**APPENDIX**

**Supplemental Table I:** Additional baseline characteristics according to COPD status (EMPHASIS-HF only)

**Supplemental Table II:** Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (RALES only)

**Supplemental Table III:** Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (EMPHASIS-HF only)

**Supplemental Table IV:** Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – RALES only

**Supplemental Table V:** Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – EMPHASIS-HF only

**Supplemental Figure I:** Causes of non-cardiovascular death in patients with and without COPD (RALES and EMPHASIS-HF combined)

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| Supplemental Table I: Additional baseline characteristics according to COPD status (EMPHASIS-HF only) |
|   | **All Patients** | **Without COPD** | **With COPD** | ***P*-value** |
|  | **(N=2737)\*** | **(N=2343)** | **(N=391)** |  |
| BMI (kg/m2) | 27.5 ± 4.9 | 27.6 ± 4.8 | 27.4 ± 5.1 | 0.47 |
| BMI Classification |  |  |  | 0.29 |
| * Underweight (BMI<18.5)
 | 50 (1.8) | 40 (1.7) | 10 (2.6) |  |
| * Normal weight (BMI 18.5-24.9)
 | 765 (28.1) | 644 (27.6) | 121 (31.1) |  |
| * Overweight (BMI 25-29.9)
 | 1165 (42.8) | 1010 (43.3) | 155 (39.8) |  |
| * Obesity (BMI≥30)
 | 739 (27.2)  | 636 (27.3) | 103 (26.5) |  |
| Smoking status |  |  |  | <0.001 |
| * Never
 | 1222 (44.7) | 1125 (48.0)  | 97 (24.8) |  |
| * Former
 | 1219 (44.6) | 1010 (43.1) | 209 (53.5) |  |
| * Current
 | 293 (10.7)  | 208 (8.9) | 85 (21.7) |  |
| Haemoglobin (g/L) | 138.0 ± 15.7 | 137.8 ± 15.7 | 139.3 ± 15.9 | 0.079 |
| Anaemia | 616 (23.1) | 533 (23.3) | 83 (21.7) | 0.49 |
| PCI | 596 (21.8) | 524 (22.4) | 72 (18.4) | 0.079 |
| CABG | 516 (18.9)  | 434 (18.5) | 82 (21.0)  | 0.25 |
| CRT-P/CRT-D | 230 (8.7) | 201 (8.8)  | 29 (7.8) | 0.51 |
| ICD/CRT-D | 421 (15.8) | 358 (15.6) | 63 (16.7) | 0.59 |
| Data are presented as mean ± SD for continuous measures and n (%) for categorical measures.Chronic obstructive pulmonary disease (COPD); body mass index (BMI); percutaneous coronary intervention (PCI); coronary artery bypass graft (CABG); cardiac resynchronisation therapy (CRT) with pacemaker (P) or defibrillator (D); implantable cardioverter-defibrillator (ICD).Units: kilograms per square metre (kg/m2), grams per litre (g/L).\*3 patients missing COPD data |

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| **Supplemental Table II: Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (RALES only)** |
|  | **Without COPD** | **With COPD** | ***P-*value** |
|  | **(N=** **1429)** | **(N=234)** |
| **HF hospitalisation or cardiovascular death** |  |  |  |
| Events – no. (%) | 695 (48.6) | 123 (52.6) |  |
| Event rate per 100 pt. years | 33.1 (30.7 – 35.7) | 38.7 (32.4 – 46.2) |  |
| Unadjusted HR | 1.00 (ref.) | 1.15 (0.95 – 1.39) | 0.151 |
| Adjusted HR\* | 1.00 (ref.) | 1.05 (0.86 – 1.28) | 0.608 |
| Adjusted HR† | 1.00 (ref.) | 1.03 (0.85 – 1.26) | 0.740 |
| **HF hospitalisation** |  |  |  |
| Events – no. (%) | 440 (30.8) | 76 (32.5) |  |
| Event rate per 100 pt. years | 21.0 (19.1 – 23.1) | 23.9 (19.1 – 29.9) |  |
| Unadjusted HR | 1.00 (ref.) | 1.11 (0.87 – 1.42) | 0.387 |
| Adjusted HR\* | 1.00 (ref.) | 1.01 (0.79 – 1.30) | 0.929 |
| Adjusted HR† | 1.00 (ref.) | 0.99 (0.77 – 1.28) | 0.955 |
| **All-cause hospitalisation**  |  |  |  |
| Events – no. (%) | 766 (53.6) | 140 (59.8) |  |
| Event rate per 100 pt. years | 43.4 (40.5 – 46.6) | 54.8 (46.4 – 64.7)  |  |
| Unadjusted HR | 1.00 (ref.) | 1.23 (1.03 – 1.48) | 0.022 |
| Adjusted HR\* | 1.00 (ref.) | 1.13 (0.94 – 1.36) | 0.195 |
| Adjusted HR† | 1.00 (ref.) | 1.12 (0.93 – 1.35) | 0.219 |
| **Non-Cardiovascular hospitalisation** |  |  |  |
| Events – no. (%) | 248 (17.4) | 56 (23.9) |  |
| Event rate per 100 pt. years | 14.1 (12.4 – 15.9) | 21.7 (16.6 – 28.2) |  |
| Unadjusted HR | 1.00 (ref.) | 1.51 (1.13 – 2.03) | 0.005 |
| Adjusted HR\* | 1.00 (ref.) | 1.44 (1.07 – 1.94) | 0.017 |
| Adjusted HR† | 1.00 (ref.) | 1.45 (1.07 – 1.95) | 0.015 |
| **Cardiovascular death** |  |  |  |
| Events – no. (%) | 455 (31.8) | 85 (36.3) |  |
| Event rate per 100 pt. years | 17.7 (16.2 – 19.4) | 20.8 (16.8 – 25.8) |  |
| Unadjusted HR | 1.00 (ref.) | 1.18 (0.94 – 1.49) | 0.163 |
| Adjusted HR\* | 1.00 (ref.) | 1.05 (0.83 – 1.33) | 0.684 |
| Adjusted HR† | 1.00 (ref.) | 1.04 (0.82 – 1.32) | 0.769 |
| **Non-Cardiovascular death** |  |  |  |
| Events – no. (%) | 101 (7.1) | 29 (12.4) |  |
| Event rate per 100 pt. years | 3.9 (3.2 – 4.7) | 7.1 (4.9 – 10.2) |  |
| Unadjusted HR | 1.00 (ref.) | 1.83 (1.21 – 2.77) | 0.004 |
| Adjusted HR\* | 1.00 (ref.) | 1.84 (1.20 – 2.82) | 0.005 |

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| Adjusted HR† | 1.00 (ref.) | 1.80 (1.17 – 2.76) | 0.007 |
| **All-cause death** |  |  |  |
| Events – no. (%) | 556 (38.9) | 114 (48.7) |  |
| Event rate per 100 pt. years | 21.6 (19.9 – 23.5) | 27.9 (23.2 – 33.6) |  |
| Unadjusted HR | 1.00 (ref.) | 1.30 (1.06 – 1.59) | 0.012 |
| Adjusted HR\* | 1.00 (ref.) | 1.19 (0.96 – 1.46) | 0.105 |
| Adjusted HR† | 1.00 (ref.) | 1.17 (0.95 – 1.44) | 0.140 |
| **Pump failure death** |  |  |  |
| Events – no. (%) | 275 (19.2) | 41 (17.5) |  |
| Event rate per 100 pt. years | 10.7 (9.5 – 12.0) | 10.0 (7.4 – 13.6) |  |
| Unadjusted HR | 1.00 (ref.) | 0.94 (0.68 – 1.31) | 0.727 |
| Adjusted HR\* | 1.00 (ref.) | 0.78 (0.56 – 1.09) | 0.150 |
| Adjusted HR† | 1.00 (ref.) | 0.77 (0.55 – 1.08) | 0.127 |
| **Sudden cardiac death** |  |  |  |
| Events – no. (%) | 155 (10.8) | 37 (15.8) |  |
| Event rate per 100 pt. years | 6.0 (5.2 – 7.1) | 9.1 (6.6 – 12.5) |  |
| Unadjusted HR | 1.00 (ref.) | 1.51 (1.06 – 2.17) | 0.024 |
| Adjusted HR\* | 1.00 (ref.) | 1.44 (1.00 – 2.09) | 0.052 |

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| Adjusted HR† | 1.00 (ref.) | 1.42 (0.98 – 2.05) | 0.062 |
| \*Model adjusted for age, sex, race, heart rate, systolic blood pressure, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation.† Adjusted as for \* with additional adjustment for beta blocker prescription at baseline. Chronic obstructive pulmonary disease (COPD); heart failure (HF); hazard ratio (HR).  |

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| **Supplemental Table III: Event rate (per 100 patient-years) and risk of study endpoints according to COPD status (EMPHASIS-HF only)** |
|  | **Without COPD** | **With COPD** | ***P-*value** |
|  | **(N=** **2343)** | **(N=** **391)** |
| **HF hospitalisation or cardiovascular death** |  |  |  |
| Events – no. (%) | 500 (21.3) | 104 (26.6) |  |
| Event rate per 100 pt. years | 12.8 (11.8 – 14.0) | 17.8 (14.7 – 21.6) |  |
| Unadjusted HR | 1.00 (ref.) | 1.39 (1.13 – 1.72) | 0.002 |
| Adjusted HR\* | 1.00 (ref.) | 1.32 (1.05 – 1.64) | 0.015 |
| Adjusted HR† | 1.00 (ref.) | 1.26 (1.01 – 1.58) | 0.042 |
| **HF hospitalisation** |  |  |  |
| Events – no. (%) | 343 (14.6) | 74 (18.9) |  |
| Event rate per 100 pt. years | 8.8 (7.9 – 9.8) | 12.7 (10.1 – 15.9) |  |
| Unadjusted HR | 1.00 (ref.) | 1.44 (1.12 – 1.86) | 0.004 |
| Adjusted HR\* | 1.00 (ref.) | 1.35 (1.03 – 1.75) | 0.028 |
| Adjusted HR† | 1.00 (ref.) | 1.29 (0.98 – 1.69) | 0.065 |
| **All-cause hospitalisation**  |  |  |  |
| Events – no. (%) | 744 (31.8) | 154 (39.4) |  |
| Event rate per 100 pt. years | 21.8 (20.3 – 23.5) | 32.1 (27.4 – 37.5)  |  |
| Unadjusted HR | 1.00 (ref.) | 1.43 (1.20 – 1.70) | <0.001 |
| Adjusted HR\* | 1.00 (ref.) | 1.37 (1.14 – 1.65) | 0.001 |
| Adjusted HR† | 1.00 (ref.) | 1.33 (1.11 – 1.60) | 0.002 |
| **Non-Cardiovascular hospitalisation** |  |  |  |
| Events – no. (%) | 146 (6.2) | 49 (12.5) |  |
| Event rate per 100 pt. years | 3.6 (3.0 – 4.2) | 8.2 (6.2 – 10.8) |  |
| Unadjusted HR | 1.00 (ref.) | 2.25 (1.63 – 3.12) | <0.001 |
| Adjusted HR\* | 1.00 (ref.) | 2.09 (1.48 – 2.94) | <0.001 |
| Adjusted HR† | 1.00 (ref.) | 2.13 (1.51 – 3.03) | <0.001 |
| **Cardiovascular death** |  |  |  |
| Events – no. (%) | 274 (11.7) | 57 (14.6) |  |
| Event rate per 100 pt. years | 6.5 (5.8 – 7.3) | 8.8 (6.8 – 11.4) |  |
| Unadjusted HR | 1.00 (ref.) | 1.36 (1.03 – 1.81) | 0.033 |
| Adjusted HR\* | 1.00 (ref.) | 1.30 (0.96 – 1.75) | 0.089 |
| Adjusted HR† | 1.00 (ref.) | 1.26 (0.93 – 1.71) | 0.132 |
| **Non-Cardiovascular death** |  |  |  |
| Events – no. (%) | 41 (1.7)  | 11 (2.8) |  |
| Event rate per 100 pt. years | 1.0 (0.7 – 1.3) | 1.7 (0.9 – 3.1) |  |
| Unadjusted HR | 1.00 (ref.) | 1.77 (0.91 – 3.45) | 0.092 |
| Adjusted HR\* | 1.00 (ref.) | 1.81 (0.92 – 3.57) | 0.086 |

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| Adjusted HR† | 1.00 (ref.) | 1.82 (0.92 – 3.61) | 0.086 |
| **All-cause death** |  |  |  |
| Events – no. (%) | 315 (13.4) | 68 (17.4) |  |
| Event rate per 100 pt. years | 7.5 (6.7 – 8.4) | 10.5 (8.3 – 13.3) |  |
| Unadjusted HR | 1.00 (ref.) | 1.42 (1.09 – 1.84) | 0.009 |
| Adjusted HR\* | 1.00 (ref.) | 1.37 (1.04 – 1.80) | 0.025 |
| Adjusted HR† | 1.00 (ref.) | 1.34 (1.02 – 1.77) | 0.038 |
| **Pump failure death** |  |  |  |
| Events – no. (%) | 83 (3.5) | 23 (5.9) |  |
| Event rate per 100 pt. years | 2.0 (1.6 – 2.4) | 3.5 (2.4 – 5.3) |  |
| Unadjusted HR | 1.00 (ref.) | 1.82 (1.15 – 2.89) | 0.011 |
| Adjusted HR\* | 1.00 (ref.) | 1.74 (1.05 – 2.87) | 0.031 |
| Adjusted HR† | 1.00 (ref.) | 1.77 (1.06 – 2.94) | 0.028 |
| **Sudden cardiac death** |  |  |  |
| Events – no. (%) | 112 (4.8) | 23 (5.9) |  |
| Event rate per 100 pt. years | 2.7 (2.2 – 3.2) | 3.5 (2.4 – 5.3) |  |
| Unadjusted HR | 1.00 (ref.) | 1.34 (0.85 – 2.09) | 0.205 |
| Adjusted HR\* | 1.00 (ref.) | 1.24 (0.77 – 1.99) | 0.373 |

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| Adjusted HR† | 1.00 (ref.) | 1.20 (0.74 – 1.93) | 0.462 |
| \*Model adjusted for age, sex, race, heart rate, systolic blood pressure, New York Heart Association classification, left ventricular ejection fraction, estimated glomerular filtration rate, history of myocardial infarction, diabetes and atrial fibrillation.† Adjusted as for \* with additional adjustment for beta blocker prescription at baseline. Chronic obstructive pulmonary disease (COPD); heart failure (HF); hazard ratio (HR).  |

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| **Supplemental Table IV: Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – RALES only** |
|  | **Without COPD** | **With COPD** |  |
|  | **Placebo****(N=725)** | **MRA****(N=704)** | **Placebo****(N=116)** | **MRA****(N=118)** | ***P*-value for interaction** |
| **HF hospitalisation or cardiovascular death** |  |  |  |  |  |
| Events – no. (%) | 405 (55.9) | 290 (41.2) | 67 (57.8) | 56 (47.5) |  |
| Event rate per 100 pt. yrs. | 41.7 (37.9 – 46.0) | 25.7 (22.9 – 28.8) | 46.2 (36.4 – 58.8) | 32.4 (24.9 – 42.1) |  |
| Unadjusted HR | 0.64 (0.55 – 0.75) | 0.74 (0.52 – 1.05) | 0.50 |
| **HF hospitalisation** |  |  |  |
| Events – no. (%) | 257 (35.4) | 183 (26.0)  | 43 (37.1) | 33 (28.0) |  |
| Event rate per 100 pt. yrs. | 26.6 (23.5 – 30.0) | 16.3 (14.1 – 18.8) | 29.7 (22.0 – 40.0) | 19.1 (13.6 – 26.9) |  |
| Unadjusted HR | 0.65 (0.53 – 0.78) | 0.68 (0.43 – 1.07) | 0.84 |
| **All-cause hospitalisation** |  |  |  |
| Events – no. (%) | 407 (56.1) | 359 (51.0) | 75 (64.7) | 65 (55.1) |  |
| Event rate per 100 pt. yrs. | 49.0 (44.4 – 54.0) | 38.5 (34.7 – 42.7) | 68.4 (54.6 – 85.8) | 44.4 (34.8 – 56.7) |  |
| Unadjusted HR | 0.81 (0.70 – 0.93) | 0.70 (0.50 – 0.98) | 0.34 |
| **Non-Cardiovascular hospitalisation** |  |  |  |
| Events – no. (%) | 116 (16.0) | 132 (18.8) | 31 (26.7) | 25 (21.2) |  |
| Event rate per 100 pt. yrs. | 14.0 (11.6 – 16.7) | 14.2 (11.9 – 16.8) | 28.3 (19.9 – 40.2) | 16.6 (11.2 – 24.8) |  |
| Unadjusted HR | 1.03 (0.80 – 1.33) | 0.61 (0.35 – 1.04) | 0.08 |
| **Cardiovascular death** |  |  |  |
| Events – no. (%) | 267 (36.8) | 188 (26.7) | 47 (40.5) | 38 (32.2) |  |
| Event rate per 100 pt. yrs. | 21.3 (18.9 – 24.0) | 14.3 (12.4 – 16.5) | 23.8 (17.9 – 31.7) | 18.0 (13.1 – 24.8) |  |
| Unadjusted HR | 0.68 (0.56 – 0.82) | 0.77 (0.50 – 1.17) | 0.63 |
| **All-cause death** |  |  |  |
| Events – no. (%) | 323 (44.6) | 233 (33.1) | 63 (54.3) | 51 (43.2) |  |
| Event rate per 100 pt. yrs. | 25.8 (23.1 – 28.7) | 17.7 (15.5 – 20.1) | 31.9 (25.0 – 40.9) | 24.2 (18.4 – 31.8) |  |
| Unadjusted HR | 0.69 (0.58 – 0.82) | 0.76 (0.53 – 1.11) | 0.64 |
| **Pump failure death** |  |  |  |
| Events – no. (%) | 164 (22.6) | 111 (15.8) | 25 (21.6) | 16 (13.6) |  |
| Event rate per 100 pt. yrs. | 13.0 (11.2 – 15.2) | 8.5 (7.0 – 10.2) | 12.7 (8.6 – 18.8) | 7.6 (4.6 – 12.4) |  |
| Unadjusted HR | 0.66 (0.52 – 0.84) | 0.60 (0.32 – 1.13) | 0.80 |
| **Sudden cardiac death** |  |  |  |
| Events – no. (%) | 92 (12.7) | 63 (8.9)  | 18 (15.5) | 19 (16.1) |  |
| Event rate per 100 pt. yrs. | 7.3 (6.0 – 9.0) | 4.8 (3.7 – 6.1) | 9.1 (5.8 –14.5) | 9.0 (5.7 – 14.1) |  |
| Unadjusted HR | 0.66 (0.48 – 0.91) | 1.01 (0.53 – 1.92) | 0.26 |
| Chronic obstructive pulmonary disease (COPD); mineralocorticoid receptor antagonist (MRA); heart failure (HF); hazard ratio (HR). |

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| **Supplemental Table V: Clinical outcomes and treatment effect according to COPD status (MRA vs placebo event rates and hazard ratios with 95% confidence interval) – EMPHASIS-HF only** |
|  | **Without COPD** | **With COPD** |  |
|  | **Placebo****(N=1183)** | **MRA****(N=1160)** | **Placebo****(N=188)** | **MRA****(N=203)** | ***P*-value for interaction** |
| **HF hospitalisation or cardiovascular death** |  |  |  |  |  |
| Events – no. (%) | 295 (24.9) | 205 (17.7) | 61 (32.4) | 43 (21.2) |  |
| Event rate per 100 pt. yrs. | 15.5 (13.8 – 17.4) | 10.3 (9.0 – 11.8) | 23.4 (18.2 – 30.0) | 13.3 (9.9 – 18.0) |  |
| Unadjusted HR | 0.67 (0.56 – 0.80) | 0.57 (0.38 – 0.84) | 0.54 |
| **HF hospitalisation** |  |  |  |
| Events – no. (%) |  208 (17.6) | 135 (11.6)  | 45 (23.9) | 29 (14.3) |  |
| Event rate per 100 pt. yrs. | 10.9 (9.5 – 12.5) | 6.8 (5.7 – 8.0) | 17.2 (12.9 – 23.1) | 9.0 (6.3 – 12.9) |  |
| Unadjusted HR | 0.62 (0.50 – 0.77) | 0.51 (0.32 – 0.83) | 0.56 |
| **All-cause hospitalisation** |  |  |  |
| Events – no. (%) | 407 (34.4) | 337 (29.1) | 83 (44.1) | 71 (35.0)  |  |
| Event rate per 100 pt. yrs. | 24.6 (22.4 – 27.1) | 19.2 (17.3 – 21.4) | 38.5 (31.0 – 47.7) | 26.8 (21.2 – 33.8) |  |
| Unadjusted HR | 0.79 (0.69 – 0.91) | 0.73 (0.53 – 1.00) | 0.58 |
| **Non-Cardiovascular hospitalisation** |  |  |  |
| Events – no. (%) | 69 (5.8) | 77 (6.6)  | 22 (11.7) | 27 (13.3) |  |
| Event rate per 100 pt. yrs. | 3.4 (2.7 – 4.3) | 3.8 (3.0 – 4.7) | 8.1 (5.3 – 12.3) | 8.2 (5.6 – 12.0) |  |
| Unadjusted HR | 1.11 (0.81 – 1.54) | 1.02 (0.58 – 1.80) | 0.80 |
| **Cardiovascular death** |  |  |  |
| Events – no. (%) | 153 (12.9) | 121 (10.4) | 32 (17.0) | 25 (12.3) |  |
| Event rate per 100 pt. yrs. | 7.3 (6.2 – 8.5) | 5.7 (4.8 – 6.8) | 10.9 (7.7 – 15.4) | 7.0 (4.8 – 10.4) |  |
| Unadjusted HR | 0.78 (0.62 – 0.99) | 0.65 (0.39 – 1.10) | 0.52 |
| **All-cause death** |  |  |  |
| Events – no. (%) | 178 (15.0) | 137 (11.8) | 35 (18.6) | 33 (16.3) |  |
| Event rate per 100 pt. yrs. | 8.5 (7.3 – 9.8) | 6.5 (5.5 – 7.7) | 11.9 (8.6 – 16.6) | 9.3 (6.6 – 13.1) |  |
| Unadjusted HR | 0.76 (0.61 – 0.95) | 0.79 (0.49 – 1.27) | 0.92 |
| **Pump failure death** |  |  |  |
| Events – no. (%) | 48 (4.1) | 35 (3.0) | 13 (6.9) | 10 (4.9) |  |
| Event rate per 100 pt. yrs. | 2.3 (1.7 – 3.0) | 1.7 (1.2 – 2.3) | 4.4 (2.6 – 7.6) | 2.8 (1.5 – 5.2) |  |
| Unadjusted HR | 0.72 (0.46 – 1.11) | 0.64 (0.28 – 1.46) | 0.81 |
| **Sudden cardiac death** |  |  |  |
| Events – no. (%) | 62 (5.2) | 50 (4.3) | 14 (7.4) | 9 (4.4)  |  |
| Event rate per 100 pt. yrs. | 3.0 (2.3 – 3.8) | 2.4 (1.8 – 3.1) | 4.8 (2.8 –8.0) | 2.5 (1.3 – 4.9) |  |
| Unadjusted HR | 0.80 (0.55 – 1.16) | 0.55 (0.24 – 1.28) | 0.41 |
| Chronic obstructive pulmonary disease (COPD); mineralocorticoid receptor antagonist (MRA); heart failure (HF); hazard ratio (HR). |

**Supplemental Figure I: Causes of non-cardiovascular death in patients with and without COPD (RALES and EMPHASIS-HF combined)**

GI/HPB = gastrointestinal/hepatobiliary