Rivaroxaban and aspirin compared with aspirin in women and men with chronic coronary or peripheral artery disease

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On behalf of the COMPASS study investigators

Declaration of interest

- Others (Speaker for local Bayer, BI, Sanofi.)

Background

- The COMPASS trial demonstrated that in patients with CAD or PAD rivaroxaban 2.5 mg plus aspirin compared with aspirin reduced CV death, stroke or MI by 24% during a mean follow-up of 23 months, but increased major bleeding by 70%
- In patients with CV disease, women compared with men have been reported to have worse outcomes
- Possible explanations include differences in risk profile, manifestations of CV disease, treatments, and response to treatment

Objective

- To determine the effects of the combination of R+A compared with aspirin alone in women and men
- To determine the effects of combination of R+A compared with aspirin alone in women and men in subgroups defined by baseline CV risk

Outcomes

- Primary outcome: CV death, stroke or myocardial infarction
- Safety outcome: ISTH major bleeding (modified)

Methods

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

- We compared baseline characteristics and CV risk (using modified REACH score) in women and men
  - Modified REACH score included age, sex, smoking, diabetes, BMI, number of vascular beds stenosis, CV events in the past one year, congestive heart failure, lipid lowering agent use, anti-platelet use, eGFR and region of the world. The highest limit score of our study was 34
- We examined the effects of the combination of rivaroxaban and aspirin compared with aspirin in women and men using a separate log-rank test
- Kaplan-Meier estimates were used to evaluate the timing of events by treatment groups

Methods

- HRs and 95% CIs were obtained from stratified Cox proportional hazards models
- Tests for interaction assessed whether the effects of Rivaroxaban plus aspirin vs aspirin differed in the two sexes
- Results presented separately in women and men according to baseline modified REACH score above or below median (12 score)

Results

- The COMPASS trial included 27,395 participants, of whom 18,278 were randomized to receive the combination of rivaroxaban and aspirin compared with aspirin alone
- 4,048 of 18,278 (22.1%) were women and 14230 (77.9%) were men
- At the completion of follow-up, 15.9% of women and 16.7% of men in the combination arm had permanently discontinued treatment compared with 16.2% of women and 15.6% of men in the aspirin arm

Baseline characteristics

	Women (N=4,048)	Men (N=14,230)	P value
Age (yr), mean (SD)	**69.0±8.0**	**68.0±7.9**	<0.0001
SBP (mm Hg), mean (SD)	136±18	136±17	0.23
DBP (mm Hg), mean (SD)	77±10	78±10	<0.0001
Total Chol (mmol/l), mean (SD)	**4.6±1.2**	**4.1±1.0**	**<0.0001**
Tobacco use never,n (%)	**2113 (52.2)**	**3712 (26.1)**	**<0.0001**
eGFR <60 ml/min, n (%))	**1314 (32.5)**	**2854 (20.1)**	**<0.0001**

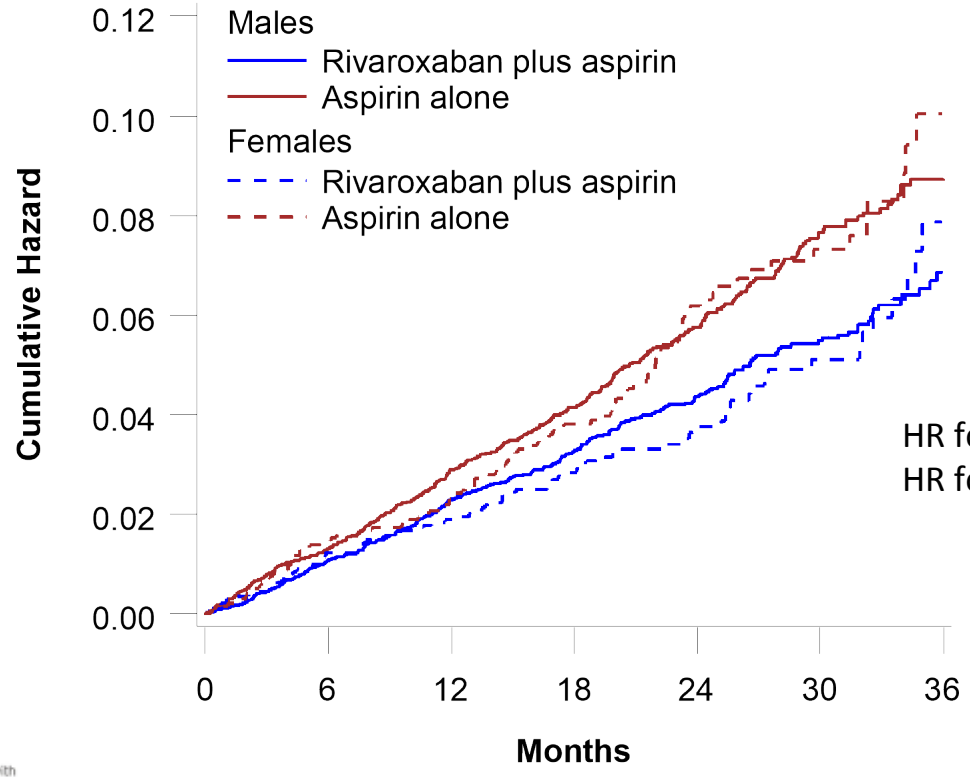
Baseline characteristics – CV risk factors

	Women (N=4,048)	Men (N=14,230)	P value
Hypertension, n (%)	**3255 (80.4)**	**10529 (74.0)**	**<0.0001**
Diabetes, n (%)	**1678 (41.5)**	**5244 (36.9)**	**<0.0001**
CAD, n (%)	**3382 (83.5)**	**13192 (92.7)**	**<0.0001**
Previous MI, n (%)	**2199 (54.3)**	**9176 (64.5)**	**<0.0001**
Heart failure, n (%)	921 (22.8)	3021 (21.2)	0.04
PAD, n (%)	**1435 (35.4)**	**3561 (25.0)**	**<0.0001**
REACH score*, mean (SD)	**12.18±3.66**	**12.09±3.49**	**0.06**

Baseline characteristics - Medications

	Women (N=4,048)	Men (N=14,230)	P value
ACE inhibitor or ARB	2841 (70.2)	10096 (70.9)	0.34
CCB	**1161 (28.7)**	**3734 (26.2)**	**0.002**
Diuretic	**1483 (36.6)**	**3990 (28.0)**	**<0.0001**
Beta blocker	2791 (68.9)	9992 (70.2)	0.12
Lipid-lowering agent	**3495 (86.3)**	**12902 (90.7)**	**<0.0001**

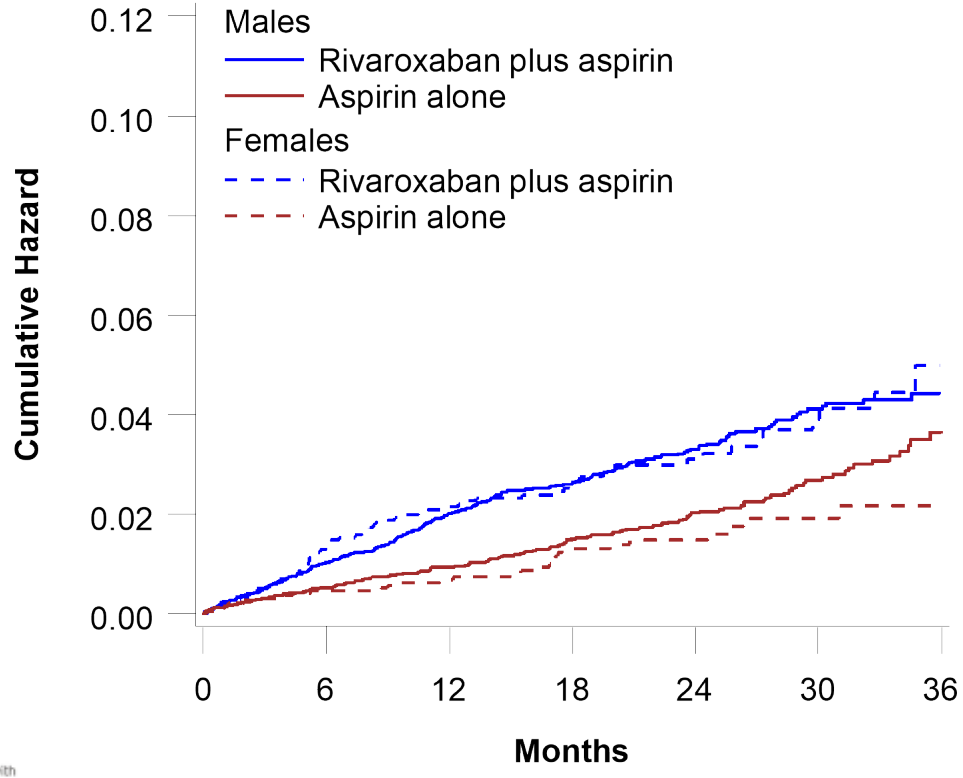
CV death, stroke, MI



P for interaction
0.75

HR for M 0.76 (0.66-0.89)
HR for F 0.72 (0.54-0.97)

Major bleeding (modified ISTH)

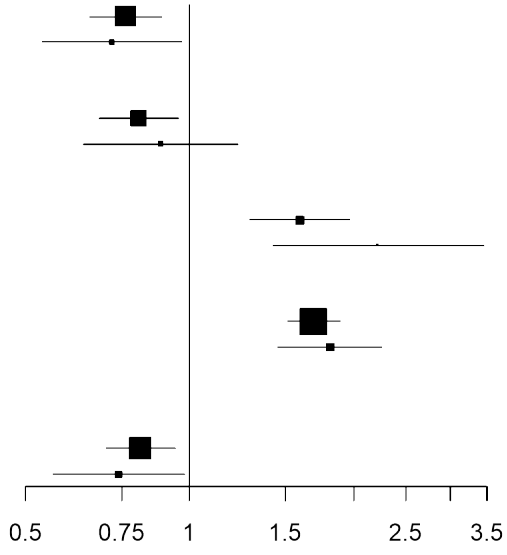


P for interaction
0.19

HR for M 1.60 (1.29-1.97)
HR for F 2.22 (1.42-3.46)

Primary efficacy, safety and other outcomes

	Rivaroxaban plus Aspirin	Aspirin Alone	HR (95% CI)	P Value for Interaction
	No. of events / patients (%)			
CV death, stroke, or myocardial infarction				0.75
Males	300 / 7093 (4.2)	393 / 7137 (5.5)	0.76 (0.66-0.89)	
Females	79 / 2059 (3.8)	103 / 1989 (5.2)	0.72 (0.54-0.97)	
Death from any cause				0.63
Males	244 / 7093 (3.4)	304 / 7137 (4.3)	0.81 (0.68-0.96)	
Females	69 / 2059 (3.4)	74 / 1989 (3.7)	0.89 (0.64-1.23)	
Major bleeding				0.19
Males	224 / 7093 (3.2)	142 / 7137 (2.0)	1.60 (1.29-1.97)	
Females	64 / 2059 (3.1)	28 / 1989 (1.4)	2.22 (1.42-3.46)	
Any bleeding				0.59
Males	850 / 7093 (12.0)	522 / 7137 (7.3)	1.69 (1.52-1.89)	
Females	226 / 2059 (11.0)	124 / 1989 (6.2)	1.81 (1.46-2.26)	
CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ				0.57
Males	343 / 7093 (4.8)	422 / 7137 (5.9)	0.81 (0.71-0.94)	
Females	88 / 2059 (4.3)	112 / 1989 (5.6)	0.74 (0.56-0.98)	



CV death, stroke, MI according to baseline REACH Score above or below the median

	Rivaroxaban plus Aspirin (N=9,152)	Aspirin Alone (N=9,126)	Rivaroxaban plus Aspirin vs. Aspirin Alone	
	No. of first events / patients (%)	No. of first events / patients (%)	Hazard Ratio (95% CI)	P for interaction
Modified REACH* score ≤12				
Men	131 / 3977 (3.3)	154 / 3989 (3.9)	0.85 (0.68-1.08)	0.43
Women	30 / 1123 (2.7)	39 / 1042 (3.7)	0.69 (0.43-1.10)	
Modified REACH score >12				
Men	169 / 3116 (5.4)	239 / 3148 (7.6)	0.71 (0.58-0.86)	0.69
Women	49 / 936 (5.2)	64 / 947 (6.8)	0.77 (0.53-1.12)	

Major Bleeding according to baseline REACH Score above or below the median

	Rivaroxaban plus Aspirin (N=9,152)	Aspirin Alone (N=9,126)	Rivaroxaban plus Aspirin vs. Aspirin Alone	
	No. of first events / patients (%)	No. of first events / patients (%)	Hazard Ratio (95% CI)	P for interaction
Modified REACH* score ≤12				
Men	129 / 3977 (3.2)	83 / 3989 (2.1)	1.58 (1.20-2.08)	0.32
Women	42 / 1123 (3.7)	18 / 1042 (1.7)	2.16 (1.24-3.75)	
Modified REACH score >12				
Men	95 / 3116 (3.0)	59 / 3148 (1.9)	1.63 (1.17-2.25)	0.43
Women	22 / 936 (2.4)	10 / 947 (1.1)	2.27 (1.07-4.79)	

Summary

- Women comprised only 22.1% of patients in our analyses
- Women vs. men had different baseline individual risk factor profiles and treatment patterns but similar modified REACH scores
- Despite baseline differences, rivaroxaban 2.5mg twice-daily plus aspirin 100mg once-daily vs. aspirin 100mg once-daily produced similar benefits and similar risks of bleeding in women and men

Acknowledgements

- COMPASS Steering Committee
- COMPASS Investigators
- Bayer AG
- All participants