Effect of Rivaroxaban on Thromboembolic Events in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

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COMMANDER HF

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The study was supported by Janssen.

We thank all the patients, investigators and site staff for participating in this trial.

Background for COMMANDER HF

- Rates of readmission and death following an episode of worsening chronic heart failure (HF) remain high.[1,2]
- Therapies targeting a variety of mechanisms have thus far failed to improve outcomes following HF hospitalization.
- Activation of thrombin-related pathways may contribute to HF disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis.[3]
- However, prospective studies using warfarin in HF patients with reduced EF failed to demonstrate overall benefit.[5-7]

1. Maggioni AP, et al. *Eur J Heart Fail.* 2013.
2. Solomon SD, et al. *Circulation.* 2007.
3. Borissoff JI, et al. *Cardiovas Res.* 2009.
4. *Cokkinos DV, et al. Eur J Heart Fail. 2006*
5. Massie BM, et al. Circulation. 2009
6. Cleland JG, et al. Am Heart J. 2004
7. Homma S, et al. N Engl J Med. 2012

Background for COMMANDER HF (cont.)

- Unlike warfarin, rivaroxaban directly targets thrombin generation.

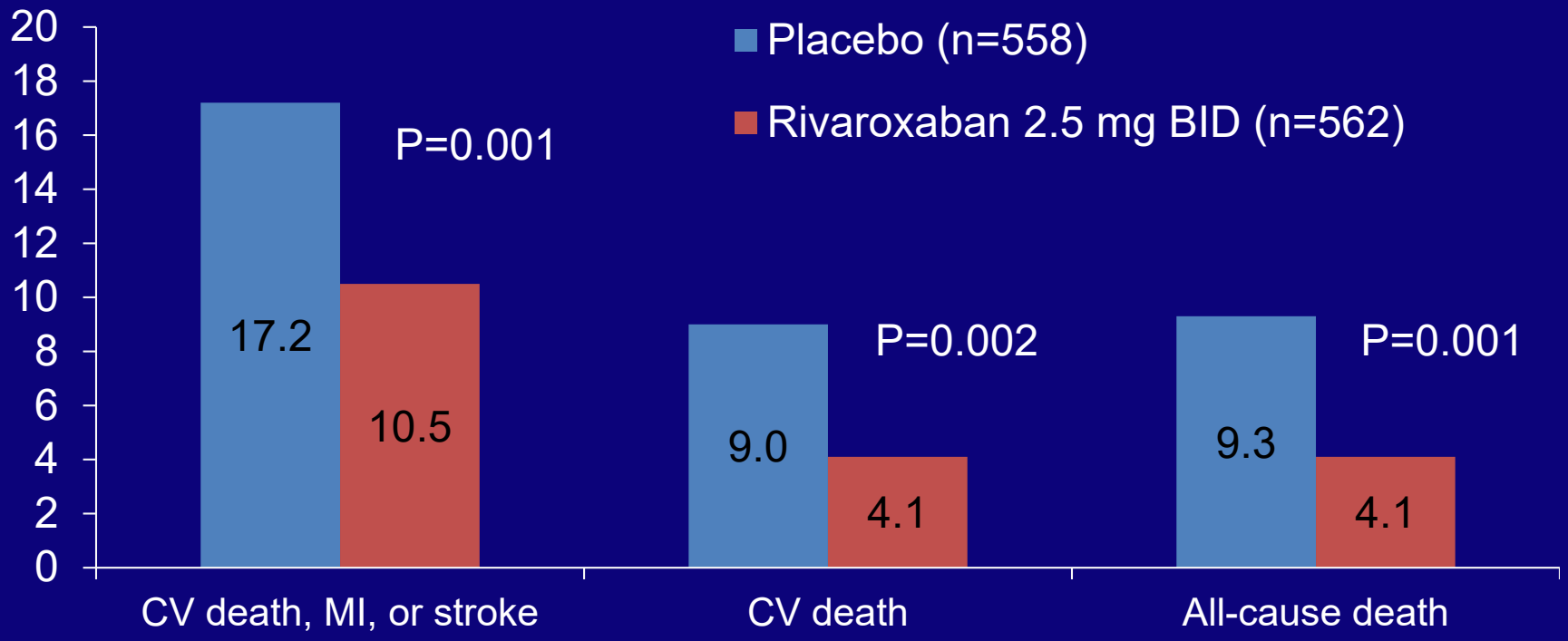
- Rivaroxaban (2.5 mg twice daily), in addition to antiplatelet agents reduced CV death, MI, and stroke in two trials:
  - ATLAS ACS 2 TIMI 51 (post-MI and unstable angina)[1]
  - COMPASS (stable CAD or PVD)[2]

- Both of these trials included patients with HF[3,4].

1. Mega JL, et al. N Engl J Med. 2012
2. Eikelboom JW, et al. N Engl J Med. 2017
3. Korjian et al Am J Cardiol. 2018 Sep 7. Published online ahead of print
4. Branch K et al. ESC HFA, Vienna

Rivaroxaban Reduces Morbidity and Mortality in Patients with Recent ACS who Had HF at Presentation[1]

From ATLAS ACS 2 TIMI 51



- Major bleeding, according to TIMI criteria, occurred in slightly fewer patients receiving rivaroxaban 2.5mg bid than placebo (0.4% vs. 0.7%)

1. Korjian S et al Am J Cardiol. 2018 Sep 7. Published online ahead of print

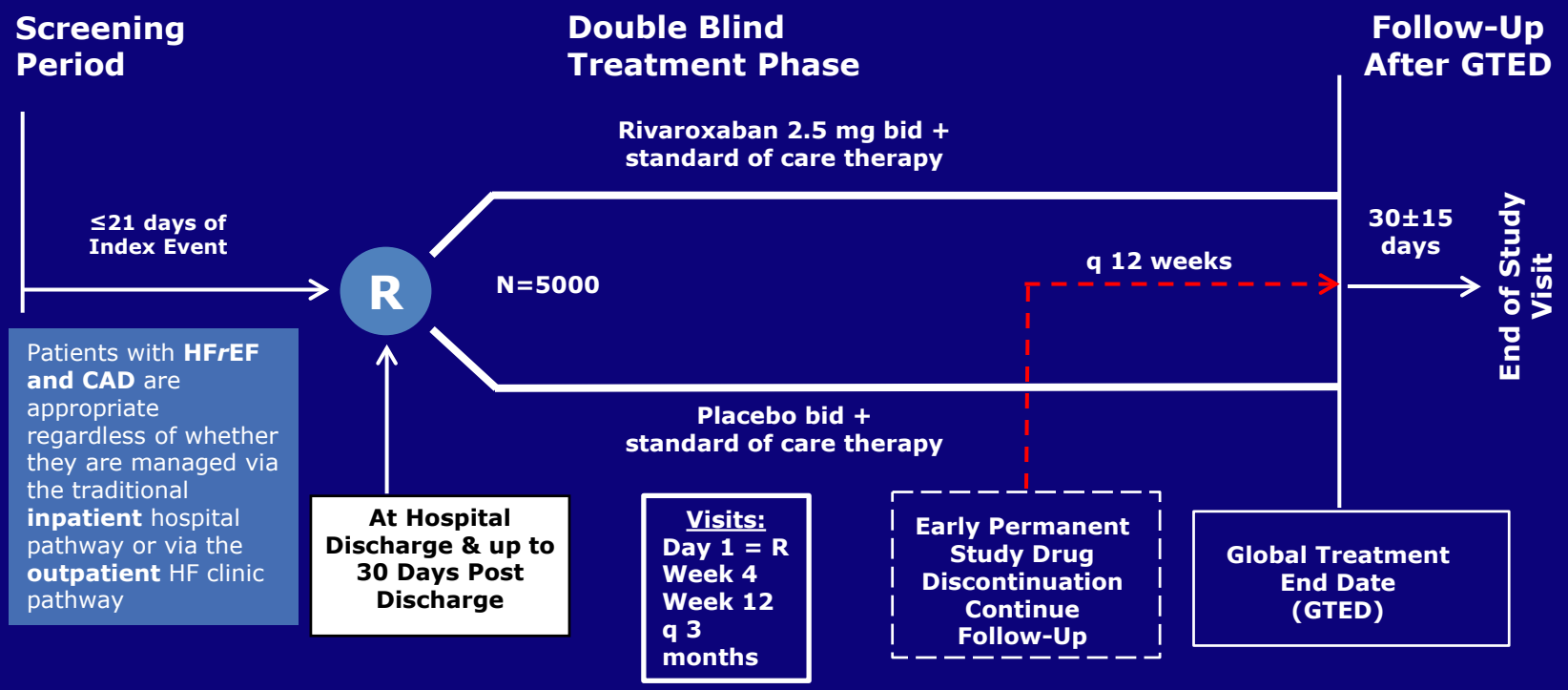
COMMANDER HF

- COMMANDER HF tested the hypothesis that, compared with placebo, rivaroxaban 2.5 mg twice daily added to background anti-platelet therapy, would reduce rates of death and CV events in patients with recent worsening of chronic HF, reduced EF, CAD, and sinus rhythm.

- The primary efficacy outcome was a composite of all-cause mortality, MI, or stroke.

- The main secondary outcome was a composite of CV death and HF hospitalization.

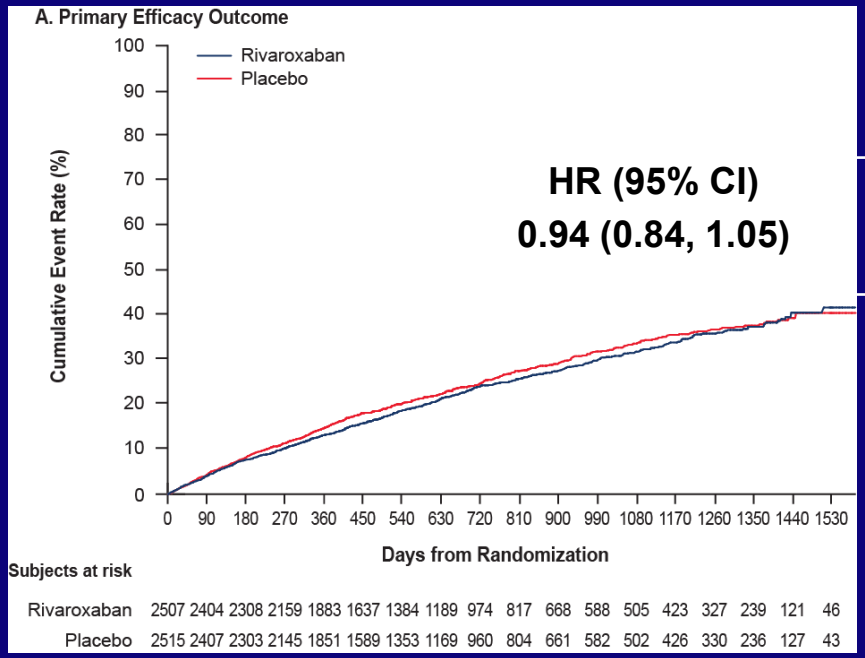
Study Design



Zannad F, et al. *Eur J Heart Fail*. 2015:17(7):735-742.

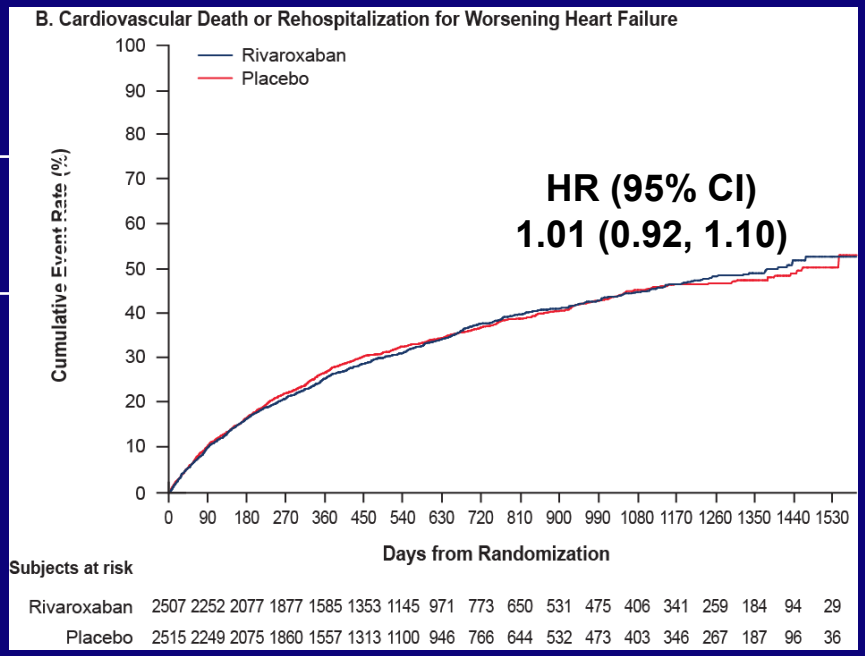
Rivaroxaban Failed to Improve Outcomes in COMMANDER HF

Primary Efficacy Outcome



All cause mortality, MI and stroke

Secondary Efficacy Outcome



CV mortality and HF hospitalization

Zannad F et al. NEJM, 2018

Primary Efficacy Outcome & Components COMMANDER HF (ITT*)

	Rivaroxaban		Placebo		Rivaroxaban vs. Placebo	
		Event Rate		Event Rate		Log-rank
Outcomes	n (%)	/ (100 pt-yr)	n (%)	/ (100 pt-yr)	HR (95% CI)	P-value
	N=2507		N=2515			
Primary efficacy (composite)	626 (25.0)	13.44	658 (26.2)	14.27	0.94 (0.84, 1.05)	0.27
All-cause mortality	546 (21.8)	11.41	556 (22.1)	11.63	0.98 (0.87, 1.10)	-
MI	98 (3.9)	2.08	118 (4.7)	2.52	0.83 (0.63, 1.08)	-
Stroke	51 (2.0)	1.08	76 (3.0)	1.62	0.66 (0.47, 0.95)	-

- Primary outcome composite driven by mortality, a large proportion of which was due to worsening HF

* ITT, Intent to Treat

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- Primary outcome composite driven by mortality, a large proportion of which were due to worsening HF
- Testing for homogeneity between the 3 components of the primary outcome suggested HRs vary (p=0.06) and there were numerical advantages of rivaroxaban compared to placebo for MI and stroke, both of which are classical thromboembolic events.

* ITT, Intent to Treat

Rationale for Analysis of Thromboembolic Events

- These findings suggest that in the high risk HF population enrolled in COMMANDER HF:

  -the primary composite was driven by events that were not influenced by rivaroxaban 2.5 mg twice daily.
  -an effect of rivaroxaban on thromboembolic events might have been masked by the preponderance of events related to worsening heart failure.

- We postulated that low dose rivaroxaban would be superior to placebo in reducing the risk of thromboembolic events in patients enrolled in COMMANDER HF.

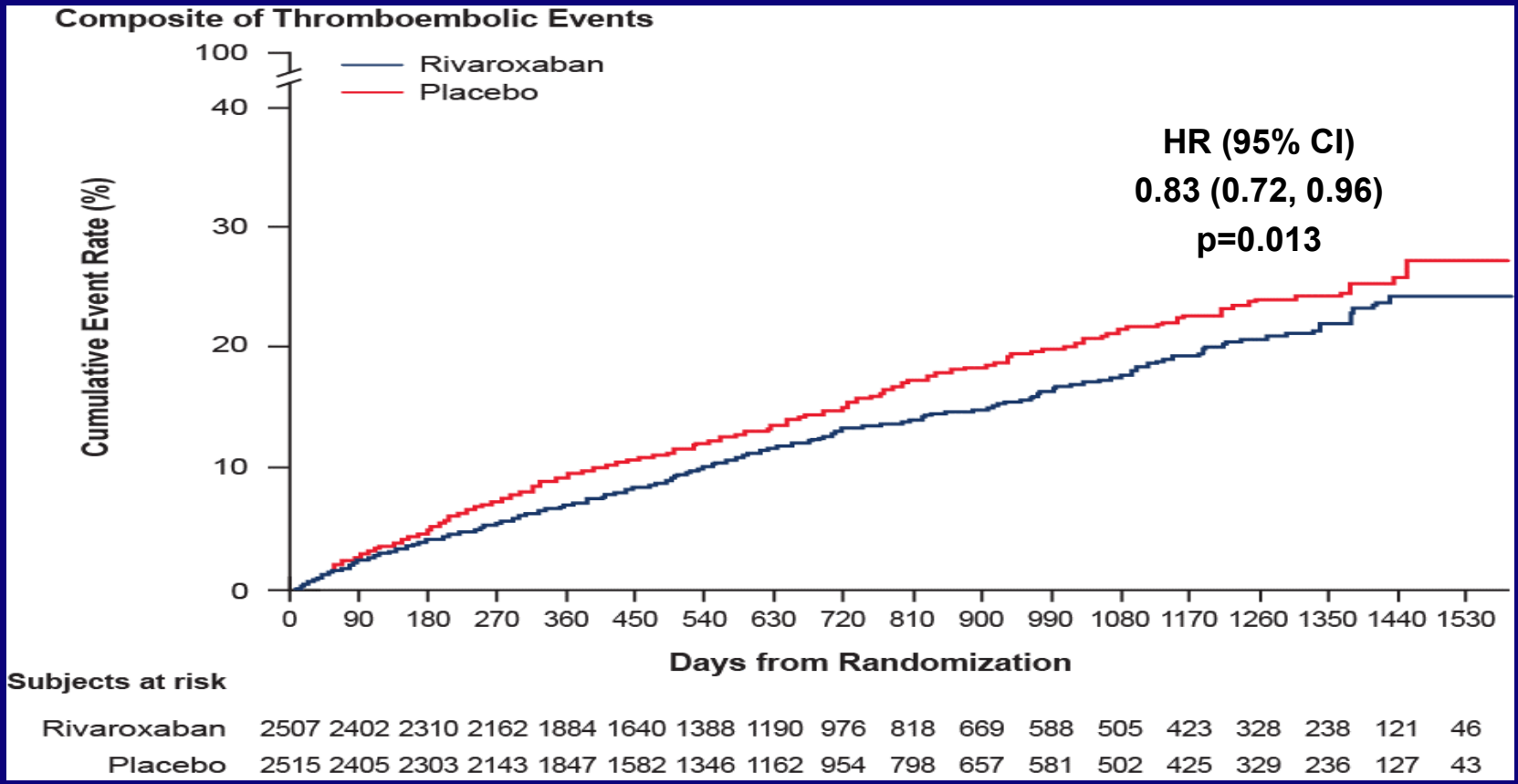
Composite Thromboembolic Event End-point

- The composite endpoint for this *post-hoc* analysis included:

  - MI
  - ischemic stroke
  - sudden/unwitnessed death
  - pulmonary embolism or symptomatic deep venous thrombosis

- All events included in this composite had been pre-defined in the study protocol and were required to fulfill specific criteria which were verified by the sponsor site team.

KM Estimates for the *Post Hoc* Thromboembolic Event Composite



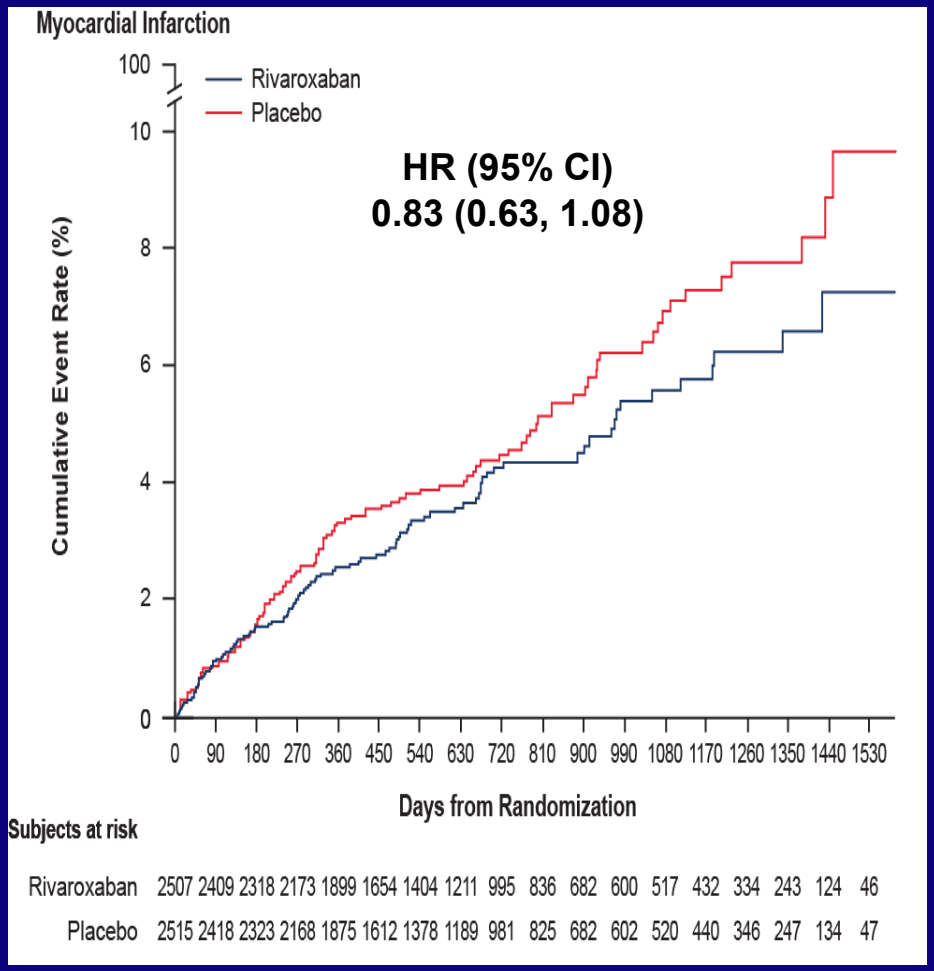
Overall, 14.3% of patients experienced a thromboembolic event over a median follow-up of 19.6 months with the event rate of 7.0 and 8.5 per 100 patient years in the rivaroxaban and placebo groups, respectively.

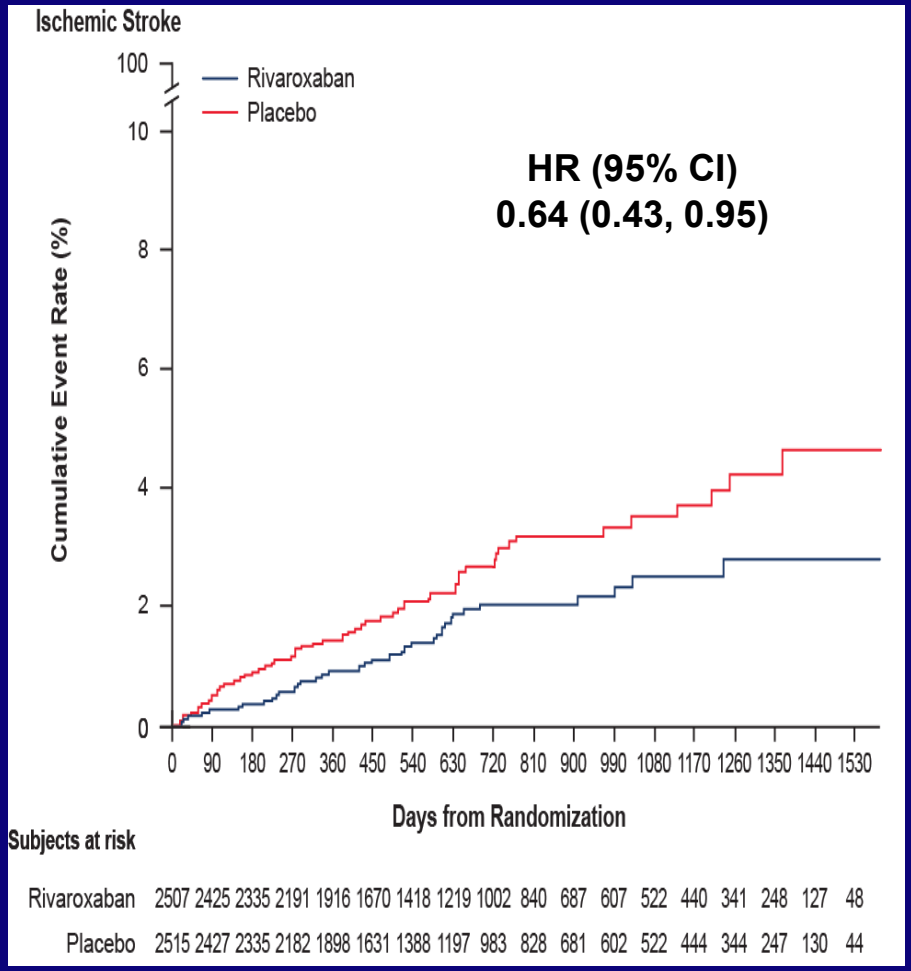
Results of the Thromboembolic Event Analysis*

	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo	
Outcomes	**n (%)**	**Event Rate/ 100 Patient-yr**	**n (%)**	**Event Rate/ 100 Patient-yr**	**Hazard Ratio (95% CI)**	**P Value**
Composite of Thromboembolic Events	**328 (13.1)**	**7.0**	**390 (15.5)**	**8.5**	**0.83 (0.72,0.96)**	**0.013**
MI	98 (3.9)	2.1	118 (4.7)	2.5	0.83 (0.63,1.08)	
Ischemic Stroke	41 (1.6)	0.9	63 (2.5)	1.3	0.64 (0.43,0.95)	
Sudden/Unwitnessed Death	190 (7.6)	4.0	215 (8.5)	4.5	0.88 (0.73,1.07)	
Symptomatic PE	11 (0.4)	0.2	9 (0.4)	0.2	1.24 (0.51,2.99)	
Symptomatic DVT	5 (0.2)	0.1	7 (0.3)	0.1	0.71 (0.23,2.24)	

*Time to First Occurrence of an Outcome Event

KM Estimates for MI and Stroke





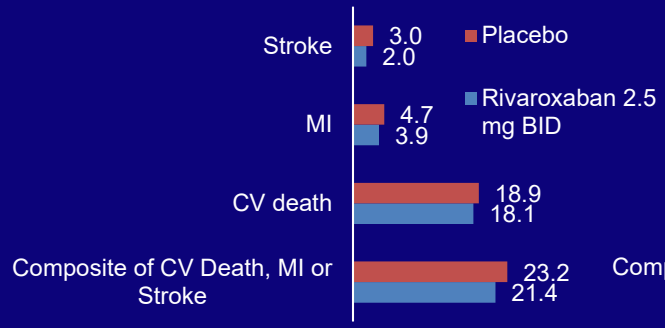
Comparing HF Patient Outcomes Between Rivaroxaban Trials

COMMANDER HF[1]
Post HF hospitalization

ATLAS (HF Subgroup)[2]
History of CHF at Randomization

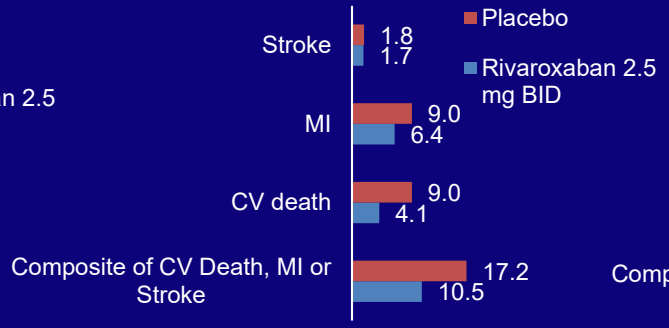
COMPASS[3]
Chronic Stable HF subgroup

Incidence rate



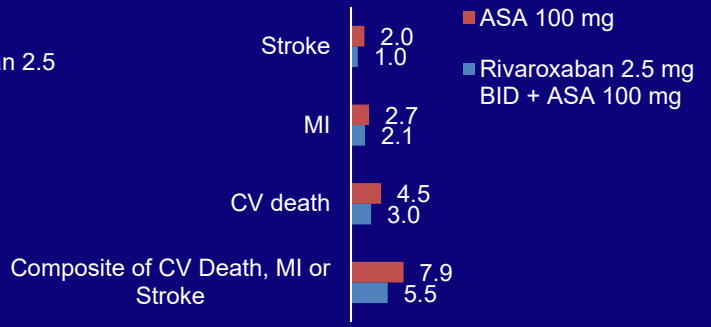
ITT up to GTED

* 34.8% of patients received DAPT at baseline, while 93.1% received ASA alone at baseline



mITT

* 86.7% of patients received DAPT at baseline, while 13.3% received ASA alone at baseline



ITT

COMMANDER HF enrolled high risk HF patients after recent worsening and HF deaths, rather than deaths mediated by atherothrombotic events, likely contributed to a substantial proportion of all deaths.

[1] **Zannad F et al., N Engl J Med 2018;** [2] Korjian S et al Am J Cardiol. 2018 Sep 7. Published online ahead of print; [3] **Branch KR. COMPASS: low-dose rivaroxaban plus aspirin may benefit patients with chronic CAD, PAD, HF. Presented at Late-breaking Trial IV: Registries, Heart Failure 2018 and World Congress on Acute Heart Failure, Vienna, May 26-29, 2018**

Limitations

- Although all of the components of the thrombotic composite had been pre-defined, this was a *post hoc* analysis.
- Endpoints were not adjudicated by an independent events committee.
- COMMANDER HF enrolled patients with reduced EF and the effect of rivaroxaban on thromboembolic events in a HFpEF population is unknown.

Summary

- Thromboembolic events, while not the major source of morbidity and mortality in COMMANDER HF, occurred commonly during follow-up.

- In this *post-hoc* analysis, rivaroxaban reduced risk of thromboembolic events compared to placebo.

Conclusion

- The findings of this *post hoc* analysis support the possibility that low-dose rivaroxaban may reduce the risk of thromboembolic events in HF patients.

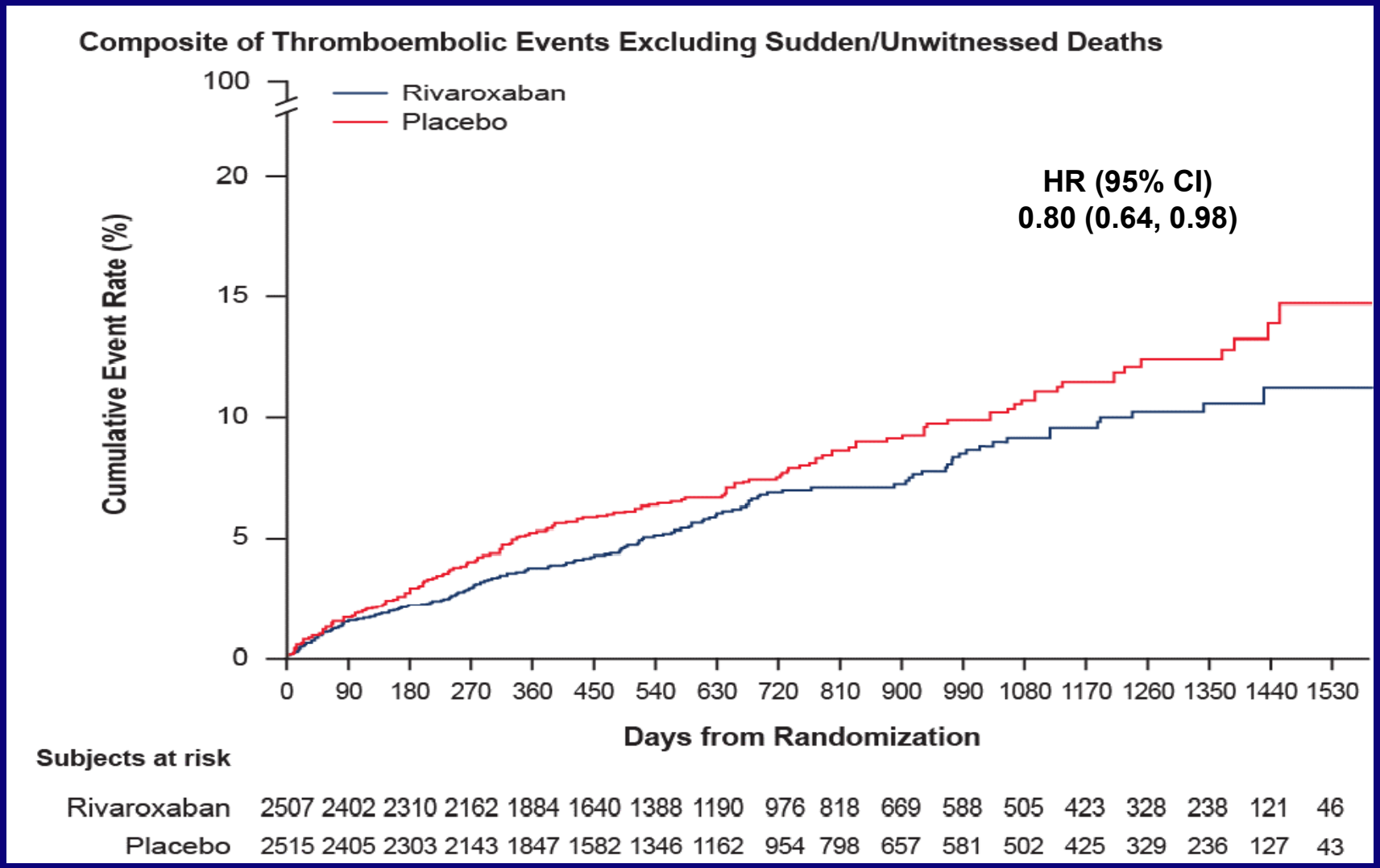
- However, confirmation of these results by a prospective trial is required in order to establish a role for low dose rivaroxaban in treating HF patients.

Back up Slides

Principal Safety Outcome (Safety, On-Treatment)

	Rivaroxaban		Placebo		Rivaroxaban vs. Placebo	P value
	N=2499		N=2509			
Principal safety (composite)	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43, 1.49)	0.484
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41, 2.59)	0.951
Bleeding in critical space with potential for permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33, 1.34)	0.253
ISTH major bleeding	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18, 2.39)	0.003
ISTH: HGB decreases ≥ 2g/dL	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20, 2.91)	0.005
ISTH: transfusions ≥ 2 Units	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98, 3.12)	0.058
ISTH: critical bleeding sites	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63, 1.97)	0.699
ISTH: fatal outcome	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12, 1.72)	0.228
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89, 1.90)	0.170

KM Estimates for the Thromboembolic Event Composite Excluding Sudden/Unwitnessed Deaths



COMMANDER-HF Patient Baseline Characteristics

Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)	Total (N=5022)
Age — yr	66.51±10.07	66.28±10.27	66.40±10.17
Female sex — no. (%)	551 (22.0)	599 (23.8)	1150 (22.9)
White Race — no. (%)	2063 (82.3)	2065 (82.1)	4128 (82.2)
Medical history — no. (%)			
Myocardial infarction	1911 (76.2)	1892 (75.2)	3803 (75.7)
Stroke	208 (8.3)	245 (9.7)	453 (9.0)
Hypertension	1897 (75.7)	1886 (75.0)	3783 (75.3)
Diabetes	1024 (40.8)	1028 (40.9)	2052 (40.9)
Clinical features of heart failure			
BNP (pg/mL)	702.0	695.5	696
NT-proBNP(pg/mL)	2840.0	2900.0	2849.5
D-dimer (ug/L)	360	360	360
Median Ejection fraction (IQR) (%)	35 (28-38)	34 (27-38)	34 (28-38)
New York Heart Association classification — no. (%)			
I	80 (3.2)	69 (2.7)	149 (3.0)
II	1122 (44.8)	1096 (43.6)	2218 (44.2)
III	1208 (48.2)	1254 (49.9)	2462 (49.0)
IV	96 (3.8)	96 (3.8)	192 (3.8)
Therapies at baseline — no. (%)			
Aspirin	2329 (92.9)	2346 (93.3)	4675 (93.1)
Thienopyridine	1043 (41.6)	972 (38.6)	2015 (40.1)
Dual antiplatelet therapy	907 (36.2)	839 (33.4)	1746 (34.8)
Cardiac devices	345 (13.8)	316 (12.6)	661 (13.2)

Time to First Occurrence of an Outcome Event

	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo	
Outcomes	n (%)	Event Rate/ 100 Patient-yr	n (%)	Event Rate/ 100 Patient-yr	Hazard Ratio (95% CI)	P Value
COMMANDER HF Primary Endpoint (Composite of ACM/MI/Stroke)	626 (25.0)	13.4	658 (26.2)	14.3	0.94 (0.84, 1.05)	0.27
ACM	546 (21.8)	11.4	556 (22.1)	11.6	0.98 (0.87,1.10)	
MI	98 (3.9)	2.1	118 (4.7)	2.5	0.83 (0.63,1.08)	
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Composite of Non-Thromboembolic Events	363 (14.5)	7.6	346 (13.8)	7.2	1.05 (0.91,1.22)	0.51
Death Other Than CV Death	93 (3.7)	1.9	80 (3.2)	1.7	1.16 (0.86,1.57)	
CV Death Other Than Sudden/ Unwitnessed Death	263 (10.5)	5.5	261 (10.4)	5.5	1.01 (0.85,1.19)	
Non-Ischemic Stroke	11 (0.4)	0.2	13 (0.5)	0.3	0.85 (0.38,1.90)	
Composite of CV Death, MI or Stroke	537 (21.4)	11.5	584 (23.2)	12.7	0.91 (0.81,1.02)	0.11
CV Death	453 (18.1)	9.5	476 (18.9)	10.0	0.95 (0.84,1.08)	
MI	98 (3.9)	2.1	118 (4.7)	2.5	0.83 (0.63,1.08)	
Stroke	51 (2.0)	1.1	76 (3.0)	1.6	0.66 (0.47,0.95)	