

Online Appendix

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Online Table 1. Subsequent risk of clinical outcomes after incident pneumonia in PARADIGM-HF and PARAGON-HF excluding patients who had pneumonia and coincident hospital admission for worsening HF.

	Unadjusted HR* (95% CI)	Adjusted HR*† (95% CI)
PARADIGM-HF		
All-cause death	4.54 (3.83-5.37), p<0.001	3.79 (3.19-4.49), p<0.001
CV death	3.47 (2.81-4.29), p<0.001	2.85 (2.30-3.53), p<0.001
HF hospitalization	2.45 (1.86-3.24), p<0.001	2.00 (1.51-2.64), p<0.001
CV death or HF hospitalization	3.07 (2.54-3.70), p<0.001	2.50 (2.07-3.03), p<0.001
PARAGON-HF		
All-cause death	4.24 (3.44-5.22), p<0.001	3.56 (2.88-4.39), p<0.001
CV death	3.03 (2.23-4.11), p<0.001	2.57 (1.89-3.50), p<0.001
HF hospitalization	2.07 (1.56-2.73), p<0.001	1.85 (1.39-2.46), p<0.001
CV death or HF hospitalization	2.37 (1.88-2.98), p<0.001	2.13 (1.68-2.69), p<0.001

*Hazard ratios were estimated with stratification of geographic region.

†Adjusted variables include randomized treatment, age, sex, LVEF, NYHA class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log transformed NT-proBNP.

Patients who had pneumonia and coincident hospital admission for worsening HF were excluded, and the number was 98 (19% of pneumonia cases) in PARADIGM-HF and 77 (15% of pneumonia cases) in PARAGON-HF.

CI denotes confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Nepilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality

and Morbidity in Heart failure trial; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial.

Online Table 2. Subsequent risk of clinical outcomes after incident pneumonia in PARADIGM-HF and PARAGON-HF excluding patients who died during a pneumonia event

	Unadjusted HR* (95% CI)	Adjusted HR*† (95% CI)
PARADIGM-HF		
All-cause death	3.52 (2.95-4.20), p<0.001	2.92 (2.44-3.49), p<0.001
CV death	3.37 (2.75-4.11), p<0.001	2.75 (2.25-3.37), p<0.001
HF hospitalization	2.84 (2.20-3.66), p<0.001	2.30 (1.78-2.98), p<0.001
CV death or HF hospitalization	2.87 (2.37-3.48), p<0.001	2.33 (1.92-2.83), p<0.001
PARAGON-HF		
All-cause death	3.32 (2.67-4.13), p<0.001	2.73 (2.19-3.40), p<0.001
CV death	2.82 (2.10-3.79), p<0.001	2.33 (1.74-3.14), p<0.001
HF hospitalization	2.22 (1.71-2.87), p<0.001	1.99 (1.53-2.59), p<0.001
CV death or HF hospitalization	2.24 (1.78-2.81), p<0.001	2.01 (1.60-2.54), p<0.001

*Hazard ratios were estimated with stratification of geographic region.

†Adjusted variables include randomized treatment, age, sex, LVEF, NYHA class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log transformed NT-proBNP.

Patients who died during a pneumonia event were excluded, and the number was 73 (14% of pneumonia cases) in PARADIGM-HF and 41 (8% of pneumonia cases) in PARAGON-HF.

CI denotes confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio;

PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart failure trial;

PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial.

Online Table 3. Subsequent risk of clinical outcomes after incident pneumonia in PARADIGM-HF and PARAGON-HF excluding patients who died during a pneumonia event or within 4 weeks after such an event

	Unadjusted HR* (95% CI)	Adjusted HR*† (95% CI)
PARADIGM-HF		
All-cause death	3.17 (2.63-3.81), p<0.001	2.63 (2.18-3.16), p<0.001
CV death	2.96 (2.39-3.65), p<0.001	2.42 (1.95-3.00), p<0.001
HF hospitalization	2.81 (2.17-3.62), p<0.001	2.28 (1.76-2.95), p<0.001
CV death or HF hospitalization	2.70 (2.21-3.29), p<0.001	2.19 (1.79-2.68), p<0.001
PARAGON-HF		
All-cause death	2.98 (2.38-3.74), p<0.001	2.45 (1.95-3.08), p<0.001
CV death	2.55 (1.88-3.46), p<0.001	2.12 (1.56-2.88), p<0.001
HF hospitalization	2.23 (1.72-2.89), p<0.001	2.01 (1.54-2.61), p<0.001
CV death or HF hospitalization	2.17 (1.72-2.73), p<0.001	1.95 (1.54-2.47), p<0.001

*Hazard ratios were estimated with stratification of geographic region.

†Adjusted variables include randomized treatment, age, sex, LVEF, NYHA class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log transformed NT-proBNP.

Patients who died during a pneumonia event or within 4 weeks after such an event were excluded, and the number was 87 (16.5% of pneumonia cases) in PARADIGM-HF and 51 (10% of pneumonia cases) in PARAGON-HF.

CI denotes confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Nepriylsin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality

and Morbidity in Heart failure trial; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial.

Online Table 4. Patient characteristics at baseline according to incident urinary tract infection during follow-up in PARADIGM-HF and PARAGON-HF

	PARADIGM-HF		p value	PARAGON-HF		p value
	No UTI N=8004	UTI N=395		No UTI N=4217	UTI N=579	
Age, years	63.64±11.39	67.01±10.89	<0.0001	72.36±8.48	75.52±7.59	<0.0001
Men, n(%)	6330 (79.1)	237 (60.0)	<0.0001	2152 (51.0)	165 (28.5)	<0.0001
Race, n(%)			0.0047			<0.0001
White	5287 (66.1)	257 (65.1)		3459 (82.0)	448 (77.4)	
Black	409 (5.1)	19 (4.8)		82 (1.9)	20 (3.5)	
Asian	1453 (18.2)	56 (14.2)		547 (13.0)	60 (10.4)	
Other	855 (10.7)	63 (15.9)		129 (3.1)	51 (8.8)	
Region, n(%)			<0.0001			<0.0001
North America	540 (6.7)	62 (15.7)		428 (10.1)	131 (22.6)	
Latin America	1342 (16.8)	91 (23.0)		301 (7.1)	69 (11.9)	
Western Europe and other*	1925 (24.1)	126 (31.9)		1208 (28.6)	182 (31.4)	

Central Europe	2765 (34.5)	61 (15.4)		1608 (38.1)	107 (18.5)	
Asia-Pacific	1432 (17.9)	55 (13.9)		672 (15.9)	90 (15.5)	
Body mass index, kg/m ²	28.16±5.51	28.29±5.72	0.643	30.13±4.97	30.88±5.23	0.0007
Systolic blood pressure, mmHg	121.39±15.24	121.24±16.89	0.8442	130.58±15.13	130.40±17.61	0.8028
Diastolic blood pressure, mmHg	73.67±10.08	71.84±9.77	0.0004	74.54±10.40	72.66±11.31	<0.0001
Heart rate, beats/min	72.43±12.03	70.72±11.45	0.0057	70.47±12.28	70.15±12.09	0.5469
LVEF, %	29.50±6.20	29.23±6.60	0.4007	57.40±7.88	58.48±7.81	0.002
NYHA class, n(%)			0.3913			0.0414
I	370 (4.6)	19 (4.8)		124 (2.9)	13 (2.2)	
II	5639 (70.6)	280 (71.1)		3273 (77.7)	433 (74.8)	
III	1923 (24.1)	95 (24.1)		799 (19.0)	133 (23.0)	
IV	60 (0.8)	0 (0.0)		19 (0.5)	0 (0.0)	
Ischemic etiology of HF, n(%)	4798 (59.9)	238 (60.3)	0.9029	1553 (36.8)	170 (29.4)	0.0004
Heart failure duration, n(%)			0.0288			0.8488
within 1 year	2423 (30.3)	100 (25.3)		1736 (41.3)	239 (41.4)	
>1 year to 5 years	3083 (38.5)	149 (37.7)		1466 (34.8)	206 (35.7)	

>5 years	2498 (31.2)	146 (37.0)		1005 (23.9)	132 (22.9)	
Current smoking, n(%)	1159 (14.5)	49 (12.4)	0.2512	326 (7.8)	27 (4.7)	0.0082
Alcohol use†, n(%)			0.2659			0.0001
<1 drink per day	7074 (88.4)	342 (86.6)		2692 (83.7)	398 (91.1)	
1-2 drinks per day	760 (9.5)	40 (10.1)		455 (14.1)	30 (6.9)	
≥ 3 drinks per day	170 (2.1)	13 (3.3)		71 (2.2)	9 (2.1)	
Medical history, n(%)						
Hospitalization for heart failure	5042 (63.0)	232 (58.7)	0.0873	2044 (48.5)	262 (45.3)	0.1459
Myocardial infarction	3456 (43.2)	178 (45.1)	0.4604	967 (22.9)	116 (20.0)	0.118
Angina	2183 (27.3)	121 (30.6)	0.1441	1229 (29.1)	159 (27.5)	0.4024
CABG or PCI	2494 (31.2)	146 (37.0)	0.0153	1174 (27.8)	147 (25.4)	0.2157
Hypertension	5638 (70.4)	302 (76.5)	0.0103	4028 (95.5)	556 (96.0)	0.576
Diabetes	2740 (34.2)	167 (42.3)	0.001	1775 (42.1)	287 (49.6)	0.0007
Atrial fibrillation	2950 (36.9)	141 (35.7)	0.6406	2210 (52.4)	311 (53.7)	0.555
Atrial fibrillation or flutter on ECG	2006 (25.1)	84 (21.3)	0.0884	1390 (33.0)	162 (28.0)	0.0163
Stroke	674 (8.4)	51 (12.9)	0.0019	436 (10.4)	72 (12.5)	0.1211

COPD	1014 (12.7)	66 (16.7)	0.0192	570 (13.5)	100 (17.3)	0.0142
Asthma	293 (3.7)	21 (5.3)	0.0904	280 (6.6)	68 (11.8)	<0.0001
Influenza vaccination	440 (5.5)	37 (9.4)	0.0012	649 (15.5)	151 (26.3)	<0.0001
Treatment, n(%)						
Digoxin	2431 (30.4)	108 (27.3)	0.2004	396 (9.4)	54 (9.3)	0.9604
Diuretics	6432 (80.4)	306 (77.5)	0.159	4036 (95.7)	549 (94.8)	0.3279
Pretrial use of ACE inhibitors or ARBs	7985 (99.8)	394 (99.7)	0.9499	3670 (87.0)	469 (81.0)	<0.0001
Randomized treatment‡	3989 (49.8)	198 (50.1)	0.9107	2133 (50.6)	274 (47.3)	0.1415
Beta-blockers	7450 (93.1)	361 (91.4)	0.1998	3370 (79.9)	451 (77.9)	0.257
Aldosterone antagonists	4492 (56.1)	179 (45.3)	<0.0001	1107 (26.3)	132 (22.8)	0.0751
Antiplatelets	4501 (56.2)	235 (59.5)	0.2023	1934 (45.9)	260 (44.9)	0.6647
Anticoagulants	2555 (31.9)	130 (32.9)	0.6805	1381 (32.7)	170 (29.4)	0.1023
Statins	4471 (55.9)	252 (63.8)	0.0019	2670 (63.3)	385 (66.5)	0.1358
Pacemakers	1009 (12.6)	79 (20.0)	0.0001	395 (9.4)	64 (11.1)	0.1958
Implantable cardioverter defibrillator	1172 (14.6)	71 (18.0)	0.0687	15 (0.4)	3 (0.5)	0.5489
Cardiac resynchronization therapy	534 (6.7)	40 (10.1)	0.0079	-	-	-

Symptoms, signs and HRQL, n (%)

Dyspnea on effect	6873 (86.0)	334 (84.8)	0.4823	3887 (92.3)	537 (92.7)	0.7221
Dyspnea at rest	294 (3.7)	15 (3.8)	0.896	125 (3.0)	14 (2.4)	0.4589
Orthopnea	561 (7.0)	47 (11.9)	0.0002	747 (17.7)	139 (24.0)	0.0003
Paroxysmal nocturnal dyspnea	374 (4.7)	25 (6.3)	0.1301	173 (4.1)	18 (3.1)	0.2487
Rales	1657 (20.7)	91 (23.1)	0.2612	302 (7.2)	43 (7.4)	0.8251
Edema	771 (9.7)	47 (11.9)	0.1371	1575 (37.4)	251 (43.4)	0.0057
Jugular venous distention	638 (8.0)	25 (6.3)	0.2388	551 (13.2)	104 (18.1)	0.0013
Third heart sound	772 (9.7)	24 (6.1)	0.0195	94 (2.2)	17 (3.0)	0.2774
Fatigue	4150 (52.0)	193 (49.0)	0.2497	2137 (50.8)	300 (51.8)	0.6384
KCCQ clinical summary score	80 (63-92)	77 (60-88)	0.0005	75 (61-87)	70 (54-84)	<0.0001

Laboratory measures

Creatinine, mg/dL	1.12±0.30	1.17±0.34	0.0016	1.09±0.31	1.11±0.31	0.0928
eGFR, ml/min/1.73m ²	68.01±20.10	61.44±19.47	<0.0001	63.24±19.11	57.73±18.39	<0.0001
eGFR <60 ml/min/1.73m ² , n (%)	2864 (35.8)	197 (49.9)	<0.0001	1995 (47.3)	346 (59.8)	<0.0001
Hemoglobin, g/L	139.52±16.03	136.47±15.77	0.0004	135.57±15.61	131.10±14.30	<0.0001

Albumin, g/L	42.81±3.14	42.11±3.27	<0.0001	42.34±3.00	41.64±3.14	<0.0001
Hemocrit, %	42.36±4.87	41.42±4.90	0.0004	43.11±4.76	42.01±4.56	<0.0001
Neutrophil-to-lymphocyte rate	2.67±1.60	2.83±1.55	0.0748	2.80±1.46	2.88±1.63	0.2447
NT-proBNP, pg/ml	1608 (886-3204)	1723 (1007-3645)	0.0398	913 (463-1613)	889 (475-1640)	0.6456
No atrial fibrillation or flutter on ECG	1490 (819-2990)	1569 (882-3362)		594 (377-1051)	636 (398-1091)	
Atrial fibrillation or flutter on ECG	1981 (1161-3846)	2521 (1381-4389)		1568 (1162-2233)	1847 (1268-2838)	

Values are mean ± SD, median (interquartile range), or n (%).

*This category includes South Africa and Israel.

†One drink equals 12-ounces of beer, or 8-ounces of malt liquor, or 5-ounces of wine, or 1.5-ounces or a “shot” of 80-proof distilled spirits or liquor (e.g., gin, rum, vodka, or whiskey).

‡It was sacubitril/valsartan versus enalapril in PARADIGM-HF, and sacubitril/valsartan versus valsartan in PARAGON-HF.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HRQL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire, KCCQ clinical summary score -range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure.; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Nepriylsin Inhibitor With Angiotensin Converting Enzyme Inhibitor to

Determine Impact on Global Mortality and Morbidity in Heart failure trial; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial; PCI, percutaneous coronary intervention; UTI, urinary tract infection.

Online Table 5. Subsequent risk of clinical outcomes after incident urinary tract infection in PARADIGM-HF and PARAGON-HF

	Unadjusted HR* (95% CI)	Adjusted HR*† (95% CI)
PARADIGM-HF		
All-cause death	2.19 (1.77-2.72), p<0.001	2.06 (1.66-2.56), p<0.001
CV death	1.93 (1.49-2.50), p<0.001	1.81 (1.40-2.35), p<0.001
HF hospitalization	1.31 (0.93-1.86), p=0.122	1.25 (0.89-1.78), p=0.201
CV death or HF hospitalization	1.34 (1.03-1.74), p=0.029	1.27 (0.97-1.65), p=0.08
PARAGON-HF		
All-cause death	2.14 (1.72-2.66), p<0.001	2.01 (1.61-2.51), p<0.001
CV death	2.23 (1.68-2.96), p<0.001	2.12 (1.58-2.83), p<0.001
HF hospitalization	1.73 (1.37-2.18), p<0.001	1.63 (1.28-2.08), p<0.001
CV death or HF hospitalization	1.80 (1.47-2.21), p<0.001	1.72 (1.40-2.12), p<0.001

*Hazard ratios were estimated with stratification of geographic region.

†Adjusted variables include randomized treatment, age, sex, LVEF, NYHA class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log transformed NT-proBNP.

CI denotes confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor-Nepilysin Inhibitor With Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart failure trial; PARAGON-HF, Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction trial.