

## 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)

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

	All Patients (N=2737)*	Without COPD (N=2343)	With COPD (N=391)	P-value
<b>BMI (kg/m<sup>2</sup>)</b>	27.5 ± 4.9	27.6 ± 4.8	27.4 ± 5.1	0.47
<b>BMI Classification</b>				0.29
• <b>Underweight (BMI&lt;18.5)</b>	50 (1.8)	40 (1.7)	10 (2.6)	
• <b>Normal weight (BMI 18.5-24.9)</b>	765 (28.1)	644 (27.6)	121 (31.1)	
• <b>Overweight (BMI 25-29.9)</b>	1165 (42.8)	1010 (43.3)	155 (39.8)	
• <b>Obesity (BMI≥30)</b>	739 (27.2)	636 (27.3)	103 (26.5)	
<b>Smoking status</b>				<0.001
• <b>Never</b>	1222 (44.7)	1125 (48.0)	97 (24.8)	
• <b>Former</b>	1219 (44.6)	1010 (43.1)	209 (53.5)	
• <b>Current</b>	293 (10.7)	208 (8.9)	85 (21.7)	
<b>Haemoglobin (g/L)</b>	138.0 ± 15.7	137.8 ± 15.7	139.3 ± 15.9	0.079
<b>Anaemia</b>	616 (23.1)	533 (23.3)	83 (21.7)	0.49
<b>PCI</b>	596 (21.8)	524 (22.4)	72 (18.4)	0.079
<b>CABG</b>	516 (18.9)	434 (18.5)	82 (21.0)	0.25
<b>CRT-P/CRT-D</b>	230 (8.7)	201 (8.8)	29 (7.8)	0.51
<b>ICD/CRT-D</b>	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/m<sup>2</sup>), grams per litre (g/L).

\*3 patients missing COPD data

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

	Without COPD (N= 1429)	With COPD (N=234)	P-value
<b>HF hospitalisation or cardiovascular death</b>			
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 <sup>†</sup>	1.00 (ref.)	1.03 (0.85 – 1.26)	0.740
<b>HF hospitalisation</b>			
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 <sup>†</sup>	1.00 (ref.)	0.99 (0.77 – 1.28)	0.955
<b>All-cause hospitalisation</b>			
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 <sup>†</sup>	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 <sup>†</sup>	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 <sup>†</sup>	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

Adjusted HR <sup>†</sup>	1.00 (ref.)	1.80 (1.17 – 2.76)	0.007
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#### 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 <sup>†</sup>	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 <sup>†</sup>	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

Adjusted HR <sup>†</sup>	1.00 (ref.)	1.42 (0.98 – 2.05)	0.062
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\* 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.

<sup>†</sup> 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)**

	<b>Without COPD (N= 2343)</b>	<b>With COPD (N= 391)</b>	<b>P-value</b>
<b>HF hospitalisation or cardiovascular death</b>			
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 <sup>†</sup>	1.00 (ref.)	1.26 (1.01 – 1.58)	0.042
<b>HF hospitalisation</b>			
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 <sup>†</sup>	1.00 (ref.)	1.29 (0.98 – 1.69)	0.065
<b>All-cause hospitalisation</b>			
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 <sup>†</sup>	1.00 (ref.)	1.33 (1.11 – 1.60)	0.002
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### 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 <sup>†</sup>	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 <sup>†</sup>	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



Adjusted HR <sup>†</sup>	1.00 (ref.)	1.82 (0.92 – 3.61)	0.086
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#### 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 <sup>†</sup>	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 <sup>†</sup>	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

Adjusted HR <sup>†</sup>	1.00 (ref.)	1.20 (0.74 – 1.93)	0.462
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\* 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.

<sup>†</sup> 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		P-value for interaction
	Placebo (N=725)	MRA (N=704)	Placebo (N=116)	MRA (N=118)	
<b>HF hospitalisation or cardiovascular death</b>					
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
<b>HF hospitalisation</b>					
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
<b>All-cause hospitalisation</b>					
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
<b>Non-Cardiovascular hospitalisation</b>					
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
<b>Cardiovascular death</b>					
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
<b>All-cause death</b>					
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

<b>Pump failure death</b>					
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
<b>Sudden cardiac death</b>					
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).

**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		P-value for interaction
	Placebo (N=1183)	MRA (N=1160)	Placebo (N=188)	MRA (N=203)	
<b>HF hospitalisation or cardiovascular death</b>					
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
<b>HF hospitalisation</b>					
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
<b>All-cause hospitalisation</b>					
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
<b>Non-Cardiovascular hospitalisation</b>					
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
<b>Cardiovascular death</b>					
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
<b>All-cause death</b>					
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

<b>Pump failure death</b>					
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
<b>Sudden cardiac death</b>					
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

