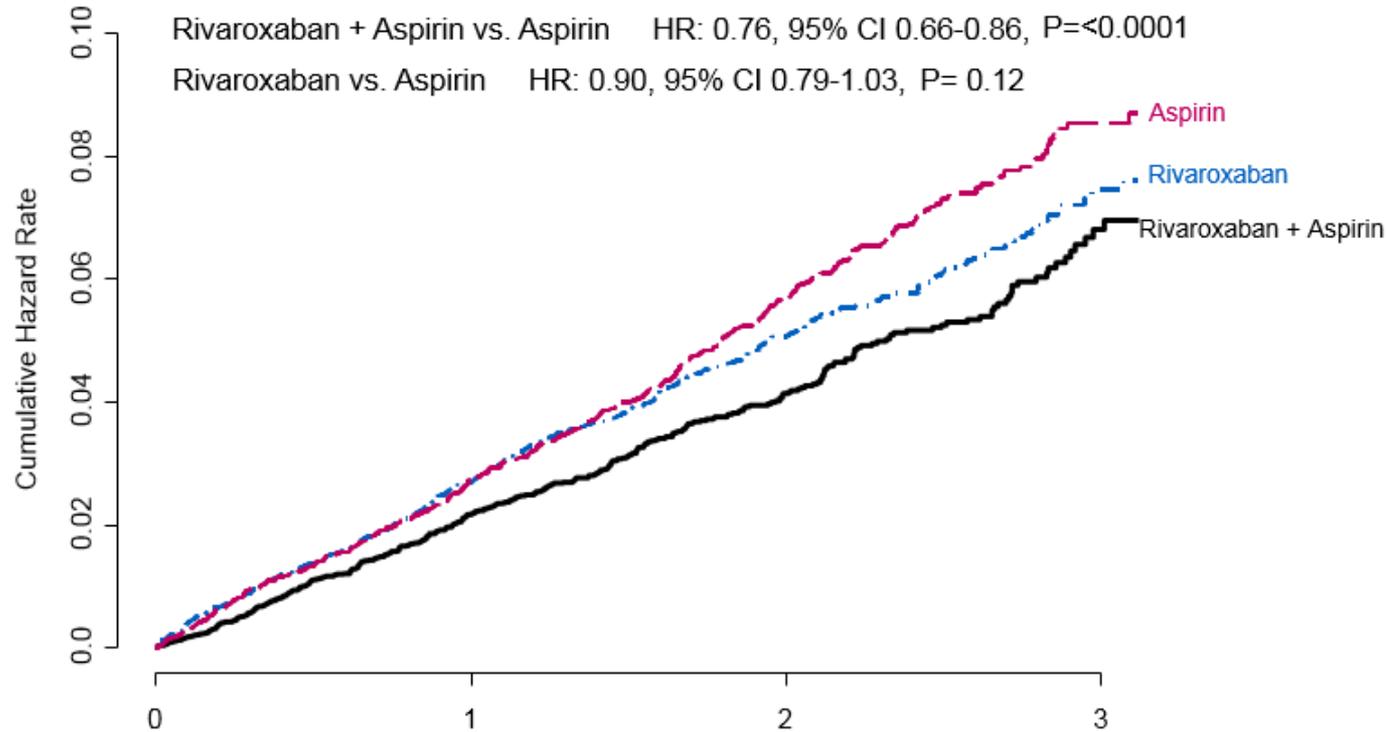
Primary components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
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
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

Secondary outcomes

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P*
CHD death, IS, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63-0.83)	<0.0001
CV death, IS, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65-0.85)	<0.0001
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

* pre-specified threshold P=0.0025

Eligibility: PAD

- Peripheral artery revascularization

- Limb or foot amputation for arterial vascular disease

- Intermittent claudication plus:

  – Low ABI (<0.90), or

  – Significant peripheral artery stenosis (≥50%)

- Previous carotid revascularization, asymptomatic carotid artery stenosis ≥50%

- CAD + low ABI (<0.90)

Key Efficacy Outcomes

- Primary Cardiovascular Outcome (MACE):

- CV death, stroke, or MI

- Major Adverse Limb Events (MALE):
  - Severe limb ischemia leading to an intervention (angioplasty, bypass surgery, amputation, thrombolysis)
  - Major Amputation above forefoot due to vascular cause

Baseline Characteristics

Characteristic	Riva + aspirin N=2,492	Rivaroxaban N=2,474	Aspirin N=2,504
Age, years (mean)	68	68	68
Current Smoker	27%	28%	27%
Former Smoker	46%	47%	46%
Diabetes	44%	44%	44%
Hypertension	79%	78%	81%
Prior CAD or Stroke	69%	69%	68%
Lipid Lowering	84%	84%	83%
ACE-I/ARB	69%	71%	70%

Primary outcome & components

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57-0.90)	0.005	0.86 (0.69-1.08)	0.19
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53-1.09)	-	0.84 (0.59-1.20)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33-0.87)	-	0.93 (0.61-1.40)	-
CV Death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59-1.14)	-	0.86 (0.62-1.19)	-

Limb outcomes

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MALE	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35-0.84)	0.005	0.63 (0.41-0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11-0.80)	0.01	0.46 (0.20-1.08)	0.07

Key Composite Outcome

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MACE, MALE or Major amputation	157 (6.3)	188 (7.6)	225 (9.0)	0.69 (0.56-0.85)	0.0003	0.84 (0.69-1.02)	0.08

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MACE or MALE or Major Amputation

Rivaroxaban + Aspirin vs. Aspirin HR: 0.69 (0.56-0.85) P=0.0003

Rivaroxaban vs. Aspirin   HR: 0.84 (0.69-1.02) P=0.08
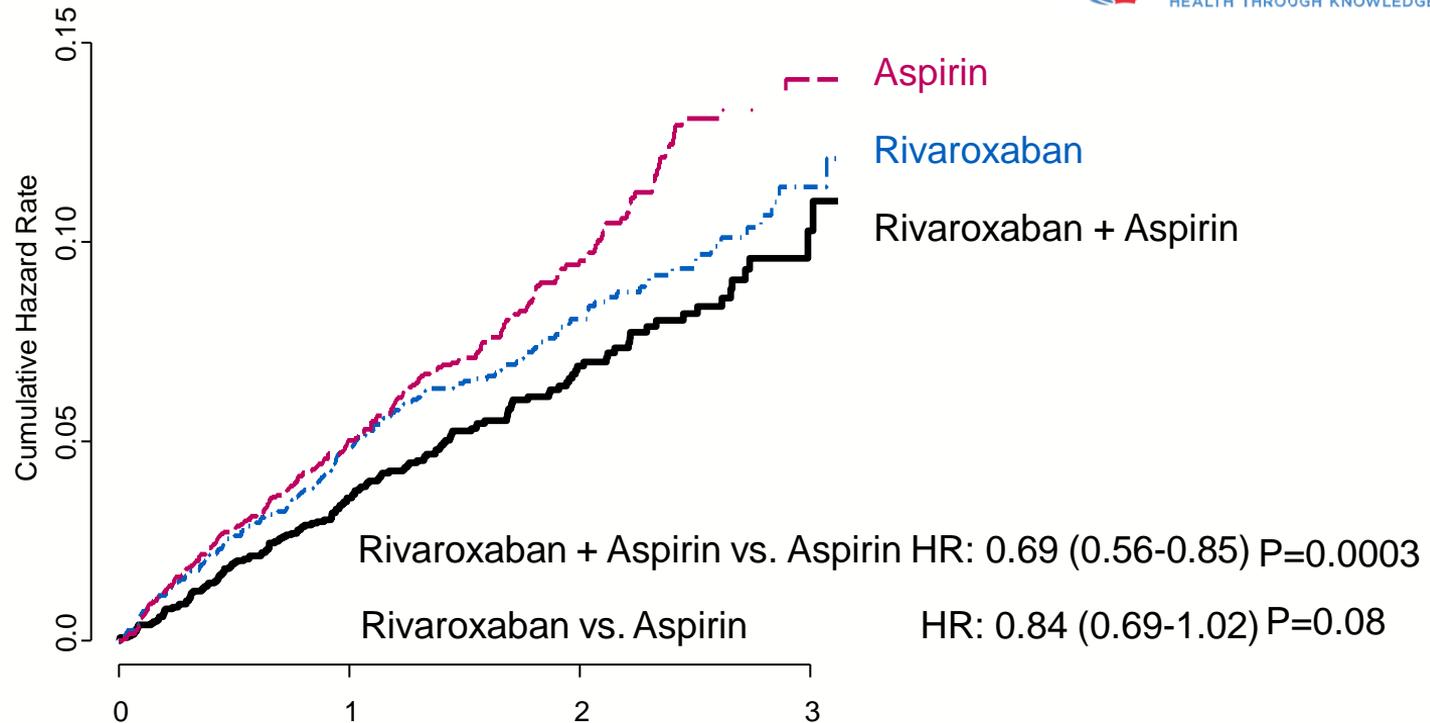
No. at Risk

	0	1	2	3
Riva + ASA	2492	2069	893	124
Riva	2474	2023	864	147
ASA	2504	2034	911	113

Conclusions

Rivaroxaban 2.5 mg BID plus aspirin is:

-Significantly superior to aspirin alone in reducing   MACE or MALE or major amputation (31% RRR)

-Increased non-critical major bleeding