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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

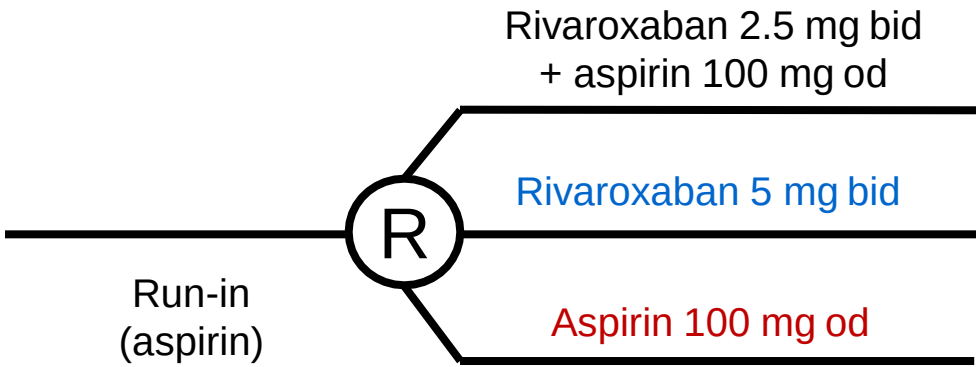
reduces CV death, stroke or myocardial infarction compared with aspirin 100 mg od

And whether:

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

COMPASS design

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

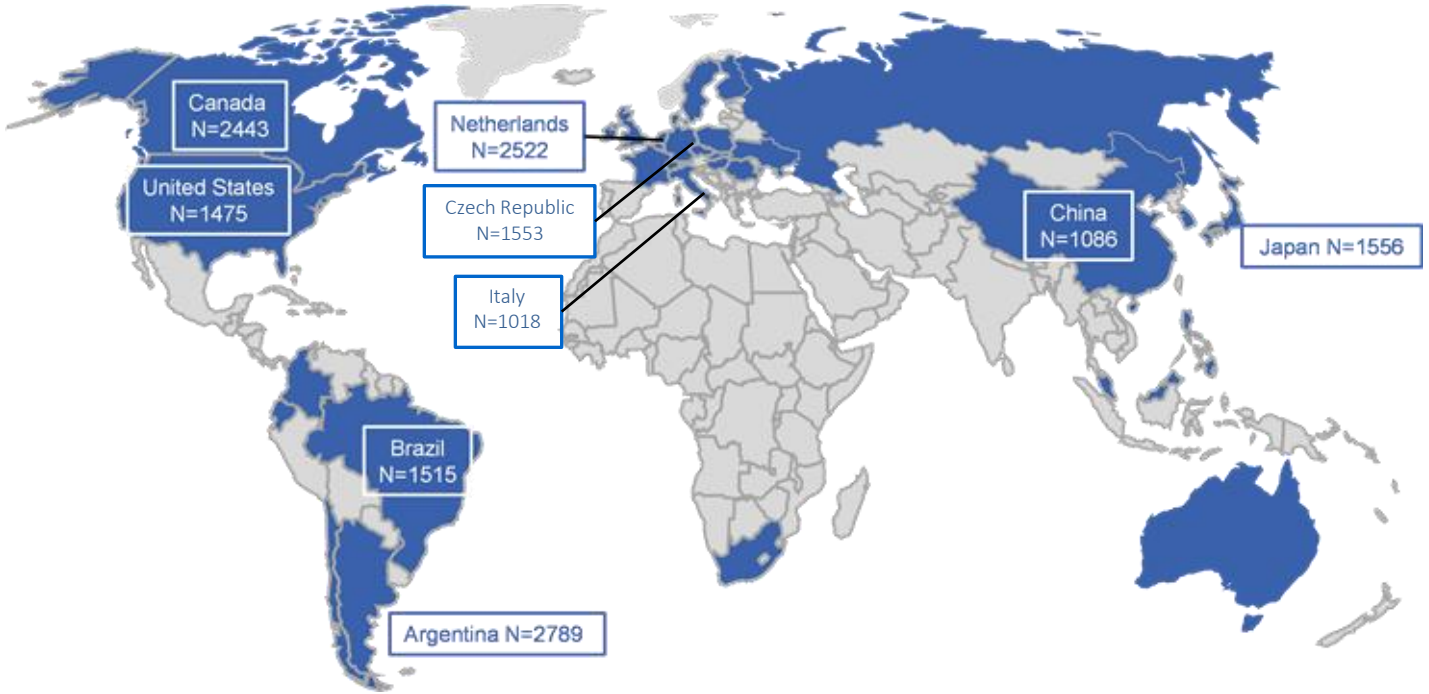


Expected follow up
3-4 years

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

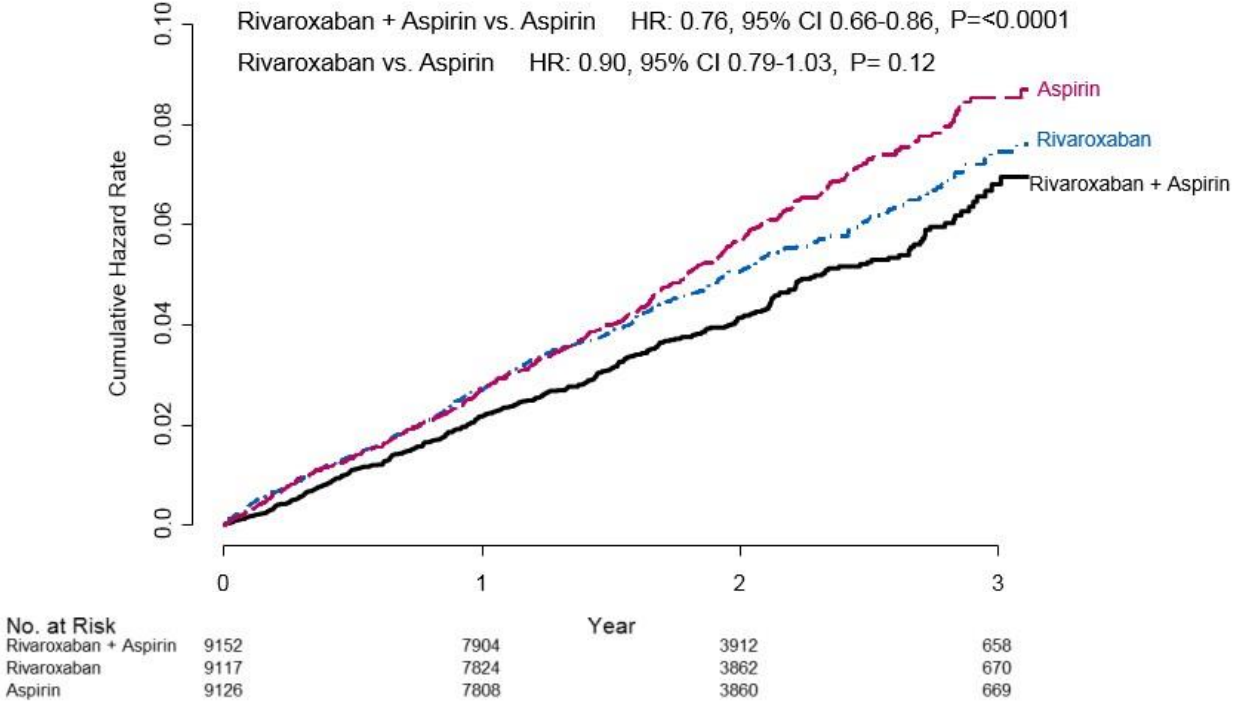
Baseline characteristics

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



Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

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

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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

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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

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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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