Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

Faiez Zannad

Université de Lorraine, Inserm U1116 and CIC 1433, FCRIN INI-CRCT, CHRU de Nancy, Vandoeuvre les Nancy, France

ESC Congress Munich 2018

COMMANDER HF

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Steering committee Janssen and Bayer)

Oversight Committees

Steering Committee Members	Independent Data Monitoring Committee Members
Faiez Zannad, Barry Greenberg, Co-Chairs Stefan D. Anker, William M. Byra, John G.F. Cleland, Mihai Gheorghiade (deceased), Carolyn S.P. Lam, Mandeep R. Mehra, James Neaton, Dirk J. van Veldhuisen	W. Douglas Weaver, Henry J. Dargie, Marc Klapholz, Bertram Pitt, Stuart J. Pocock, Yoshihiko Seino

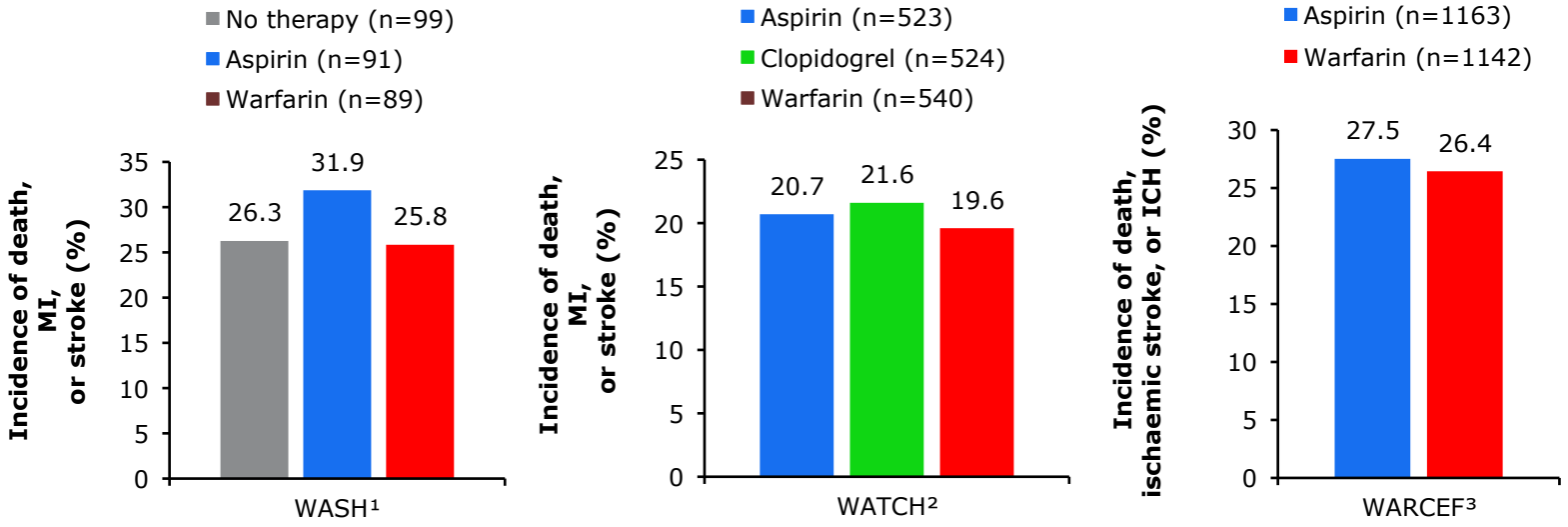
Background and Rationale (1/4)

- Despite the remarkable progress in treating chronic HF*r*EF, following an episode of worsening chronic heart failure, rates of readmission and death remain high.[1,2]
- Trials in worsening HF of a large number of therapies targeting a variety of mechanisms have failed so far to improve outcome.
- Activation of thrombin-related pathways may contribute to disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis.[3]

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.

Background and Rationale (2/4)

Warfarin has not improved outcomes for patients with HF*r*EF who are in sinus rhythm, and is associated with an increase in bleeding complications.



1. Cleland JGF, et al. *Am Heart J.* 2004.
2. Massie BM, et al. *Circulation.* 2009
3. Homma S *et al*, *N Engl J Med.* 2012.
4. Zannad F, et al. *Eur J Heart Fail.* 2015;17:735–742.

Background and Rationale (3/4)

- Unlike warfarin, rivaroxaban directly targets thrombin generation
- In doses of 10 to 20 mg daily, approved for
  - Prevention and treatment of venous thromboembolism, and
  - the prevention of stroke or systemic embolism in patients with AF.
- Lower doses of rivaroxaban (2.5 mg twice daily), in combination with antiplatelet agents, have been found to reduce cardiovascular mortality, MI, and stroke
  - in patients with acute coronary syndromes (ATLAS ACS TIMI 51)
  - or stable coronary artery disease (COMPASS).

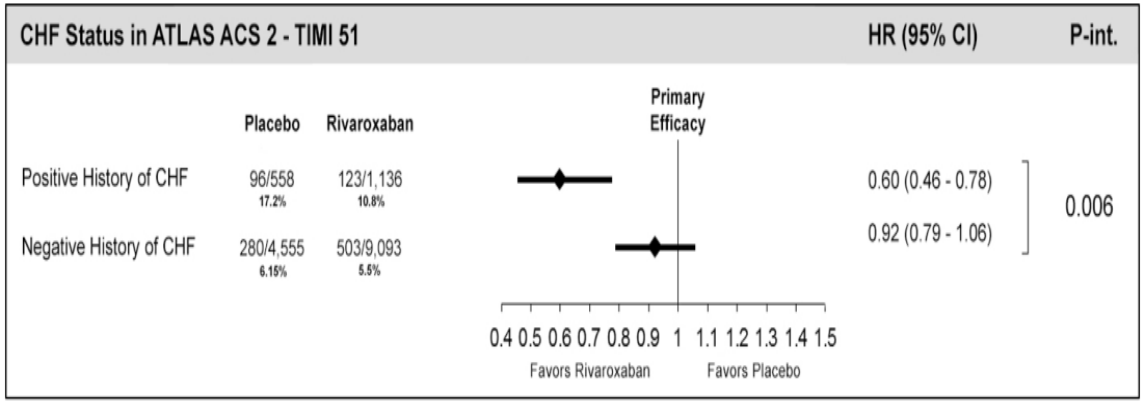
Background and Rationale (4/4)

Rivaroxaban significantly reduced morbidity and mortality in patients with history of HF and

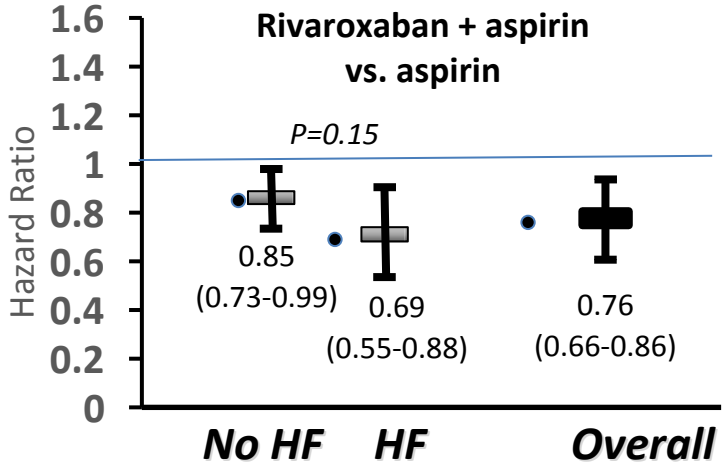
Recent ACS
ATLAS ACS 2-TIMI 51

Figure 1.

Primary Efficacy Endpoint among Subjects with History of CHF vs. Patient Without Prior History of CHF



Chronic CAD
COMPASS



Korjian S et al. AJC in press

Burch K et al. ESC HFA, Vienna

Objectives

The COMMANDER HF trial was designed to test the hypothesis that, compared with placebo, rivaroxaban 2.5 mg twice daily added to background antiplatelet therapy could reduce rates of death and cardiovascular events in patients with recent worsening of chronic HF, reduced ejection fraction, CAD, and no AF.

Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Chronic HF (>3mths) with reduced LVEF (≤40%)	• Bleeding risk, AF, acute MI
• Within 21 days after an episode of hospitalization for worsening HF	• Planned cardiac surgery within 28 days (eg, PCIs and EP devices)
• Elevated plasma BNP (≥200 pg/mL) or NT-proBNP (≥800 pg/mL) during the index event	• History of severe valvular disease, chronic episodes of ventricular tachycardia, severe peptic ulcer disease, or HIV
• CAD (Hx MI, Revasc, angiogram, ECG+Echo)	• eGFR <20 mL/min
• Receiving appropriate guidelines medical treatment†	• Prior stroke (within 90 days)
• No anticoagulation	• Anemia (Hb<8 g/dL) or severe thrombocytopenia (platelets <50,000/μL)

†The dose of ASA was to be 100 mg or less per day, unless not clinically appropriate.
Dual antiplatelet therapy (i.e., ticagrelor, clopidogrel, ticlopidine, prasugrel) was allowed where indicated

Study Outcomes

Primary Efficacy Outcome

- Composite of all-cause mortality, MI, or stroke following an index event

Principal Safety Outcome

- Composite of fatal bleeding, or bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability

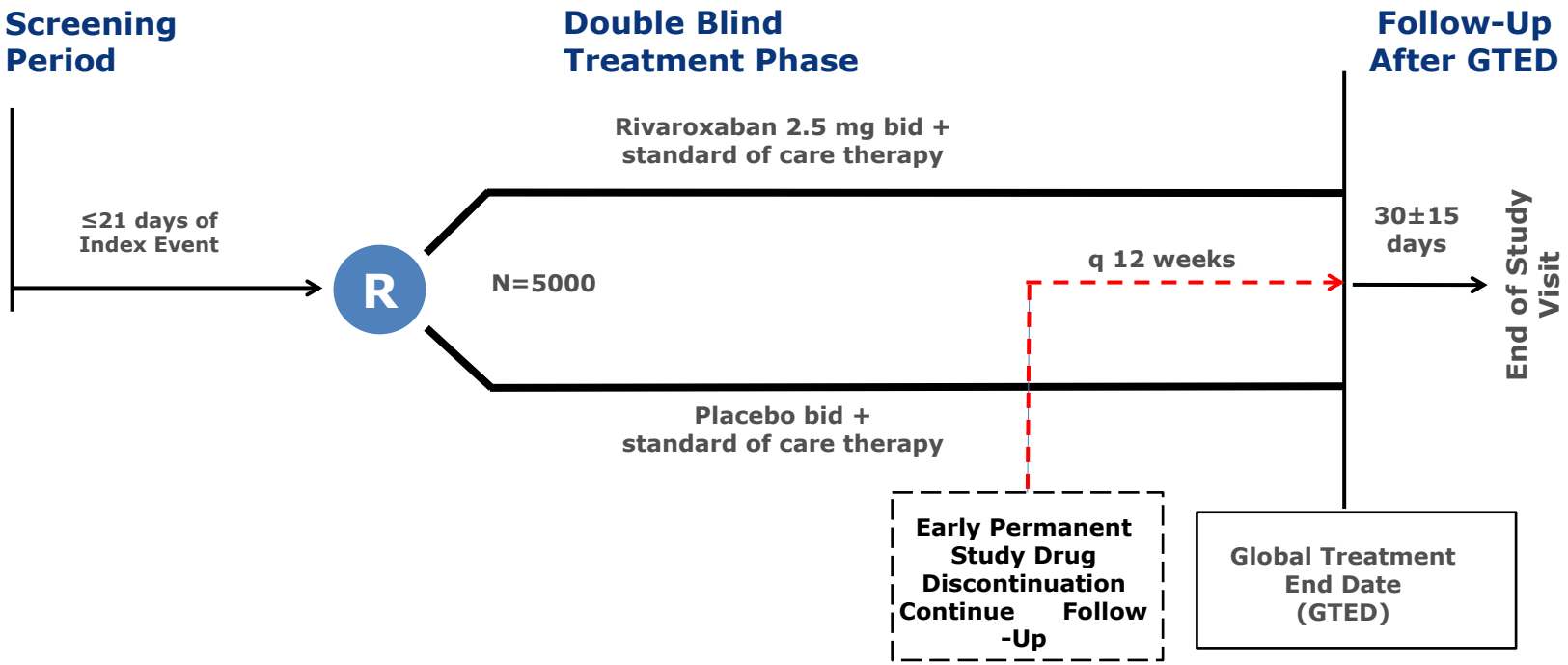
Secondary Efficacy Outcomes

- Composite of CV mortality or rehospitalization for worsening of HF
- CV mortality
- Rehospitalization for worsening of HF
- Rehospitalization for CV events

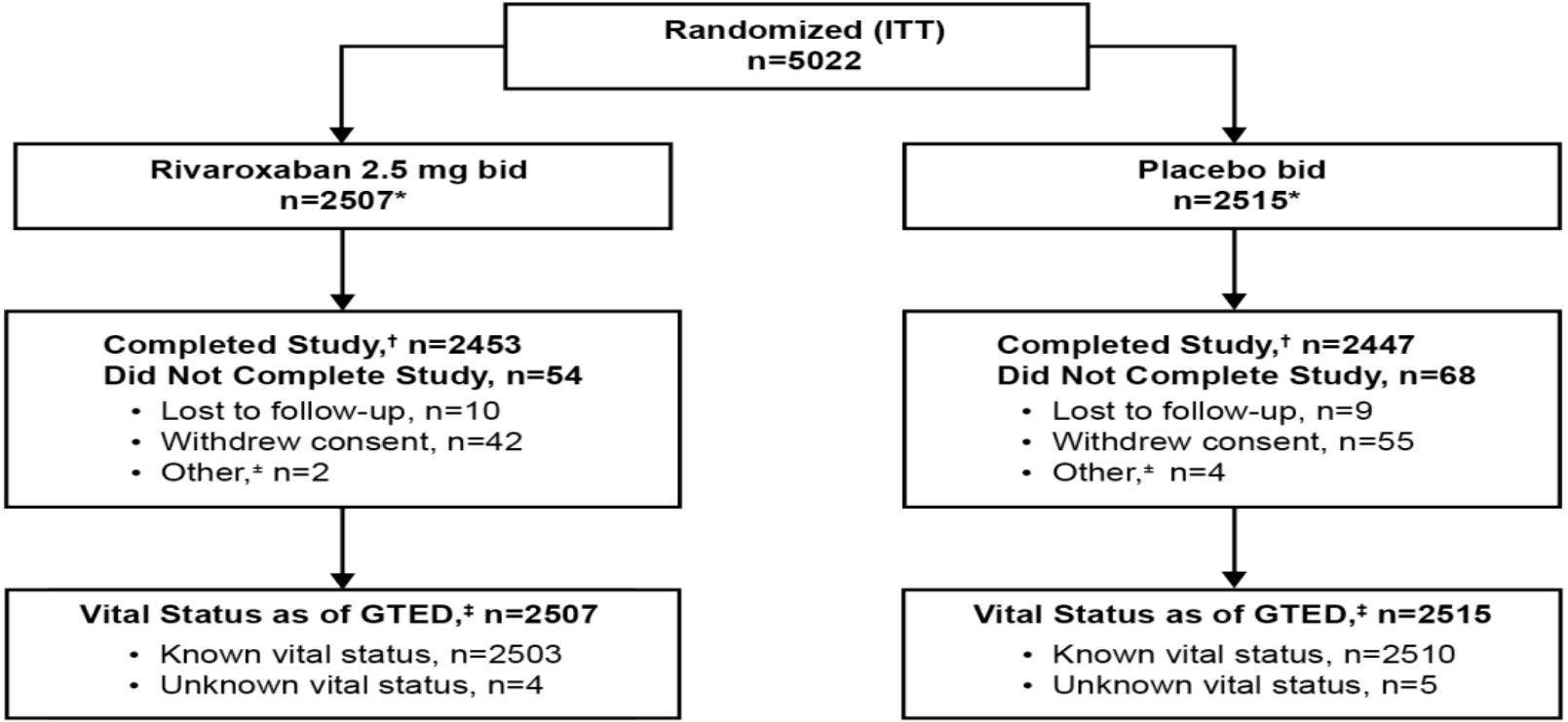
Other Safety Outcomes

- Bleeding events requiring hospitalization
- Major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria

Study Design



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



MEDIAN FOLLOW UP TIME 21.1 MONTHS

*Three patients, 1 in the rivaroxaban 2.5 mg bid group and 2 in the placebo group, were randomized twice; only the first randomization was counted.

†Completed study: patients who died or were followed according to the visit schedule until the End of Study Visit.

‡Other category primarily includes patients at sites in Ukraine and Turkey affected by local military action.

‡Vital status was collected as of the GTED (March 5, 2018), which included all sources allowed by local regulations.

Abbreviation: GTED = Global Treatment End Date.

Key Baseline Characteristics (ITT)

Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)
Age, yr	66.5±10.1	66.3±10.3
Female sex, n (%)	551 (22.0)	599 (23.8)
Race, n (%)		
White	2063 (82.3)	2065 (82.1)
Black or African American	29 (1.2)	36 (1.4)
Asian	362 (14.4)	365 (14.5)
Other	53 (2.1)	49 (1.9)
Region, n (%)		
Eastern Europe	1610 (64.2)	1614 (64.2)
North America	74 (3.0)	75 (3.0)
Asia Pacific	367 (14.6)	366 (14.6)
Latin America	229 (9.1)	229 (9.1)
Western Europe and South Africa	227 (9.1)	231 (9.2)
Body mass index (kg/m^2)	27.6±5.1	27.8±5.3
eGFR ($mL/min/1.73\ m^2$), n (%)		
<30	81 (3.2)	82 (3.3)
30 to <60	884 (35.3)	898 (35.7)
60 to <90	1101 (43.9)	1137 (45.2)
≥90	441 (17.6)	398 (15.8)

Key Baseline Characteristics (ITT) (cont.)

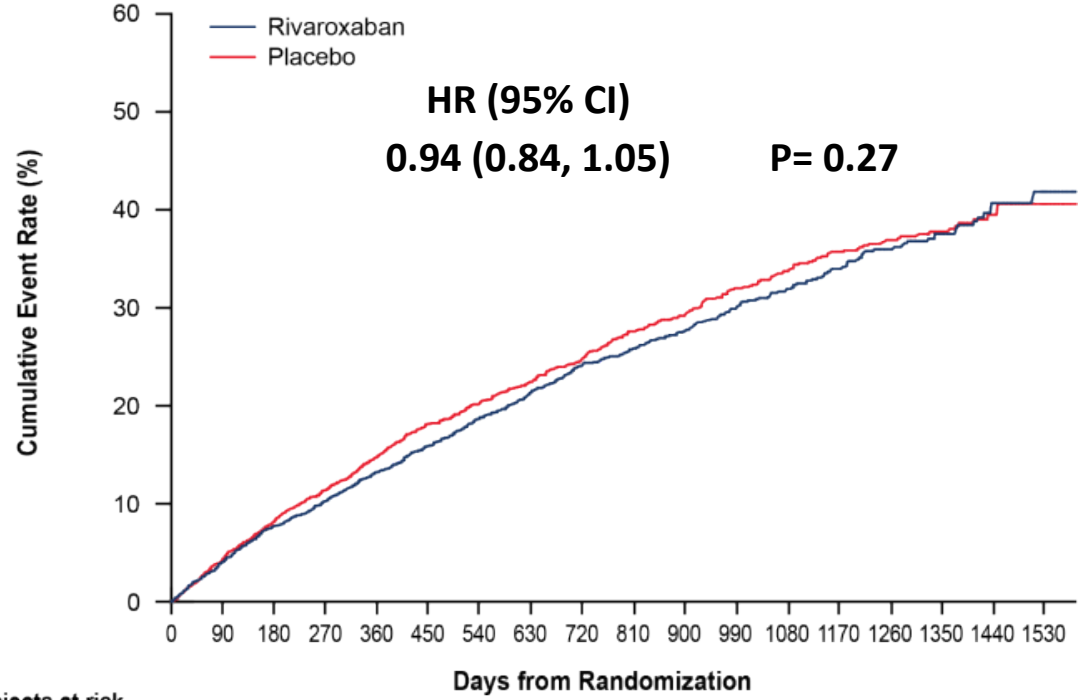
Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)
Clinical features of HF		
BNP (pg/mL) (IQR)	702.0 (403.4-1237.0)	695.5 (380.0-1266.3)
NT-proBNP (pg/mL) (IQR)	2840.0 (1537.0-6394.0)	2900.0 (1520.0-6270.5)
D-dimer (ug/L) (IQR)	360 (215-680)	360 (215-650)
Ejection fraction (IQR) (%)	35 (28-38)	34 (27-38)
New York Heart Association classification, n (%)		
I	80 (3.2)	69 (2.7)
II	1122 (44.8)	1096 (43.6)
III	1208 (48.2)	1254 (49.9)
IV	96 (3.8)	96 (3.8)
Medical history, n (%)		
MI	1911 (76.2)	1892 (75.2)
Stroke	208 (8.3)	245 (9.7)
Diabetes	1024 (40.8)	1028 (40.9)
Hypertension	1897 (75.7)	1886 (75.0)

Baseline Therapies (ITT)

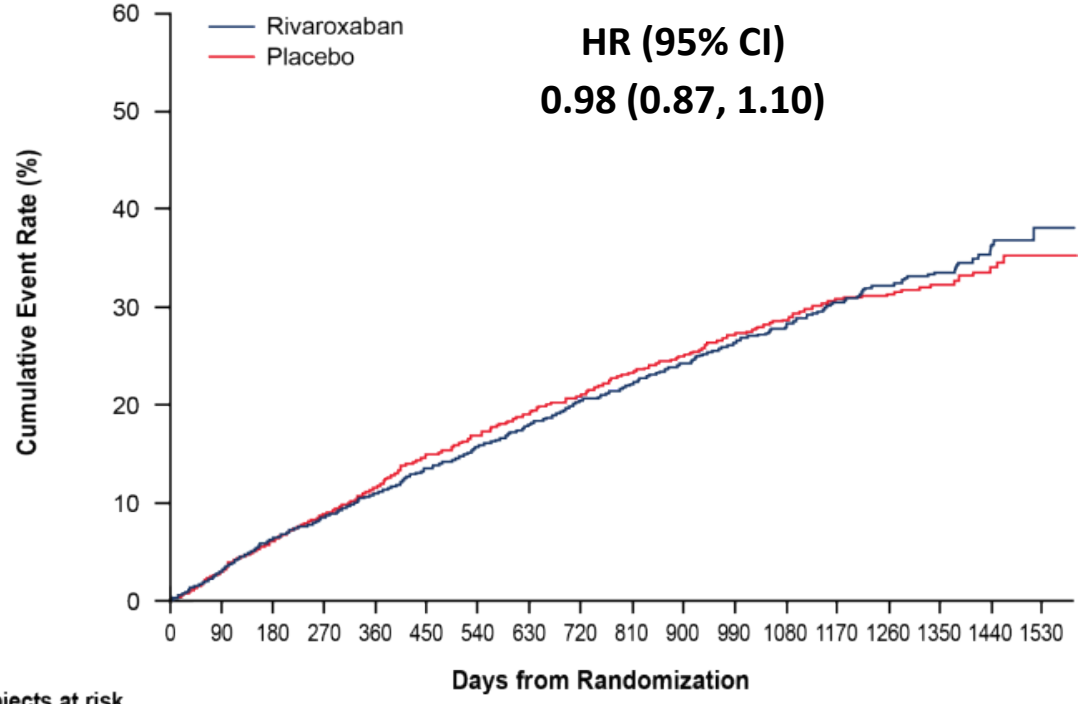
	Rivaroxaban (N=2507)	Placebo (N=2515)
Diuretic use, n (%)	2495 (99.5)	2504 (99.6)
Angiotensin-converting enzyme inhibitor use, n (%)	1813 (72.3)	1779 (70.7)
Angiotensin receptor blocker use, n (%)	544 (21.7)	541 (21.5)
Angiotensin receptor-neprilysin inhibitor use, n (%)	18 (0.7)	23 (0.9)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, n (%)	2346 (93.6)	2314 (92.0)
Nitrate use, n (%)	528 (21.1)	480 (19.1)
Hydralazine use, n (%)	24 (1.0)	31 (1.2)
Beta blocker use, n (%)	2300 (91.7)	2342 (93.1)
Mineralocorticoid Receptor Antagonist use, n (%)	1918 (76.5)	1922 (76.4)
Digoxin use, n (%)	223 (8.9)	210 (8.3)
Aspirin use, n (%)	2329 (92.9)	2346 (93.3)
Thienopyridine use, n (%)	1043 (41.6)	972 (38.6)
Aspirin vs. dual antiplatelet use, n (%)		
Aspirin alone	1422 (56.7)	1507 (59.9)
Thienopyridine alone	136 (5.4)	133 (5.3)
Dual antiplatelet therapy	907 (36.2)	839 (33.4)
None	42 (1.7)	36 (1.4)
Cardiac Devices	345 (13.8)	316 (12.6)

Results

Primary Efficacy Outcome
(ITT, All-cause mortality, MI, or stroke)



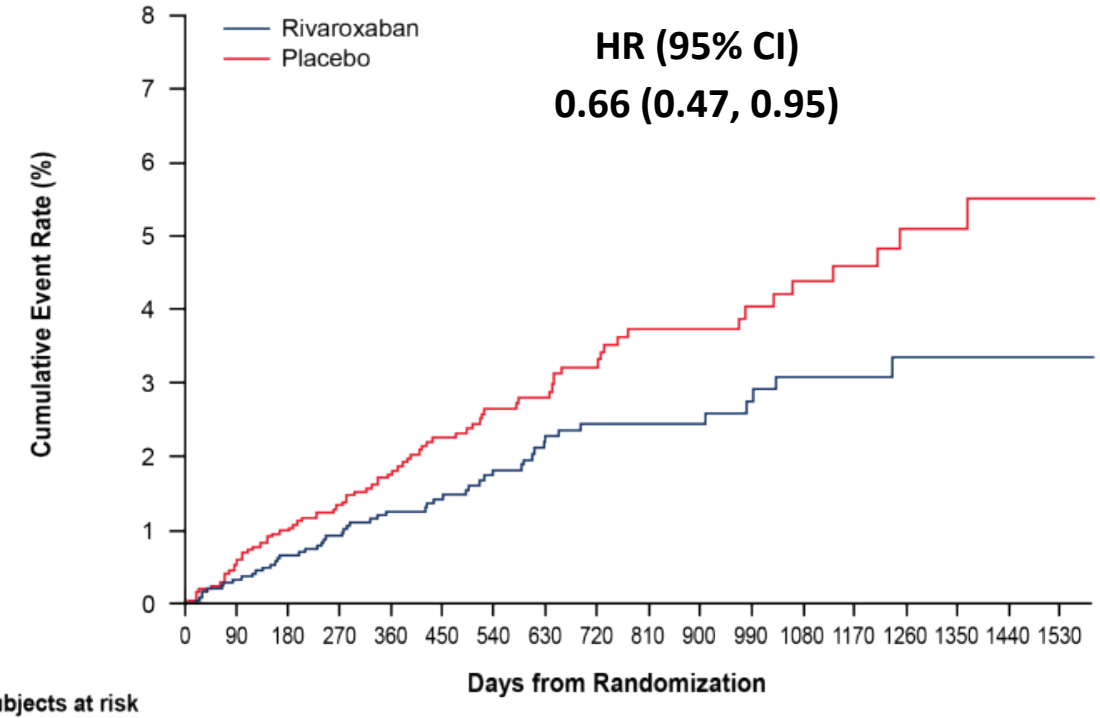
All-Cause Mortality (ITT)



Subjects at risk

Rivaroxaban	2507	2429	2342	2200	1928	1683	1433	1236	1018	854	698	616	532	447	346	252	130	48
Placebo	2515	2437	2353	2204	1919	1653	1415	1219	1007	850	703	622	539	457	359	257	137	48

Stroke (ITT)



Subjects at risk

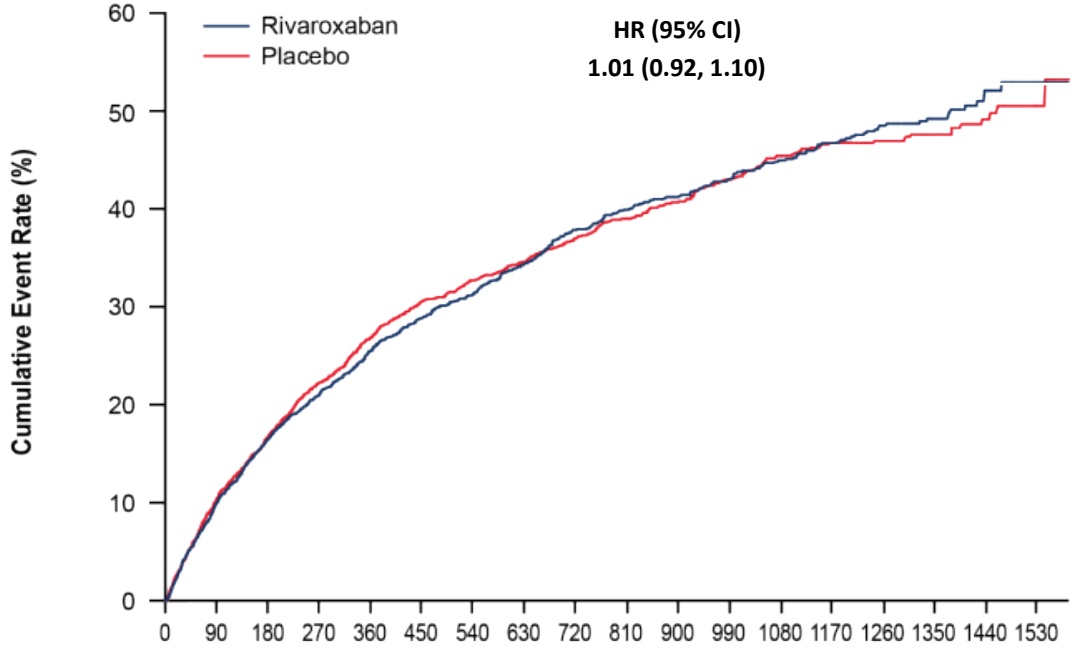
Rivaroxaban	2507	2424	2332	2186	1912	1666	1413	1214	997	835	684	604	520	438	339	248	127	48
Placebo	2515	2426	2333	2181	1895	1629	1388	1197	983	828	681	601	520	443	343	246	130	44

Primary Efficacy Outcome & Components (ITT)

	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo	
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)	Log-rank P value
Primary efficacy (all-cause mortality, MI, or stroke)	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)	-

Note: HR (95% CI): Hazard ratios (95% confidence interval) are from a Cox proportional hazards model stratified by region with treatment assignment as the only effect.

Secondary Efficacy Outcome (CV Death or Rehospitalization for Worsening of HF) (ITT)



Subjects at risk

Rivaroxaban	2507	2252	2077	1877	1585	1353	1145	971	773	650	531	475	406	341	259	184	94	29
Placebo	2515	2249	2075	1860	1557	1313	1100	946	766	644	532	473	403	346	267	187	96	36

Secondary and Exploratory Efficacy Outcomes (ITT)

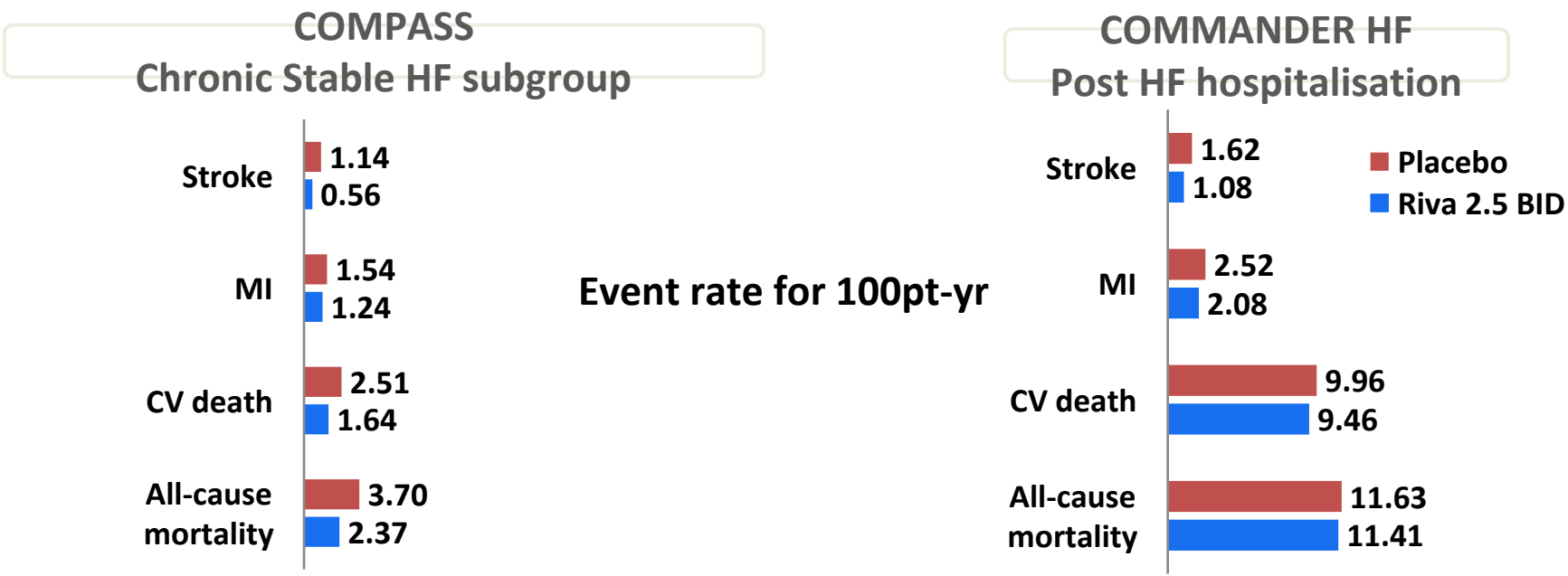
	Rivaroxaban		Placebo		Rivaroxaban vs. Placebo
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)
CV death or RHHF	932 (37.2)	23.32	929 (36.9)	23.46	0.99 (0.91, 1.09)
CV death	453 (18.1)	9.46	476 (18.9)	9.96	0.95 (0.84, 1.08)
RHHF	689 (27.5)	17.24	691 (27.5)	17.45	0.98 (0.89, 1.09)
RHCV	543 (21.7)	13.30	572 (22.7)	14.04	0.95 (0.84, 1.07)
All-cause mortality or RHHF (composite)	993 (39.6)	24.84	973 (38.7)	24.57	1.01 (0.92, 1.10)
Symptomatic deep vein thrombosis	5 (0.2)	0.10	7 (0.3)	0.15	0.71 (0.23, 2.24)
Symptomatic pulmonary embolism	11 (0.4)	0.23	9 (0.4)	0.19	1.23 (0.51, 2.96)

Safety Outcome

	Rivaroxaban (N=2499)		Placebo (N=2509)		Rivaroxaban vs. Placebo	P value
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)	Log-rank P value
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

Conclusion (1/2)

In patients with recent worsening of chronic HF and reduced ejection fraction who also have underlying CAD and are not in AF, low-dose rivaroxaban, when added to guideline-based therapy, does not improve the composite of all-cause mortality, MI, or stroke, nor does it favorably influence HF rehospitalization



- COMMANDER HF enrolled HF patients at high risk, after recent HF hospitalization.
- It is likely that in this specific population, HF deaths, rather than deaths mediated by atherothrombotic events, contributed to a substantial proportion of all deaths.

1. Zannad F et al., N Engl J Med (in press); 2. Branch K, presented at Heart Failure 2018, abstract 1591, data on file with permission from author.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

Faiez Zannad, M.D., Ph.D., Stefan D. Anker, M.D., Ph.D., William M. Byra, M.D., John G.F. Cleland, M.D., Min Fu, Ph.D., Mihai Gheorghiade, M.D.,* Carolyn S.P. Lam, M.D., Ph.D., Mandeep R. Mehra, M.D., James D. Neaton, Ph.D., Christopher C. Nessel, M.D., Theodore E. Spiro, M.D., Dirk J. van Veldhuisen, M.D., Ph.D., and Barry Greenberg, M.D., for the COMMANDER HF Investigators†

The study was supported by Janssen.

We thank all the patients, investigators, and site staff for participating in this trial and the entire Janssen Cross Functional Trial Team for their contributions to the statistical monitoring and analyses and the protocol development, safety monitoring, data management, and operational implementation of the trial.

Back Up Slides

Evidence of Coronary Artery Disease at Baseline (ITT)

	Rivaroxaban N= 2507	Placebo N= 2515	Total N= 5022
Evidence of Coronary Artery Disease	**2505 (99.9)**	**2514 (>99.9)**	**5019 (99.9)**
Angiography (At least 50% ≥1 Artery), n (%)	1472 (58.7)	1510 (60.0)	2982 (59.4)
History of PCI (with or without Stent), n (%)	1280 (51.1)	1303 (51.8)	2583 (51.4)
History of Prior CABG, n (%)	479 (19.1)	516 (20.5)	995 (19.8)
Pathologic Q Waves on ECG w/corresponding Wall Motion on Echo, n (%)	865 (34.5)	879 (35.0)	1744 (34.7)
Previous Myocardial Infarction	1911 (76.2)	1892 (75.2)	3803 (75.7)

Note: Intent-to-Treat Analysis Set includes all randomized unique subjects who have a signed valid informed consent.
Note: Percentages are calculated with the number of subjects in each treatment group as denominator.
Note: A subject may appear in more than one category and the same subject is counted only once in a category.
Abbreviations: CABG - coronary artery bypass graft; ECG - electrocardiogram; PCI - percutaneous coronary intervention.

Treatment Disposition

(Safety Analysis Set)

	Rivaroxaban N= 2499 n (%)	Placebo N= 2509 n (%)	Total N= 5008 n (%)
Total No. Subjects Who Completed the Double-Blind Treatment Phase	1808 (72.3)	1884 (75.1)	3692 (73.7)
On Study Drug at GTED	1518 (60.7)	1570 (62.6)	3088 (61.7)
Died Within 7 Days of the Last Dose of Study Drug*	290 (11.6)	314 (12.5)	604 (12.1)
Total No. Subjects Who Did Not Complete the Double-Blind Treatment Phase	691 (27.7)	625 (24.9)	1316 (26.3)
Early Termination Study Medication (Excludes Subjects Who Died Within 7 Days of Last Dose of Study Drug)	668 (26.7)	605 (24.1)	1273 (25.4)
Adverse Event	146 (5.8)	119 (4.7)	265 (5.3)
Atrial Fibrillation	124 (5.0)	117 (4.7)	241 (4.8)
Bleeding Event	86 (3.4)	41 (1.6)	127 (2.5)
Investigator Choice	28 (1.1)	17 (0.7)	45 (0.9)
Outcome Event	71 (2.8)	95 (3.8)	166 (3.3)
Prohibited Medication	20 (0.8)	28 (1.1)	48 (1.0)
Subject Choice	153 (6.1)	146 (5.8)	299 (6.0)
Other	40 (1.6)	42 (1.7)	82 (1.6)
Died > 7 Days After the Last Dose of Study Drug	3 (0.1)	2 (0.1)	5 (0.1)
Withdrew Consent	20 (0.8)	18 (0.7)	38 (0.8)

Early Discontinuation from the Double Blind Treatment Phase by Region (Safety)

Endpoint		Rivaroxaban			Placebo		
		J	N (%)	Event Rate (100 Pt-Yr) (CI)	J	N (%)	Event Rate (100 Pt-Yr) (CI)
Early Discontinuation Double Blind Treatment Phase	Overall	2499	647 (25.89)	16.33 (15.09, 17.63)	2509	551 (21.96)	13.62 (12.51, 14.81)
	Asia Pacific	366	111 (30.33)	24.18 (19.89, 29.12)	363	90 (24.79)	19.68 (15.83, 24.19)
	Eastern Europe	1607	340 (21.16)	11.84 (10.62, 13.17)	1613	288 (17.85)	9.82 (8.72, 11.02)
	Latin America	228	58 (25.44)	19.98 (15.18, 25.84)	229	41 (17.9)	13.60 (9.76, 18.45)
	North America	73	36 (49.32)	35.07 (24.56, 48.55)	75	38 (50.67)	35.81 (25.34, 49.16)
	Western Europe And South Africa	225	102 (45.33)	42.44 (34.60, 51.51)	229	94 (41.05)	37.99 (30.70, 46.49)

Incidence of Cardiovascular Deaths (ITT, Up to GTED)

CV Deaths
n=929 (18.5%)

Rivaroxaban	453 (18.1)
MI	40 (1.6)
Non-Hemorrhagic Stroke	10 (0.4)
ICH	3 (0.1)
Arterosclerotic Vascular Disease (Excluding Coronary)	12 (0.5)
CHF Or Cardiogenic Shock	175 (7.0)
Directly Related To Revascularization (CABG/PCI)	1 (<0.1)
Dysrhythmia	7 (0.3)
PE	2 (<0.1)
Sudden Or Unwitnessed	190 (7.6)
Hemorrhage, Not ICH	2 (<0.1)
Other CV	11 (0.4)

Placebo	476 (18.9)
MI	33 (1.3)
Non-Hemorrhagic Stroke	9 (0.4)
ICH	7 (0.3)
Arterosclerotic Vascular Disease (Excluding Coronary)	9 (0.4)
CHF Or Cardiogenic Shock	171 (6.8)
Directly Related To Revascularization (CABG/PCI)	2 (<0.1)
Dysrhythmia	12 (0.5)
PE	2 (<0.1)
Sudden Or Unwitnessed	215 (8.5)
Hemorrhage, Not ICH	6 (0.2)
Other CV	10 (0.4)

Bleeding Events Resulting in Early Permanent Discontinuation of Study Drug by Bleeding Site (Safety)

Bleeding Site	Rivaroxaban (N=2499) n (%)	Placebo (N=2509) n (%)	Total (N=5008) n (%)
Total No. subjects with the specified type of bleeding event	88 (3.5)	46 (1.8)	134 (2.7)
Bleeding associated with non-cardiac surgery	0	1 (<0.1)	1 (<0.1)
Epistaxis	16 (0.6)	1 (<0.1)	17 (0.3)
GI-Lower	7 (0.3)	4 (0.2)	11 (0.2)
GI-Upper (hematemesis or melena)	12 (0.5)	9 (0.4)	21 (0.4)
Gingival	4 (0.2)	0	4 (0.1)
Hematoma	1 (<0.1)	0	1 (<0.1)
Hemoptysis	4 (0.2)	2 (0.1)	6 (0.1)
Increased or prolonged menstrual or abnormal vaginal bleeding	1 (<0.1)	0	1 (<0.1)
Intracranial	12 (0.5)	17 (0.7)	29 (0.6)
Intraocular, other than sub-conjunctival	0	2 (0.1)	2 (<0.1)
Macroscopic (gross) hematuria	9 (0.4)	3 (0.1)	12 (0.2)
Non-observed site	6 (0.2)	2 (0.1)	8 (0.2)
Puncture site	1 (<0.1)	0	1 (<0.1)
Rectal	7 (0.3)	3 (0.1)	10 (0.2)
Skin (ecchymosis other than instrumented site)	4 (0.2)	2 (0.1)	6 (0.1)
Subconjunctival or other ocular	3 (0.1)	0	3 (0.1)
--Other--	1 (<0.1)	0	1 (<0.1)
Urethra	1 (<0.1)	0	1 (<0.1)

Incidence of ISTH Major, Non-Major Clinically Relevant and Minimal Bleeding Events (Japan Subjects Only) (Safety, On-Treatment)

Bleeding Site	Rivaroxaban (N=133) n (%)	Placebo (N=132) n (%)	Total (N=265) n (%)
Total No. subjects with the specified type of bleeding event	76 (57.1)	54 (40.9)	130 (49.1)
ISTH major bleeding event	16 (12.0)	8 (6.1)	24 (9.1)
Non-major clinically relevant bleeding event	18 (13.5)	17 (12.9)	35 (13.2)
Minimal bleeding event	62 (46.6)	44 (33.3)	106 (40.0)

Note: Safety analysis set includes all intent-to-treat subjects who received at least one dose of study drug.
Note: On-Treatment is the observation period from the first dose of the study drug to 2 days after the last dose of the study drug, inclusively.
Note: Percentages are calculated with the number of subjects in each treatment group as denominator.
Note: A subject may appear in more than one category and the same subject is counted only once in a category.
Note: Non-major clinically relevant and minimal bleeding events were recorded only in Japan subjects.