Supplemental Material

Supplemental Table 1. Baseline characteristics in women in PARAGON-HF according to treatment.

	Sacubitril-valsartan (n=1241)	Valsartan (n=1238)	P value
Age – years	73.5±7.8	73.7±8.2	0.63
Age category			0.025
50-59	74 (6.0)	69 (5.6)	
60-69	262 (21.1)	300 (24.2)	
70-79	620 (50.0)	548 (44.3)	
≥80	285 (23.0)	321 (25.9)	
Region			0.89
Asia-Pacific and other	189 (15.2)	190 (15.3)	
Central Europe	432 (34.8)	453 (36.6)	
Latin America	112 (9.0)	110 (8.9)	
North America	137 (11.0)	127 (10.3)	
Western Europe	371 (29.9)	358 (28.9)	
Race			0.59
Asian	148 (11.9)	139 (11.2)	
Black	35 (2.8)	26 (2.1)	
Other	64 (5.2)	60 (4.8)	
White	994 (80.1)	1013 (81.8)	
Duration of heart failure			0.38
0-3 months	214 (17.3)	203 (16.4)	
3-6 months	178 (14.4)	162 (13.1)	
6-12 months	245 (19.8)	263 (21.3)	
1-2 years	163 (13.2)	156 (12.6)	
2-5 years	296 (24.0)	282 (22.8)	
>5 years	139 (11.3)	170 (13.8)	
Systolic blood pressure – mmHg	131±16	131±15	0.65
Diastolic blood pressure – mmHg	74±11	74±10	0.66
Pulse pressure – mmHg	56±15	57±15	0.44
Heart rate – beats/min	71±12	71±12	0.76
Left ventricular ejection fraction – %	58.9±7.9	59.0±8.0	0.60
Body mass index – kg/m^2	30.4±5.1	30.5±5.3	0.50
Body mass index >30 kg/m^2	631 (50.8)	641 (51.8)	0.64
Waist circumference – cm	101.7±14.4	102.0±14.6	0.68
Abnormal*	988 (83.4)	965 (82.2)	0.45
Waist/hip ratio	0.93±0.12	0.94±0.12	0.15
Estimated GFR – mL/min/1.73m2	60±18	60±18	0.74
Estimated GFR <60 mL/min/1.73m2	675 (54.4)	645 (52.1)	0.25

N-terminal-pro B-type natriuretic peptide – pg/ml	876 (460-1584)	808 (431-1608)	0.24
In patients with atrial fibrillation†	1639 (1241-2294)	1749 (1258-2522)	0.13
In patients without atrial fibrillation†	600 (391-1090)	540 (365-960)	0.021
Urinary cGMP/creatinine	129±73	130±67	0.78
NYHA functional class			0.48
I	29 (2.3)	20 (1.6)	
II	924 (74.5)	941 (76.0)	
III	283 (22.8)	271 (21.9)	
IV	4 (0.3)	6 (0.5)	
KCCQ			
Clinical summary score	70.8 (56.2-83.3)	70.8 (56.8-84.4)	0.84
Overall summary score	70.3 (55.2-83.9)	71.4 (56.2-83.3)	0.98
Medical history			
Atrial fibrillation†	357 (28.8)	368 (29.9)	0.57
Any history of atrial fibrillation	618 (49.8)	662 (53.5)	0.067
Angina pectoris	350 (28.2)	314 (25.4)	0.11
Myocardial infarction	212 (17.1)	177 (14.3)	0.057
Hypertension	1198 (96.5)	1194 (96.4)	0.90
Diabetes	506 (40.8)	495 (40.0)	0.69
Prior heart failure hospitalization	541 (43.6)	572 (46.2)	0.19
Stroke	137 (11.1)	119 (9.6)	0.24
Chronic obstructive pulmonary disease	147 (11.9)	139 (11.2)	0.63
Cancer	109 (8.8)	119 (9.6)	0.47
Anemia	183 (14.8)	183 (14.8)	0.98
Renal disease	279 (22.6)	310 (25.2)	0.13
Other vascular disease	141 (11.4)	125 (10.2)	0.33
Coronary artery bypass grafting	91 (7.3)	81 (6.5)	0.44
Percutaneous coronary intervention	184 (14.8)	185 (14.9)	0.93
Smoker (current or former)	277 (22.4)	269 (21.9)	0.75
ACE inhibitor intolerance	69 (5.6)	86 (6.9)	0.15
Treatments			
Diuretic	1170 (94.3)	1182 (95.5)	0.18
Mineralocorticoid receptor antagonist	297 (23.9)	293 (23.7)	0.88
ACE inhibitor or ARB at screening	1077 (86.8)	1068 (86.3)	0.71
Beta-blocker	1008 (81.2)	977 (78.9)	0.15
Calcium channel blocker	414 (33.4)	447 (36.1)	0.15
Digoxin	126 (10.2)	122 (9.9)	0.80
Nitrate	154 (12.4)	154 (12.4)	0.98
Statin	763 (61.5)	740 (59.8)	0.38
Antiplatelet	139 (11.2)	117 (9.5)	0.15
Anticoagulant	366 (29.5)	396 (32.0)	0.18
Signs and symptoms			
Dyspnea on effort	1153 (93.1)	1163 (94.0)	0.33

Paroxysmal nocturnal dyspnea	52 (4.2)	56 (4.5)	0.69
Orthopnea	246 (19.9)	265 (21.4)	0.34
Edema	466 (37.6)	464 (37.5)	0.96
Rales	87 (7.0)	76 (6.1)	0.38
Third heart sound	32 (2.6)	25 (2.0)	0.34
Jugular venous distension	151 (12.3)	170 (13.8)	0.26
Fatigue	665 (53.7)	663 (53.6)	0.97

* Defined as >88 cm in women and >102 cm in men

† Defined as the presence of atrial fibrillation or atrial flutter on screening ECG

Data are presented as mean ± standard deviation or median (interquartile range) for continuous measures and number (%) for categorical measures.

All drugs are at randomization unless otherwise specified.

GFR = glomerular filtration rate; cGMP = cyclic guanosine monophosphate; NYHA = New York Heart Association; KCCQ = Kansas City Cardiomyopathy Questionnaire; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

Supplemental Table 2. Baseline characteristics in men in PARAGON-HF according to treatment.

	Sacubitril-valsartan (n=1666)	Valsartan (n=1151)	P value
Age – years	71.8±8.7	71.8±8.7	0.88
Age category			0.39
50-59	107 (9.2)	125 (10.9)	
60-69	351 (30.1)	325 (28.2)	
70-79	466 (40.0)	476 (41.4)	
≥80	242 (20.8)	225 (19.5)	
Region			0.78
Asia-Pacific and other	184 (15.8)	199 (17.3)	
Central Europe	424 (36.4)	406 (35.3)	
Latin America	79 (6.8)	69 (6.0)	
North America	151 (13.0)	144 (12.5)	
Western Europe	328 (28.1)	333 (28.9)	
Race			0.26
Asian	149 (12.8)	171 (14.9)	
Black	17 (1.5)	24 (2.1)	
Other	31 (2.7)	25 (2.2)	
White	969 (83.1)	931 (80.9)	
Duration of heart failure			0.46
0-3 months	184 (15.8)	172 (15.0)	
3-6 months	181 (15.6)	158 (13.7)	
6-12 months	243 (20.9)	242 (21.0)	
1-2 years	131 (11.3)	136 (11.8)	
2-5 years	263 (22.6)	296 (25.7)	
>5 years	161 (13.8)	146 (12.7)	
Systolic blood pressure – mmHg	130±15	130±15	0.87
Diastolic blood pressure – mmHg	74±10	74±10	0.49
Pulse pressure – mmHg	56±14	56±14	0.49
Heart rate – beats/min	70±12	70±12	0.42
Left ventricular ejection fraction – %	56.2±7.5	55.8±7.6	0.17
Body mass index – kg/m^2	30.0±4.7	30.0±4.9	0.95
Body mass index >30 kg/m^2	537 (46.1)	545 (47.4)	0.54
Waist circumference – cm	107.2±14.2	108.1±15.1	0.15
Abnormal*	660 (60.2)	679 (62.9)	0.19
Waist/hip ratio	1.00±0.10	1.01±0.12	0.21
Estimated GFR – mL/min/1.73m2	66±19	65±20	0.38
Estimated GFR <60 mL/min/1.73m2	489 (41.9)	532 (46.3)	0.036
N-terminal-pro B-type natriuretic peptide – pg/ml	925 (498-1617)	992 (491-1658)	0.57
In patients with atrial fibrillation†	1477 (1070-2188)	1551 (1137-2236)	0.15

In patients without atrial fibrillation†	618 (388-1045)	635 (377-1129)	0.92
Urinary cGMP/creatinine	117±60	123±62	0.29
NYHA functional class			0.38
I	44 (3.8)	44 (3.8)	
II	942 (80.9)	899 (78.1)	
III	175 (15.0)	203 (17.6)	
IV	4 (0.3)	5 (0.4)	
KCCQ			
Clinical summary score	78.6 (64.6-90.6)	79.2 (65.6-90.9)	0.32
Overall summary score	77.9 (63.0-88.5)	77.6 (64.1-89.1)	0.57
Medical history			
Atrial fibrillation†	418 (35.9)	409 (35.7)	0.89
Any history of atrial fibrillation	628 (53.9)	613 (53.3)	0.77
Angina pectoris	364 (31.2)	360 (31.3)	0.98
Myocardial infarction	349 (29.9)	345 (30.0)	0.98
Hypertension	1106 (94.9)	1086 (94.4)	0.59
Diabetes	540 (46.3)	521 (45.3)	0.61
Prior heart failure hospitalization	594 (50.9)	599 (52.0)	0.60
Stroke	129 (11.1)	123 (10.7)	0.78
Chronic obstructive pulmonary disease	196 (16.8)	188 (16.4)	0.77
Cancer	107 (9.2)	98 (8.5)	0.57
Anemia	172 (14.8)	169 (14.7)	0.96
Renal disease	315 (27.1)	320 (27.9)	0.68
Other vascular disease	179 (15.5)	175 (15.3)	0.87
Coronary artery bypass grafting	203 (17.4)	195 (16.9)	0.77
Percutaneous coronary intervention	295 (25.3)	313 (27.2)	0.30
Smoker (current or former)	661 (56.7)	647 (56.6)	0.87
ACE inhibitor intolerance	54 (4.6)	53 (4.6)	0.98
Treatments			
Diuretic	1124 (96.4)	1109 (96.4)	0.95
Mineralocorticoid receptor antagonist	295 (25.3)	354 (30.8)	0.003
ACE inhibitor or ARB at screening	997 (85.5)	997 (86.6)	0.44
Beta-blocker	914 (78.4)	922 (80.1)	0.31
Calcium channel blocker	406 (34.8)	373 (32.4)	0.22
Digoxin	104 (8.9)	98 (8.5)	0.73
Nitrate	200 (17.2)	191 (16.6)	0.72
Statin	763 (65.4)	789 (68.5)	0.11
Antiplatelet	183 (15.7)	196 (17.0)	0.39
Anticoagulant	405 (34.7)	384 (33.4)	0.49
Signs and symptoms			
Dyspnea on effort	1064 (91.4)	1044 (90.9)	0.64
Paroxysmal nocturnal dyspnea	37 (3.2)	46 (4.0)	0.29
Orthopnea	181 (15.5)	194 (16.9)	0.38

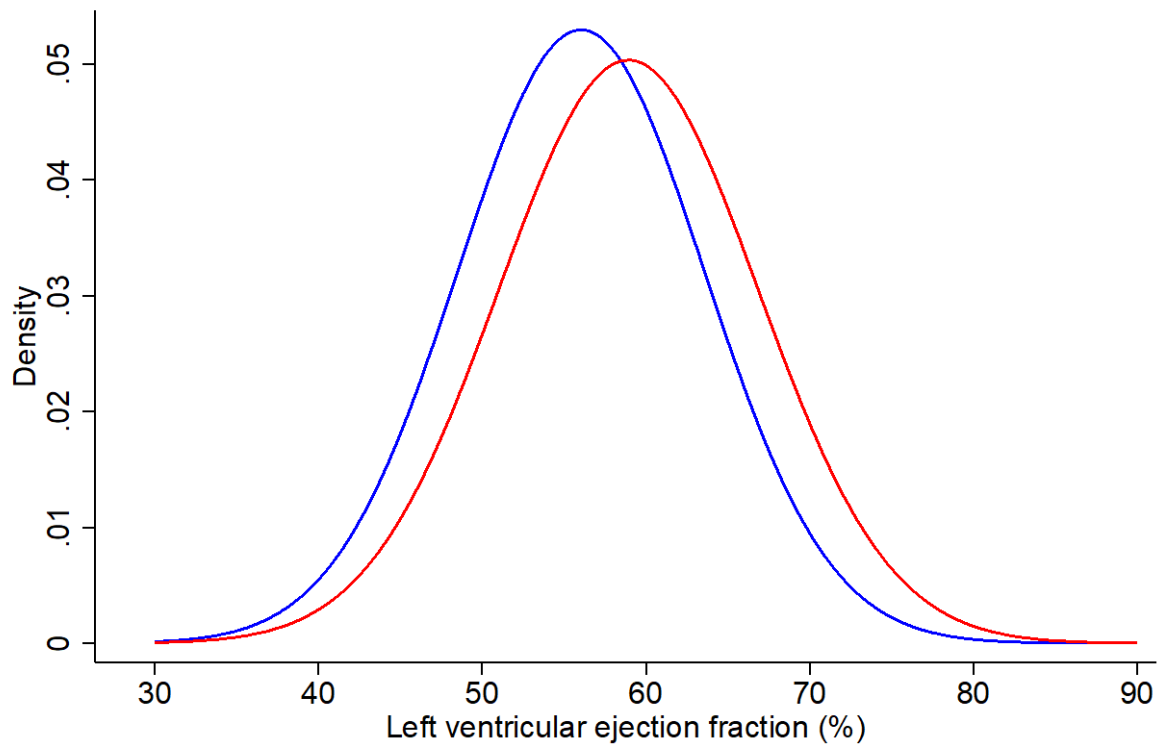|			
Edema	440 (37.8)	456 (39.7)	0.36
Rales	82 (7.0)	100 (8.7)	0.14
Third heart sound	19 (1.6)	35 (3.1)	0.024
Jugular venous distension	168 (14.6)	166 (14.6)	0.99
Fatigue	558 (48.0)	551 (48.0)	0.99

* Defined as >88 cm in women and >102 cm in men

† Defined as the presence of atrial fibrillation or atrial flutter on screening ECG

Data are presented as mean ± standard deviation or median (interquartile range) for continuous measures and number (%) for categorical measures.

All drugs are at randomization unless otherwise specified.

GFR = glomerular filtration rate; cGMP = cyclic guanosine monophosphate; NYHA = New York Heart Association; KCCQ = Kansas City Cardiomyopathy Questionnaire; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker
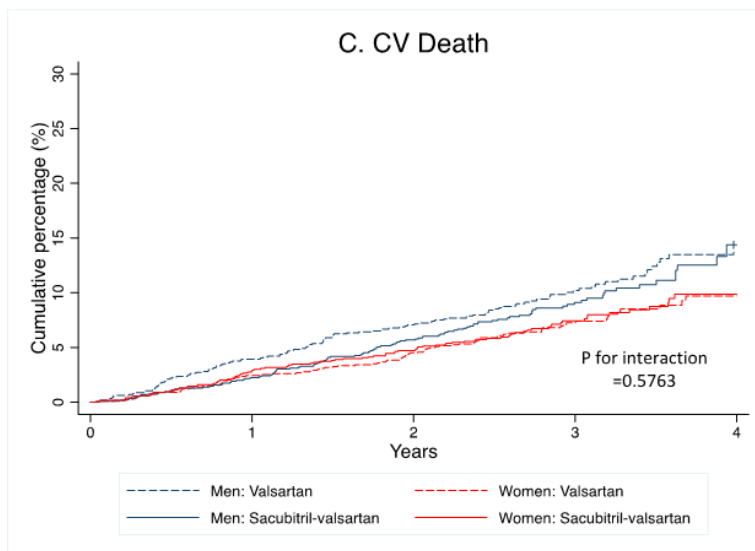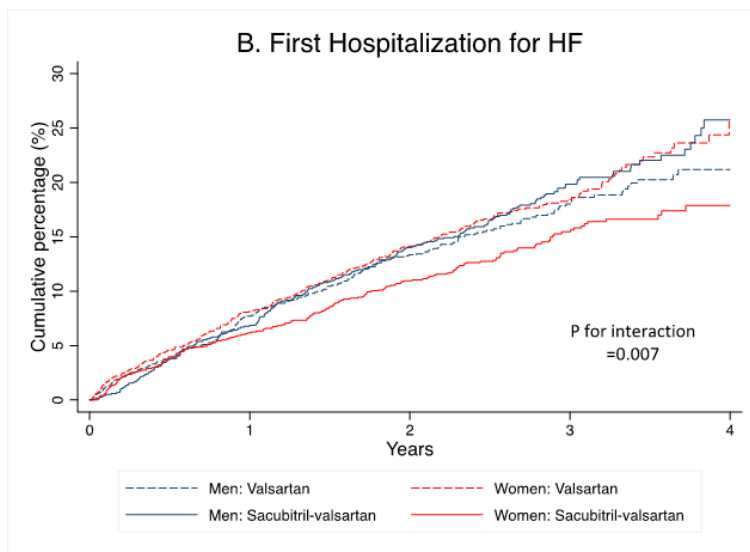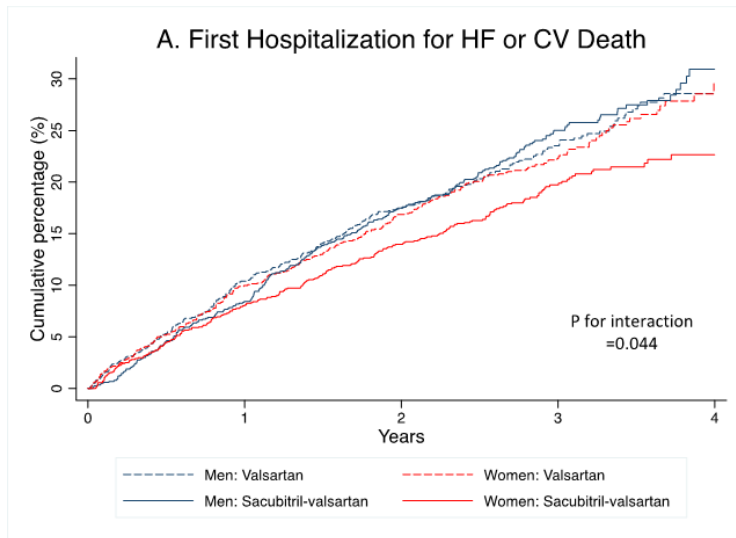
Supplemental Figure 1. Distribution of left ventricular ejection fraction in women (red) and men (blue) in PARAGON-HF.

Supplemental Figure 2. Kaplan-Meier curves for first events according to sex and treatment in PARAGON-HF.
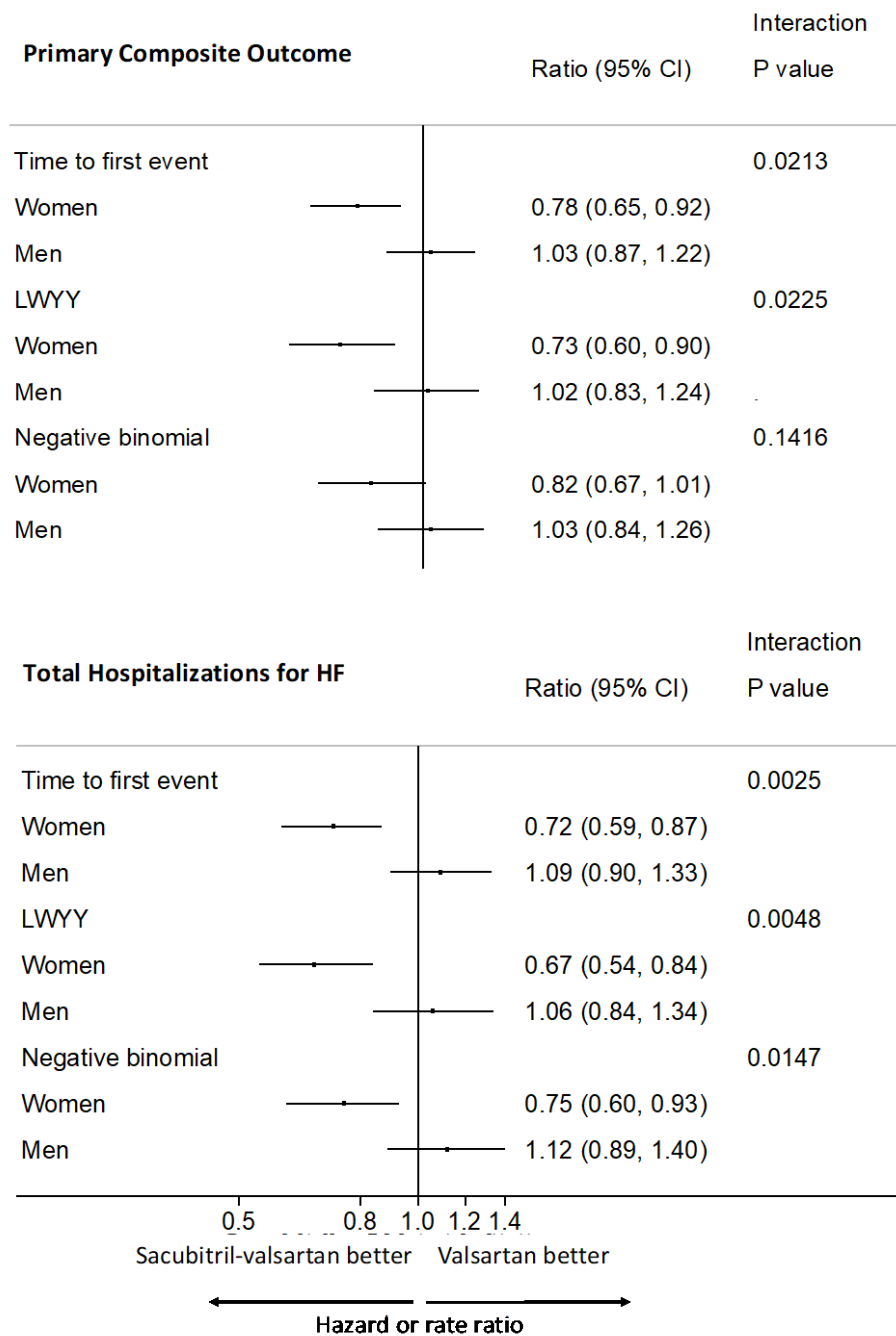
A. Cumulative percentage of first hospitalization for heart failure or cardiovascular death.

B. Cumulative percentage of first hospitalization for heart failure. C. Cumulative percentage of cardiovascular death.
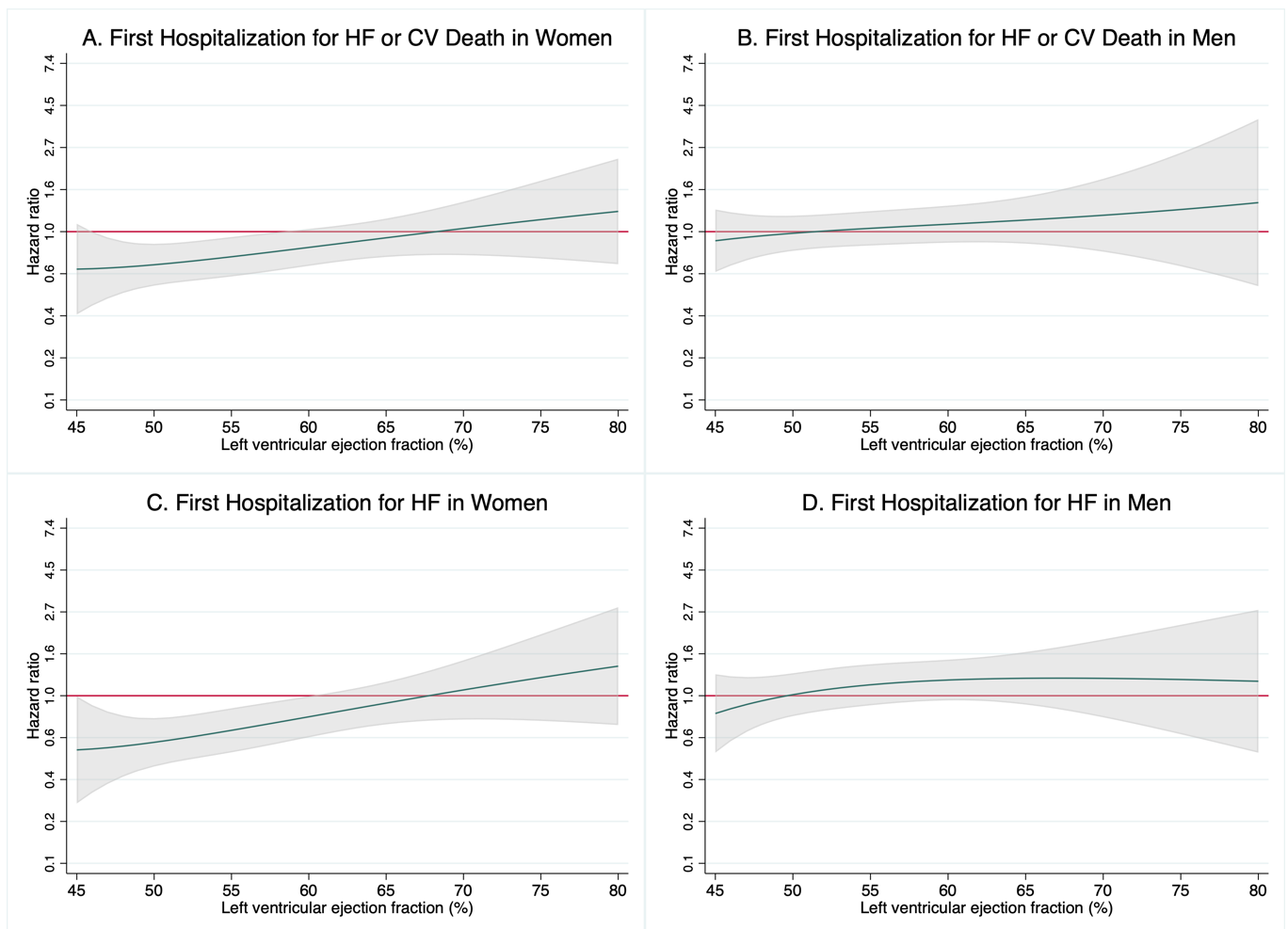
Supplemental Figure 3. Treatment effect in women and men in PARAGON-HF according to different analytical methods.

Hazard ratios and 95% confidence intervals shown for time to first event method, rate ratios and 95% confidence intervals shown for recurrent events methods. All models adjusted for age, heart rate, systolic blood pressure, body mass index, N-terminal pro-B-type natriuretic peptide level (log), estimated glomerular filtration rate, New York Heart Association functional class, left ventricular ejection fraction, prior heart failure hospitalization, myocardial infarction, diabetes, smoking, atrial fibrillation and either stratified by or adjusted for region.
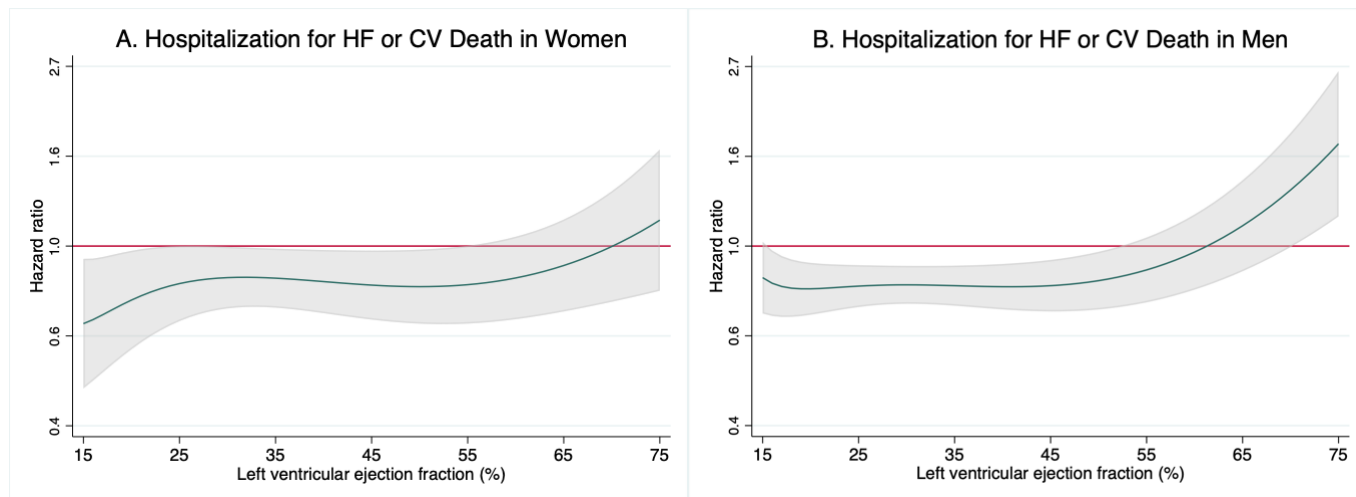
Primary Composite Outcome

	Ratio (95% CI)	Interaction P value
Time to first event		0.0213
Women	0.78 (0.65, 0.92)	
Men	1.03 (0.87, 1.22)	
LWYY		0.0225
Women	0.73 (0.60, 0.90)	
Men	1.02 (0.83, 1.24)	
Negative binomial		0.1416
Women	0.82 (0.67, 1.01)	
Men	1.03 (0.84, 1.26)	

Total Hospitalizations for HF

	Ratio (95% CI)	Interaction P value
Time to first event		0.0025
Women	0.72 (0.59, 0.87)	
Men	1.09 (0.90, 1.33)	
LWYY		0.0048
Women	0.67 (0.54, 0.84)	
Men	1.06 (0.84, 1.34)	
Negative binomial		0.0147
Women	0.75 (0.60, 0.93)	
Men	1.12 (0.89, 1.40)	

0.5   0.8 1.0 1.2 1.4

Sacubitril-valsartan better   Valsartan better

Hazard or rate ratio

Supplemental Figure 4. Treatment effect in women and men in PARAGON-HF according to left ventricular ejection fraction for first events.

A. Treatment effect on first hospitalization for heart failure or cardiovascular death in women. B. Treatment effect on first hospitalization for heart failure or cardiovascular death in men. C. Treatment effect on first hospitalization for heart failure in women. D. Treatment effect on first hospitalization for heart failure in men. Hazard ratios and 95% confidence intervals shown.

Supplemental Figure 5. Treatment effect in women and men in the CHARM programme[1] according to left ventricular ejection fraction for first events.

A. Treatment effect on first hospitalization for heart failure or cardiovascular death in women. B. Treatment effect on first hospitalization for heart failure or cardiovascular death in men. Hazard ratios and 95% confidence intervals shown.

Supplemental References

1. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-766.