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Rivaroxaban with or without aspirin in stable cardiovascular disease

**John Eikelboom, on behalf of the
COMPASS Steering Committee and Investigators
Independently conducted by PHRI, Sponsored by Bayer AG**

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Steering committees, advisory boards, honoraria, research support from Bayer, BI, BMS, Daiichi, Janssen, Pfizer, Portola, Sanofi)

Background

- CV disease affects 4% of world population (300 million persons)
- Aspirin is the single most widely used preventive treatment but produces only a 19% RRR during the long term
- Warfarin with or without aspirin is more effective than aspirin 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

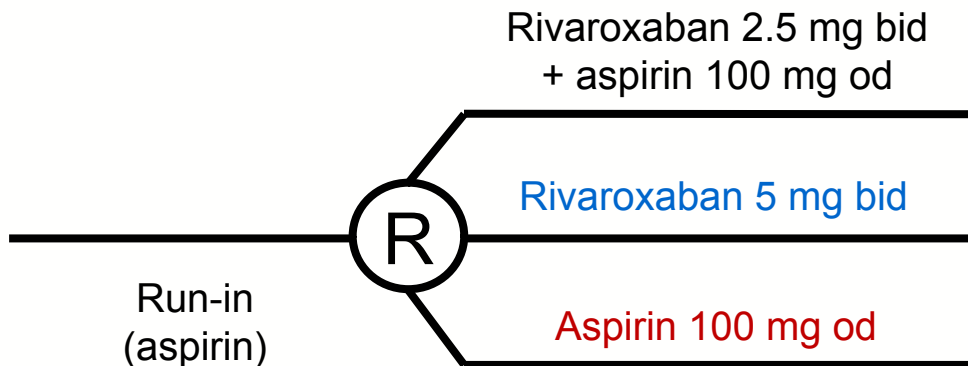
reduces CV death, stroke or myocardial infarction compared with aspirin 100 mg od

And whether:

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

COMPASS design

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

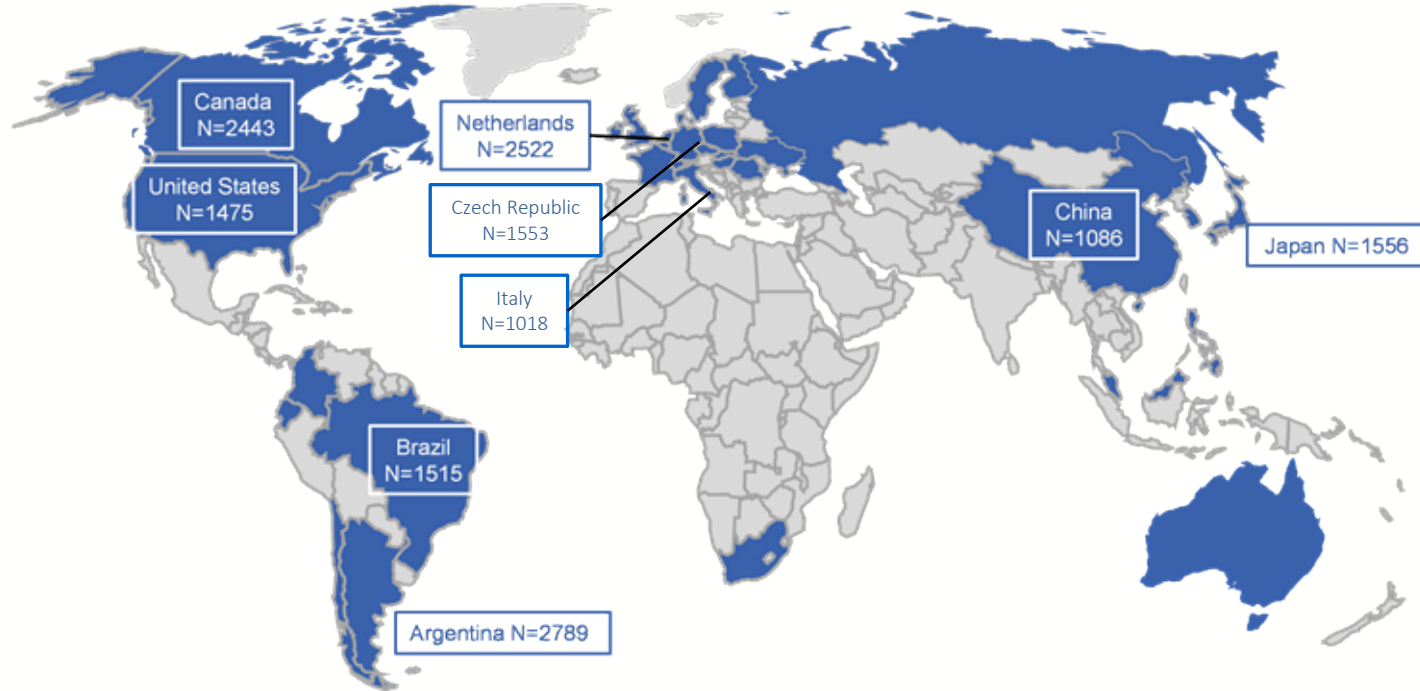


Expected follow up
3-4 years

Outcomes

- Primary
 - CV death, stroke or myocardial infarction
- Secondary
 - CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia,
 - CV death, ischemic stroke, myocardial infarction, or acute limb ischemia,
 - Mortality
- Safety and net clinical benefit
 - ISTH major bleeding (modified)
 - Primary plus fatal or critical organ bleeding

602 sites, 33 countries



Follow up, adherence

- On February 6, 2017 the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy (combination: $Z = -4.59$, $P < 0.00001$; rivaroxaban: $Z = -2.44$, $P = 0.01$)
- Close-out between March and June 2017
- Mean follow up 23 months
- Follow up 99.8% complete

Baseline characteristics

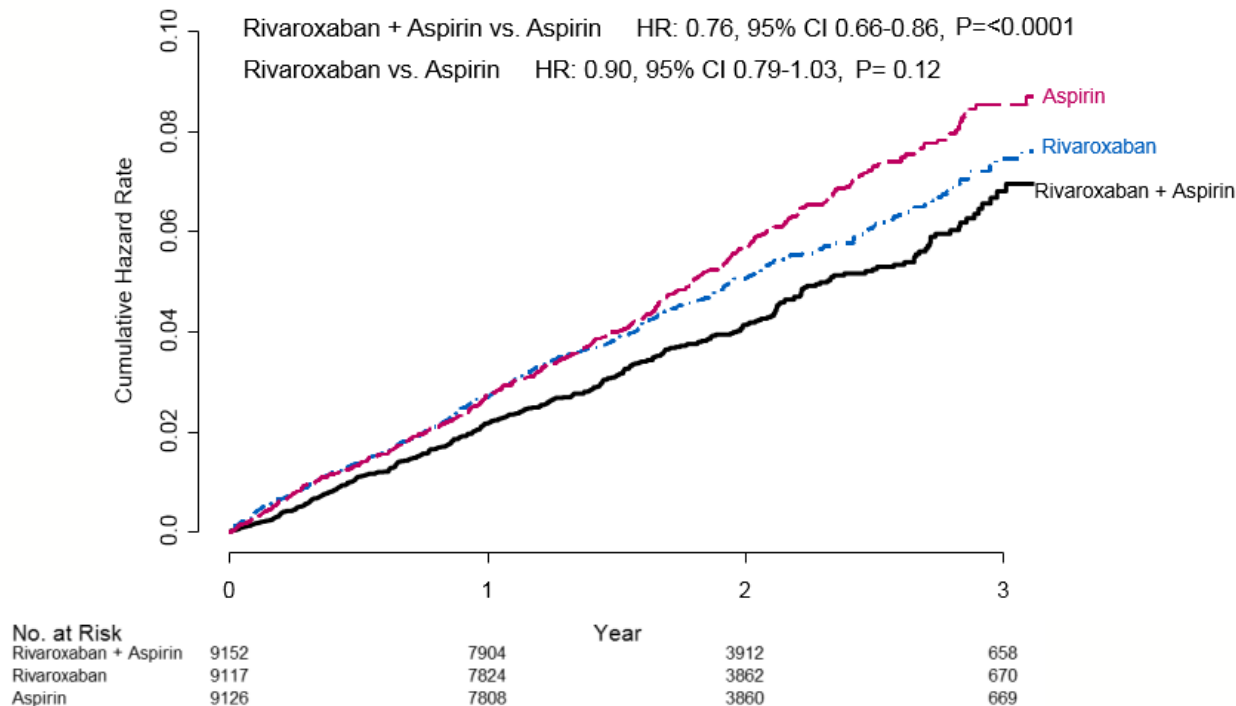
Characteristic	Rivaroxaban + aspirin N=9,152	Rivaroxaban N=9,117	Aspirin N=9,126
Age, yr	68	68	68
Blood pressure, mmHg	136/77	136/78	136/78
Total cholesterol, mmol/L	4.2	4.2	4.2
CAD	91%	90%	90%
PAD	27%	27%	27%
Diabetes	38%	38%	38%
Lipid-lowering	90%	90%	89%
ACE-I or ARB	71%	72%	71%

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



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

CAD and PAD

Subgroups for primary outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

Major bleeding

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
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

* symptomatic

Net clinical benefit

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

Conclusion

Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- Reduces CV death, stroke, MI
- Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding
- Provides a net clinical benefit

No significant benefit of rivaroxaban alone

Acknowledgments

Steering Committee: S. Yusuf (Chair), K. Fox (Co-Chair), S. Connolly (Co-PI), JW. Eikelboom (Co-PI), J. Bosch (Study Director), V. Aboyans, M. Alings, S. Anand, A. Avezum, D. Bhatt, K. Branch, P. Commerford, N. Cook-Bruns, G. Dagenais, A. Dans, R. Diaz, G. Ertl, C. Felix, , T. Guzik, J. Ha, R. Hart, M. Hori, A. Kakkar, K. Keltai, M. Keltai, J. Kim, A. Lamy, F. Lanas, B. Lewis, Y. Liang, L. Liu, E. Lonn, P. Lopez-Jaramillo, A. Maggioni, K. Metsarinne, P. Moayyedi, M. O'Donnell, A. Parkhomenko, L. Piegas, N. Pogosova, J. Probstfield, L. Ryden, M. Sharma, P.G. Steg, S. Stoerk, A. Tonkin, C. Torp-Pedersen, J. Varigos, P. Verhamme, D. Vinereanu, P. Widimsky, K. Yusoff, J. Zhu

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ORIGINAL ARTICLE

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