**Supplemental Material**

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

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| --- | --- | --- | --- |
| **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

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| --- | --- | --- | --- |
| **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 ≥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

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| --- | --- | --- | --- |
| **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 ≥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.