Supplemental Material

Supplemental Table 1. Baseline characteristics of the patients enrolled in the respective trials

Characteristic	**COMMANDER-HF**	**EPHESUS**	**EXAMINE**
N.	5022	6632	5380
Age (years)	66.4 ± 10.2	64.0 ± 11.5	60.9 ± 9.9
Women	1150 (22.9%)	1918 (28.9%)	1729 (32.1%)
White race	4128 (82.2%)	5984 (90.0%)	3909 (72.7%)
Diabetes	2052 (40.9%)	2122 (32.0%)	5380 (100.0%)
Hypertension	3783 (75.3%)	4007 (60.4%)	4469 (83.1%)
Myocardial infarction (prior)	3803 (75.7%)	1802 (27.2%)	4734 (88.0%)
Stroke	453 (9.0%)	595 (9.0%)	388 (7.2%)
Coronary revascularization	3150 (62.7%)	3006 (45.3%)	3372 (62.7%)
Body mass index (Kg/m2)	27.7 ± 5.2	27.4 ± 4.5	29.5 ± 5.6
Blood pressure, systolic (mmHg)	122.7 ± 15.4	119.1 ± 16.5	129.0 ± 16.6
Hemoglobin (g/dL)	13.5 ± 1.8	13.3 ± 1.7	13.5 ± 1.6
eGFR (mL/min/1.73m2)	68.1 ± 23.5	68.7 ± 22.5	71.1 ± 21.6
LVEF (%)	34.0 (28.0, 38.0)	35.0 (30.0, 38.0)	NA
ACE/ARB	4660 (92.8%)	5407 (81.6%)	4411 (82.0%)
Beta-blocker	4642 (92.4%)	4616 (69.7%)	4411 (82.0%)
Anti-platelet	4675 (93.1%)	1861 (28.8%)	5232 (97.2%)
Diuretic (any)	4999 (99.5%)	3970 (59.9%)	940 (17.5%)
Active treatment (vs. placebo)	2507 (49.9%)	3243 (50.1%)	2701 (50.2%)

Legend: eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ACE/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; Active treatment, rivaroxaban in COMMANDER-HF, eplerenone in EPHESUS, alogliptin in EXAMINE.

Supplemental Table 2. Event rates per 100 person-years by intervals of follow-up time

Time (months)	Person-years	Events	Rate (per100py)
Sudden death			
0 to 6	2428.8	122	5 (4.2-6)
6 to 12	2201.8	87	4 (3.2-4.9)
Beyond 12	5179.7	196	3.8 (3.3-4.4)
Total	9810.2	405	4.1 (3.7-4.6)
HF death			
0 to 6	2428.8	110	4.5 (3.8-5.5)
6 to 12	2201.8	81	3.7 (3.0-4.6)
Beyond 12	5179.7	159	3.1 (2.6-3.6)
Total	9810.2	350	3.6 (3.2-4.0)
CV Hosp. (non-HF)			
0 to 6	2310.9	468	20.3 (18.5-22.2)
6 to 12	1956.7	287	14.7 (13.1-16.5)
Beyond 12	4079.6	360	8.8 (8-9.8)
Total	8347.2	1115	13.4 (12.6-14.2)
Bleeding main			
0 to 6	2427.4	16	0.7 (0.4-1.1)
6 to 12	2197.9	13	0.6 (0.3-1)
Beyond 12	5166.6	12	0.2 (0.1-0.4)
Total	9792	41	0.4 (0.3-0.6)
Bleeding ISTH			
0 to 6	2413	65	2.7 (2.1-3.4)
6 to 12	2173.3	29	1.3 (0.9-1.9)
Beyond 12	5092	38	0.7 (0.5-1)
Total	9678.4	132	1.4 (1.1-1.6)
Bleeding hosp.			
0 to 6	2413	56	2.3 (1.8-3)
6 to 12	2177.3	23	1.1 (0.7-1.6)
Beyond 12	5107.3	30	0.6 (0.4-0.8)
Total	9697.5	109	1.1 (0.9-1.4)

Legend: HF, heart failure; CV, cardiovascular; Hosp., hospitalization; ISTH, major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) as overt bleeding associated with a decrease in hemoglobin level of at least 2 g/dL, transfusion of $\geq$2 units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome.

Supplemental Table 3. Treatment effect over time and proportional hazards assumption

Rivaroxaban vs. Placebo	HR (95%CI)	P	PH test
MI, stroke, ACM			
Up to 6 months	0.92 (0.76-1.12)	0.42	
Up to 12 months	0.88 (0.76-1.02)	0.097	0.18
Entire follow-up	0.94 (0.84-1.05)	0.27	
MI, stroke, CVD			
Up to 6 months	0.89 (0.73-1.09)	0.27	
Up to 12 months	0.84 (0.72-0.98)	0.027	0.23
Entire follow-up	0.91 (0.81-1.02)	0.11	
MI			
Up to 6 months	0.95 (0.61-1.49)	0.84	
Up to 12 months	0.78 (0.56-1.09)	0.15	0.68
Entire follow-up	0.83 (0.63-1.08)	0.17	
Stroke			
Up to 6 months	0.64 (0.34-1.19)	0.16	
Up to 12 months	0.69 (0.43-1.1)	0.12	0.74
Entire follow-up	0.66 (0.47-0.95)	0.024	
ACM			
Up to 6 months	1.01 (0.81-1.26)	0.90	
Up to 12 months	0.95 (0.8-1.12)	0.53	0.15
Entire follow-up	0.98 (0.87-1.1)	0.74	
CVD			
Up to 6 months	0.99 (0.78-1.25)	0.92	
Up to 12 months	0.9 (0.75-1.07)	0.25	0.21
Entire follow-up	0.95 (0.83-1.08)	0.43	
Sudden death			
Up to 6 months	0.89 (0.63-1.28)	0.54	
Up to 12 months	0.79 (0.6-1.04)	0.088	0.19
Entire follow-up	0.88 (0.73-1.07)	0.21	
HF death			
Up to 6 months	0.93 (0.64-1.35)	0.71	
Up to 12 months	0.95 (0.71-1.26)	0.72	0.24
Entire follow-up	1.03 (0.84-1.27)	0.77	
HFH			
Up to 6 months	0.95 (0.82-1.11)	0.54	
Up to 12 months	0.93 (0.82-1.06)	0.27	0.067
Entire follow-up	0.98 (0.89-1.09)	0.78	
CV Hosp. (non-HF)			
Up to 6 months	0.95 (0.79-1.14)	0.61	
Up to 12 months	0.96 (0.83-1.1)	0.53	0.39
Entire follow-up	0.95 (0.84-1.07)	0.38	

Bleeding main			
Up to 6 months	0.45 (0.16-1.3)	0.14	
Up to 12 months	0.76 (0.37-1.56)	0.46	0.77
Entire follow-up	0.78 (0.42-1.45)	0.43	
Bleeding ISTH			
Up to 6 months	1.61 (0.98-2.65)	0.063	
Up to 12 months	1.72 (1.14-2.61)	0.011	0.43
Entire follow-up	1.65 (1.16-2.34)	0.005	
Bleeding hosp.			
Up to 6 months	1.44 (0.85-2.46)	0.18	
Up to 12 months	1.51 (0.96-2.36)	0.073	0.15
Entire follow-up	1.28 (0.87-1.86)	0.21	

Legend: HF, heart failure; CVD, cardiovascular death; Hosp., hospitalization; MI, myocardial infarction; ISTH, major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) as overt bleeding associated with a decrease in hemoglobin level of at least 2 g/dL, transfusion of $\geq$2 units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome; PH test, proportional hazards test.