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ORIGINAL INVESTIGATIONS

Incidence and Outcomes of Pneumonia in Patients With Heart Failure

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ABSTRACT

BACKGROUND The incidence of pneumonia and subsequent outcomes has not been compared in patients with heart failure and reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).

OBJECTIVES This study aimed to examine the rate and impact of pneumonia in the 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) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction) trials.

METHODS The authors analyzed the incidence of investigator-reported pneumonia and the rates of HF hospitalization, cardiovascular death, and all-cause death before and after the occurrence of pneumonia, and estimated risk after the first occurrence of pneumonia in unadjusted and adjusted analyses (the latter including N-terminal pro-B-type natriuretic peptide).

RESULTS In PARADIGM-HF, 528 patients (6.3%) developed pneumonia after randomization, giving an incidence rate of 29 (95% CI: 27 to 32) per 1,000 patient-years. In PARAGON-HF, 510 patients (10.6%) developed pneumonia, giving an incidence rate of 39 (95% CI: 36 to 42) per 1,000 patient-years. The subsequent risk of all trial outcomes was elevated after the occurrence of pneumonia. In PARADIGM-HF, the adjusted hazard ratio (HR) for the risk of death from any cause was 4.34 (95% CI: 3.73 to 5.05). The corresponding adjusted HR in PARAGON-HF was 3.76 (95% CI: 3.09 to 4.58).

CONCLUSIONS The incidence of pneumonia was high in patients with HF, especially HFpEF, at around 3 times the expected rate. A first episode of pneumonia was associated with 4-fold higher mortality. (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF], NCT01035255; Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ARB [Angiotensin Receptor Blocker] Global Outcomes in Heart Failure With Preserved Ejection Fraction [PARAGON-HF], NCT01920711) (J Am Coll Cardiol 2021;77:1961–73) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure and preserved ejection fraction

HFrEF = heart failure and reduced ejection fraction

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

In the United States, community-acquired pneumonia affects >5 million adults and is associated with approximately 1.5 million hospital admissions and up to 100,000 deaths annually (1–3). In the United Kingdom, pneumonia accounts for more hospital admissions and bed-days than any other lung condition, and worldwide, pneumonia is a significant cause of morbidity and mortality, especially in the elderly (4). Indeed, the aging of many populations is thought to be one reason why hospitalizations for pneumonia have increased by up to 50% in Western countries over the past 2 decades and survival from pneumonia has changed little in half a century (5,6). Although usually considered to be an acute event, there is evidence that pneumonia is associated with long-term cardiovascular sequelae, particularly acute coronary events, and the same may be true for heart failure (HF), although this has not been investigated fully (1).

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Patients with HF are thought to be at 2-fold higher risk of pneumonia than age- and sex-matched individuals in the population, and survival from pneumonia is lower in patients with HF than in those without. Conversely, pneumonia increases the risk of worsening HF and is often considered a factor in decompensation leading to hospitalization (7–9). The most common cause of pneumonia is infection with the bacterium *Streptococcus pneumoniae* (10,11). Two pneumococcal vaccines are available and recommended in patients with HF. Influenza also causes pneumonia, and vaccination against influenza is widely available and inexpensive (12). However, uptake of each of these vaccines is poor and may even be declining (13). This deficiency in care may be particularly problematic for patients with HF and preserved ejection fraction (HFpEF), who have fewer other treatment options, compared with patients with HF and reduced ejection fraction (HFrEF) (14–16).

In the present post hoc analysis, we examined the incidence of pneumonia in the 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, which enrolled a large cohort of ambulatory HFrEF patients with predominantly mild symptoms who were receiving contemporary therapy, and compared this with the incidence of pneumonia in patients with HFpEF in the PARAGON-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ARB [Angiotensin Receptor Blocker] Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial (17–22). We also examined outcomes after pneumonia to assess the longer-term sequelae of this respiratory infection.

METHODS

STUDY POPULATION. This study consisted of 8,399 patients with HFrEF randomized in PARADIGM-HF and 4,796 patients with HFpEF in PARAGON-HF. The design, baseline characteristics, and results of PARADIGM-HF and PARAGON-HF have been published (17–22). Each was a randomized, double-blind, controlled trial that compared sacubitril/valsartan with a renin-angiotensin system blocker alone. Each trial enrolled adults (≥18 years of age in PARADIGM-HF and ≥50 years of age in PARAGON-HF) with symptomatic HF, defined as New York Heart Association (NYHA) functional class II to IV. Patients also needed to have functional or structural cardiac disease and elevated natriuretic peptides. In PARADIGM-HF, patients were required to have left ventricular ejection fraction (LVEF) ≤40% and in PARAGON-HF LVEF ≥45% and left ventricular hypertrophy, left atrial enlargement, or both. In both trials, patients were also required to have an elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) level (with different thresholds depending on the occurrence of recent HF hospitalization and presence of atrial fibrillation/flutter).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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In each trial, patients entered an initial run-in period during which they received the comparator (enalapril or valsartan), followed by a second period of treatment with sacubitril/valsartan. Patients tolerating both run-in periods were randomized 1:1 to sacubitril/valsartan (target dose 97/103 mg twice daily) and either enalapril (target dose 10 mg twice daily) in PARADIGM-HF or valsartan (target dose 160 mg twice daily) in PARAGON-HF. Each trial was approved by ethics committees at the investigative sites, and all patients provided written informed consent. Each trial was event driven, and the median follow-up in PARADIGM-HF was 27 months (stopped early for efficacy) and in PARAGON-HF was 35 months (completed follow-up to targeted number of events).

CASES OF PNEUMONIA. Cases of pneumonia during follow-up were identified from investigator-reported adverse events recorded in the case report form and coded according to the Medical Dictionary for Regulatory Activities. Any event with the coding "pneumonia" was included in this analysis except aspiration pneumonia, whether a specific pathogen was named or not and regardless of any named pathogen.

COMPARATOR GROUP. To determine whether infection per se identified patients at high risk ("vulnerable" patients) or increased subsequent risk, we used a comparator group with another type of infection. The only other group of sufficient size for analysis was urinary tract infection.

OUTCOMES. In PARADIGM-HF, the primary endpoint was time to first occurrence of HF hospitalization or cardiovascular death, and in PARAGON-HF the primary outcome was all HF hospitalizations (including first and repeated admissions) or cardiovascular death. In the present analysis, the primary outcome used for both trials was time to first occurrence of HF hospitalization or cardiovascular death. We also examined the components of the primary end point and death from any cause. All events in the 2 trials were adjudicated by the same endpoints committee.

STATISTICAL ANALYSIS. Baseline characteristics of patients who did and did not develop incident pneumonia are presented as mean ± SD or median (interquartile range) for continuous variables and n (%) for categoric variables. The baseline characteristics of patients who did and did not develop pneumonia during follow-up were compared by means of the Student's *t*-test or Mann-Whitney *U* test as appropriate for continuous variables and the chi-square test for categoric variables.

Incident rates for pneumonia during follow-up were calculated with the use of Kaplan-Meier estimates as 1,000 patient-years of follow-up. The effect of randomized treatment on the occurrence of pneumonia was estimated with the use of Cox proportional hazards models, with geographic region as a stratification factor. To describe the prognosis of patients who experienced an incidence of pneumonia on subsequent outcomes of interest, the time to event from the date of pneumonia occurrence to the date of the outcome of interest or end of follow-up (whichever occurred first) was used to estimate the incidence rate and cumulative incidence risk according to Kaplan-Meier estimates. Among individuals who experienced >1 episode of pneumonia, the first episode was considered as the index event. To estimate the incidence rate of outcomes that occurred from randomization to the occurrence of pneumonia or end of follow-up (whichever occurred first), the time to event from the date of randomization to the date of the outcome of interest was used. For individuals who experienced pneumonia events, only those events that occurred before the incidence of pneumonia were considered; otherwise, they were censored at the day of pneumonia occurrence. Individuals without the event of interest and who did not experience an incidence pneumonia were censored at the end of follow-up.

The association between incidence of pneumonia and subsequent risks of clinical outcomes was examined with pneumonia as a time-updated variable in a Cox regression analysis that considered the time before the onset of pneumonia and the time from the onset of pneumonia to the occurrence of clinical outcomes, with stratification by region (23). The association was further adjusted for treatment assignment and baseline covariates, including age, sex, LVEF, NYHA functional class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, estimated glomerular filtration rate (eGFR), and NT-proBNP. We conducted 3 sensitivity analyses related to the trial outcomes in patients with pneumonia: The first excluded patients with an episode of pneumonia which coincided with a HF hospitalization, the second excluded patients who died during the episode of pneumonia and the third excluded patients who died during an episode of pneumonia or within the 4 weeks after such an event,

TABLE 1 Patient Characteristics at Baseline According to Occurrence of Pneumonia During Follow-Up in PARADIGM-HF and PARAGON-HF

	PARADIGM-HF			PARAGON-HF		
	Without Pneumonia (n = 7,871)	With Pneumonia (n = 528)	p Value	Without Pneumonia (n = 4,286)	With Pneumonia (n = 510)	p Value
Age, yrs	63.6 ± 11.4	66.9 ± 11.6	<0.0001	72.4 ± 8.4	75.6 ± 8.0	<0.0001
Male	6,124 (77.8)	443 (83.9)	0.001	2,056 (48.0)	261 (51.2)	0.1707
Race			0.528			0.0679
White	5,182 (65.8)	362 (68.6)		3,510 (81.9)	397 (77.8)	
Black	404 (5.1)	24 (4.5)		86 (2.0)	16 (3.1)	
Asian	1,425 (18.1)	84 (15.9)		536 (12.5)	71 (13.9)	
Other	860 (10.9)	58 (11.0)		154 (3.6)	26 (5.1)	
Region			<0.0001			<0.0001
North America	529 (6.7)	73 (13.8)		444 (10.4)	115 (22.5)	
Latin America	1,336 (17.0)	97 (18.4)		321 (7.5)	49 (9.6)	
Western Europe and other*	1,899 (24.1)	152 (28.8)		1,372 (32.0)	171 (33.5)	
Central Europe	2,702 (34.3)	124 (23.5)		1,612 (37.6)	103 (20.2)	
Asia-Pacific	1,405 (17.9)	82 (15.5)		537 (12.5)	72 (14.1)	
Body mass index, kg/m^2	28.2 ± 5.5	27.9 ± 5.7	0.2366	30.2 ± 5.0	30.1 ± 5.1	0.4779
Systolic blood pressure, mm Hg	121.4 ± 15.2	121.7 ± 16.8	0.6438	130.7 ± 15.2	129.2 ± 17.5	0.0432
Diastolic blood pressure, mm Hg	73.7 ± 10.0	72.2 ± 10.9	0.0015	74.6 ± 10.4	72.0 ± 11.3	<0.0001
Heart rate, beats/min	72.3 ± 11.9	72.7 ± 13.2	0.4456	70.5 ± 12.3	70.1 ± 12.2	0.5727
Left ventricular ejection fraction, %	29.5 ± 6.2	29.3 ± 6.6	0.4866	57.5 ± 7.9	57.7 ± 8.1	0.6733
NYHA functional class			0.9545			0.0046
I	362 (4.6)	27 (5.1)		119 (2.8)	18 (3.5)	
II	5550 (70.6)	369 (70.2)		3343 (78.0)	363 (71.3)	
III	1892 (24.1)	126 (24.0)		805 (18.8)	127 (25.0)	
IV	56 (0.7)	4 (0.8)		18 (0.4)	1 (0.2)	
Ischemic etiology of HF	4703 (59.8)	333 (63.1)	0.1321	1535 (35.8)	188 (36.9)	0.6435
Heart failure duration			<0.0001			0.5688
Within 1 yr	2,408 (30.6)	115 (21.8)		1,773 (41.5)	202 (39.8)	
>1–5 yrs	3,026 (38.4)	206 (39.0)		1,496 (35.0)	176 (34.6)	
>5 yrs	2,437 (31.0)	207 (39.2)		1,007 (23.6)	130 (25.6)	
Current smoking	1,129 (14.3)	79 (15.0)	0.6951	316 (7.4)	37 (7.3)	0.9129
Alcohol use†			0.0319			0.8205
<1 drink per day	6,968 (88.5)	448 (84.8)		2,751 (84.5)	339 (85.0)	
1–2 drinks per day	733 (9.3)	67 (12.7)		432 (13.3)	53 (13.3)	
≥3 drinks per day	170 (2.2)	13 (2.5)		73 (2.2)	7 (1.8)	

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and in the third we examined the risk associated with pneumonia according to the time interval after an episode of this infection: ≤1 month, >1 month to 3 months, and >3 months.

A 2-sided p value of <0.05 was considered to be statistically significant. All analyses were performed with the use of Stata version 15 (Statacorp, College Station, Texas).

RESULTS

In PARADIGM-HF, 528 patients (6.3%) developed pneumonia after randomization, giving an incidence rate of 29 (95% CI: 27 to 32) per 1,000 patient-years. In PARAGON-HF, 510 patients (10.6%) developed pneumonia, giving an incidence rate of 39 (95% CI: 36 to 42) per 1,000 patient-years.

BASELINE CHARACTERISTICS. PARADIGM-HF. Table 1 summarizes the baseline characteristics of patients who did and did not develop pneumonia during follow-up. Patients with pneumonia, compared with those without, were older (66.9 years vs. 63.6 years; p < 0.001) and were more likely to be male (83.9% vs. 77.8%; p < 0.001). Participants developing pneumonia also had HF for longer, but there was no difference in the frequency of previous HF hospitalization. They also had a lower (worse) Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) than patients not developing pneumonia (76 vs. 80), although there was no

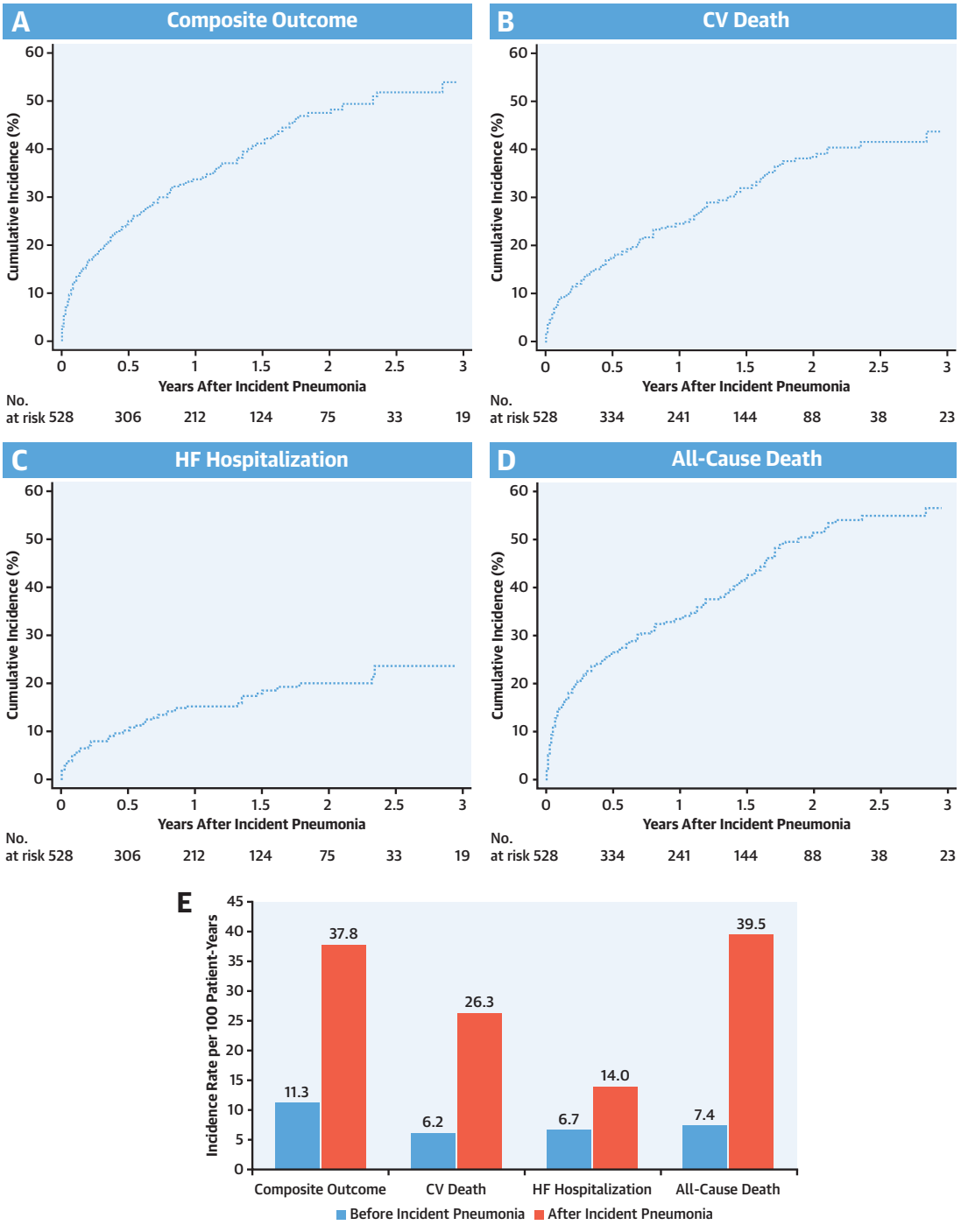
TABLE 1 Continued

	PARADIGM-HF			PARAGON-HF		
	Without Pneumonia (n = 7,871)	With Pneumonia (n = 528)	p Value	Without Pneumonia (n = 4,286)	With Pneumonia (n = 510)	p Value
Medical history						
Hospitalization for heart failure	4,927 (62.6)	347 (65.7)	0.1507	2,027 (47.3)	279 (54.7)	0.0015
Myocardial infarction	3,387 (43.0)	247 (46.8)	0.0923	969 (22.6)	114 (22.4)	0.8962
Angina	2,151 (27.3)	153 (29.0)	0.411	1,235 (28.8)	153 (30.0)	0.5769
CABG or PCI	2,429 (30.9)	211 (40.0)	<0.0001	1,153 (26.9)	168 (32.9)	0.0039
Hypertension	5,544 (70.4)	396 (75.0)	0.0257	4,093 (95.5)	491 (96.3)	0.4193
Diabetes	2,682 (34.1)	225 (42.6)	<0.0001	1,814 (42.3)	248 (48.6)	0.0066
Atrial fibrillation	2,850 (36.2)	241 (45.6)	<0.0001	2,208 (51.5)	313 (61.4)	<0.0001
Atrial fibrillation or flutter on ECG	1,948 (24.7)	142 (26.9)	0.2698	1,361 (31.8)	191 (37.5)	0.0093
Stroke	665 (8.4)	60 (11.4)	0.021	442 (10.3)	66 (13.0)	0.0632
COPD	945 (12.0)	135 (25.6)	<0.0001	537 (12.5)	133 (26.2)	<0.0001
Asthma	288 (3.7)	26 (4.9)	0.1379	288 (6.7)	60 (11.8)	<0.0001
Influenza vaccination	1,591 (20.2)	178 (33.7)	<0.0001	1,439 (33.7)	254 (50.1)	<0.0001
Treatment						
Digoxin	2,386 (30.3)	153 (29.0)	0.5174	408 (9.5)	42 (8.2)	0.3471
Diuretics	6,303 (80.1)	435 (82.4)	0.1975	4,093 (95.5)	492 (96.5)	0.3108
Pretrial use of ACE inhibitors or ARBs	7,853 (99.8)	526 (99.6)	0.4933	3,723 (86.9)	416 (81.6)	0.001
Randomized treatment‡	3,923 (49.8)	264 (50.0)	0.9437	2,154 (50.3)	253 (49.6)	0.7818
Beta-blockers	7,331 (93.1)	480 (90.9)	0.0519	3,424 (79.9)	397 (77.8)	0.278
Aldosterone antagonists	4,427 (56.2)	244 (46.2)	<0.0001	1,115 (26.0)	124 (24.3)	0.4067
Antiplatelets	4,416 (56.1)	320 (60.6)	0.0435	1,953 (45.6)	241 (47.3)	0.4695
Anticoagulants	2,488 (31.6)	197 (37.3)	0.0065	1,366 (31.9)	185 (36.3)	0.0445
Statins	4,403 (55.9)	320 (60.6)	0.0364	2,728 (63.6)	327 (64.1)	0.8352
Pacemaker	985 (12.5)	103 (19.5)	<0.0001	400 (9.3)	59 (11.6)	0.1047
Implantable cardioverter-defibrillator	1,130 (14.4)	113 (21.4)	<0.0001	16 (0.4)	2 (0.4)	0.9475
Cardiac resynchronization therapy	517 (6.6)	57 (10.8)	0.0002	-	-	-
Symptoms, signs, and HRQL						
Dyspnea on effort	6,769 (86.2)	438 (83.3)	0.0653	3,963 (92.6)	461 (90.7)	0.143
Dyspnea at rest	280 (3.6)	29 (5.5)	0.0216	127 (3.0)	12 (2.4)	0.443
Orthopnea	559 (7.1)	49 (9.3)	0.0597	767 (17.9)	119 (23.4)	0.0025
Paroxysmal nocturnal dyspnea	366 (4.7)	33 (6.3)	0.0922	162 (3.8)	29 (5.7)	0.0361
Rales	1,635 (20.8)	113 (21.5)	0.7128	293 (6.8)	52 (10.2)	0.0052
Edema	763 (9.7)	55 (10.5)	0.5778	1,608 (37.6)	218 (42.9)	0.0187
Jugular venous distention	618 (7.9)	45 (8.6)	0.5705	564 (13.3)	91 (18.1)	0.0031
Third heart sound	756 (9.6)	40 (7.6)	0.1259	101 (2.4)	10 (2.0)	0.5821
Fatigue	4,098 (52.2)	245 (46.6)	0.0131	2,202 (51.4)	235 (46.4)	0.0303
KCCQ clinical summary score§	80 (64–92)	76 (62–89)	0.0002	75 (61- 87)	71 (54–84)	<0.0001
Laboratory measures						
Creatinine, mg/dl	1.12 ± 0.30	1.21 ± 0.30	<0.0001	1.08 ± 0.31	1.15 ± 0.31	<0.0001
eGFR, ml/min/1.73 m^2	68.1 ± 20.2	61.9 ± 17.7	<0.0001	63.0 ± 19.2	58.7 ± 17.8	<0.0001
eGFR <60 ml/min/1.73 m^2	2796 (35.5)	265 (50.2)	<0.0001	2048 (47.8)	293 (57.5)	<0.0001
Hemoglobin, g/l	139.4 ± 15.9	139.7 ± 17.7	0.6825	135.4 ± 15.4	131.9 ± 15.8	<0.0001
Albumin, g/l	42.8 ± 3.1	42.1 ± 3.3	<0.0001	42.3 ± 3.0	41.6 ± 3.3	<0.0001
Hematocrit, %	42.3 ± 4.8	42.4 ± 5.3	0.864	43.1 ± 4.7	42.3 ± 5.0	0.0005
NT-proBNP, pg/ml	1,585 (877-3,118)	2,142 (1,094–4,326)	<0.0001	895 (458–1,583)	1,017 (546–1,821)	0.0003
No atrial fibrillation or flutter on ECG	1,465 (812–2,935)	2,078 (1,015–4,367)		591 (377-1,045)	669 (425-1,165)	
Atrial fibrillation or flutter on ECG	1,976 (1,154–3,848)	2,466 (1,307–4,093)		1,568 (1,161–2,239)	1,722 (1,231–2,530)	

Values are mean ± SD, n (%), or median (interquartile range). *This category includes South Africa and Israel. †One drink equals 12 ounces of beer, 8 ounces of malt liquor, 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). ‡Treatment was sacubitril/valsartan vs. enalapril in PARADIGM-HF, and sacubitril/valsartan vs. valsartan in PARAGON-HF. §Range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure.

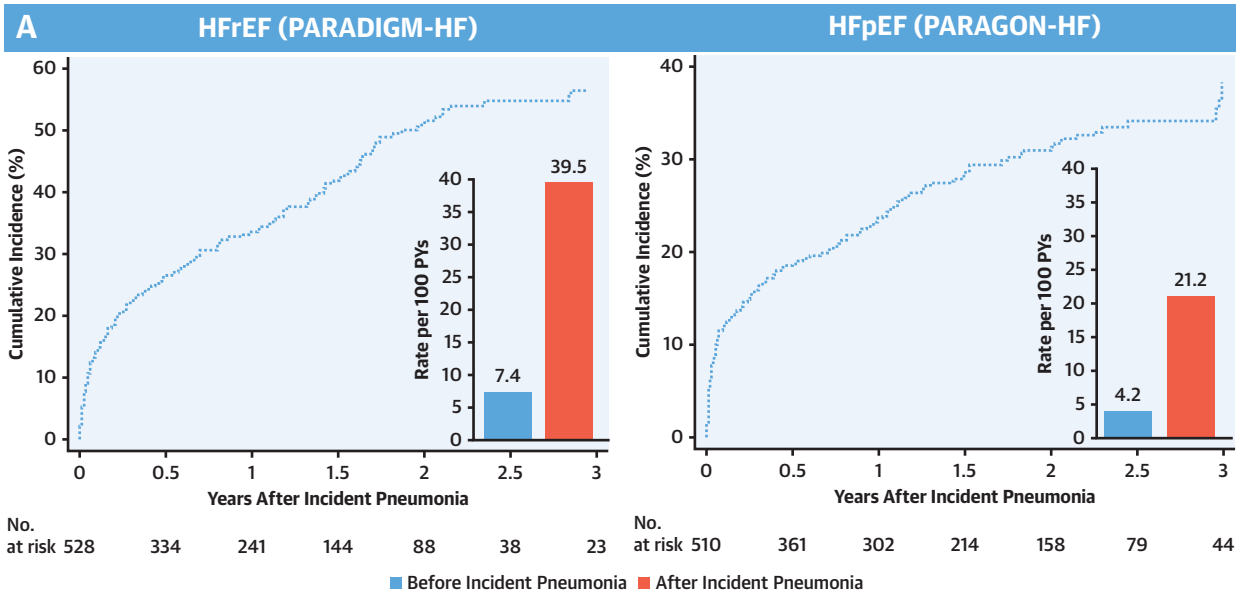
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; HRQL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; 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; PCI = percutaneous coronary intervention.

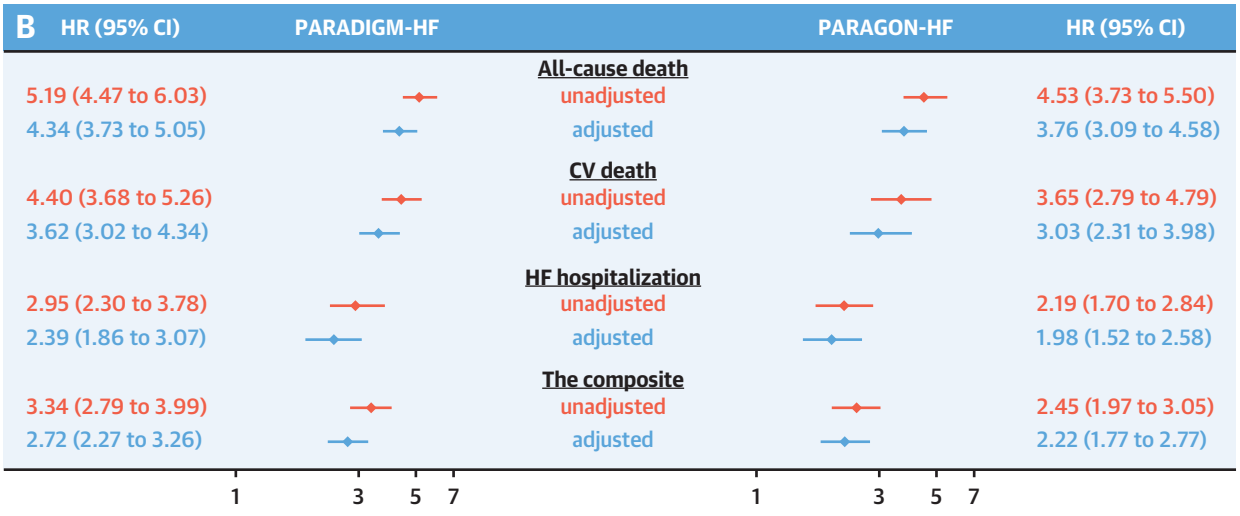
FIGURE 1 **Risk of Clinical Outcomes After Occurrence of Pneumonia in PARADIGM-HF**



The **line graphs** show the cumulative incidence risks of **(A)** the composite of the first HF hospitalization or CV death, **(B)** CV death, **(C)** the first HF hospitalization, and **(D)** all-cause death after the occurrence of pneumonia. **(E)** The **bar graph** shows the incidence rates (per 100 patient-years) for the composite outcome of the first HF hospitalization or CV death, CV death, HF hospitalization, and all-cause death. The **blue bars** are the rates before the occurrence of pneumonia, and the **red bars** are the rates after the occurrence of pneumonia. CV = cardiovascular; HF = heart failure.

CENTRAL ILLUSTRATION **Risk of Clinical Outcomes After Incident Pneumonia in Heart Failure**





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(A) The cumulative incidence of death from any cause in PARADIGM-HF and in PARAGON-HF and (included as **insets**) the incidence rates (per 100 patient-years) for all-cause death before and after incident pneumonia in PARADIGM-HF and in PARAGON-HF. **(B)** The subsequent risk of clinical outcomes after incident pneumonia in PARADIGM-HF and in PARAGON-HF. The composite outcome is the first occurrence of HF hospitalization or CV death. CI = confidence interval; CV = cardiovascular; HF = heart failure; HFrEF = heart failure and reduced ejection fraction; HFpEF = heart failure and preserved ejection fraction; 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.

difference in NYHA functional class. In general, patients who developed pneumonia had more symptoms and signs of HF than those who did not develop pneumonia. Patients with pneumonia also had more comorbidity, including chronic obstructive pulmonary disease (25.6% vs. 12.0%), diabetes (42.6% vs. 34.1%), and atrial fibrillation (45.6% vs. 36.2%). They also had a higher NT-proBNP level and a lower eGFR than patients who did not develop pneumonia (Table 1).

TABLE 2 Subsequent Risk of Clinical Outcomes After Occurrence of Pneumonia in PARADIGM-HF and PARAGON-HF

	Unadjusted HR* (95% CI)	p Value	Adjusted HR*† (95% CI)	p Value
PARADIGM-HF				
All-cause death	5.19 (4.47–6.03)	<0.001	4.34 (3.73–5.05)	<0.001
CV death	4.40 (3.68–5.26)	<0.001	3.62 (3.02–4.34)	<0.001
HF hospitalization	2.95 (2.30–3.78)	<0.001	2.39 (1.86–3.07)	<0.001
CV death or HF hospitalization	3.34 (2.79–3.99)	<0.001	2.72 (2.27–3.26)	<0.001
PARAGON-HF				
All-cause death	4.53 (3.73–5.50)	<0.001	3.76 (3.09–4.58)	<0.001
CV death	3.65 (2.79–4.79)	<0.001	3.03 (2.31–3.98)	<0.001
HF hospitalization	2.19 (1.70–2.84)	<0.001	1.98 (1.52–2.58)	<0.001
CV death or HF hospitalization	2.45 (1.97–3.05)	<0.001	2.22 (1.77–2.77)	<0.001

*Hazard ratios were estimated with stratification by geographic region. †Adjusted variables included randomized treatment, age, sex, left ventricular ejection fraction, NYHA functional 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 = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; other abbreviations as in Table 1.

PARAGON-HF. The differences in baseline characteristics between patients who did and did not develop pneumonia during follow-up were broadly similar in PARAGON-HF to the differences observed in PARADIGM-HF and are also presented in Table 1. Patients with pneumonia, compared with those without, also were older (75.6 years vs. 72.4 years; $p < 0.001$) and more likely to be male, although the sex difference was not significant in PARAGON-HF (51.2% vs. 48.0%; $p = 0.171$). Participants developing pneumonia had a higher frequency of previous HF hospitalization, but there was no difference in the duration of HF. They also had a lower KCCQ-CSS (71 vs. 75) and worse NYHA functional class than patients not developing pneumonia. Patients who developed pneumonia had more symptoms and signs of HF than those who did not develop pneumonia, and the differences were more pronounced than in PARADIGM-HF. Patients with pneumonia also had more comorbidity, including chronic obstructive pulmonary disease (26.2% vs. 12.5%), diabetes (48.6% vs. 42.3%), and atrial fibrillation (61.4% vs. 51.5%). They had also a higher NT-proBNP level and a lower eGFR than patients who did not develop pneumonia (Table 1).

Smoking. Of note, there was no difference in the rate of current smoking between those developing or not developing pneumonia in either trial.

FATAL AND NONFATAL HF OUTCOMES AFTER OCCURRENCE OF PNEUMONIA. PARADIGM-HF. The cumulative probabilities of the composite primary outcome, death from cardiovascular causes, hospitalization for HF, and death from any cause after the occurrence of pneumonia are shown in Figure 1. The incidence rates for these outcomes before and after the occurrence of pneumonia are also compared in Figure 1. A first occurrence of pneumonia was associated with a 3- to 5-fold elevation in risk of subsequent outcomes, which remained significant after extensive adjustment for other prognostic variables (Central Illustration, Table 2). Notably, the rate for death from any cause was 7.4 per 100 patient-years before the occurrence of pneumonia and 39.5 per 100 patient-years after the occurrence of pneumonia, representing a more than 4-fold elevation in risk of death from any cause (adjusted HR: 4.34; 95% CI: 3.73 to 5.05).

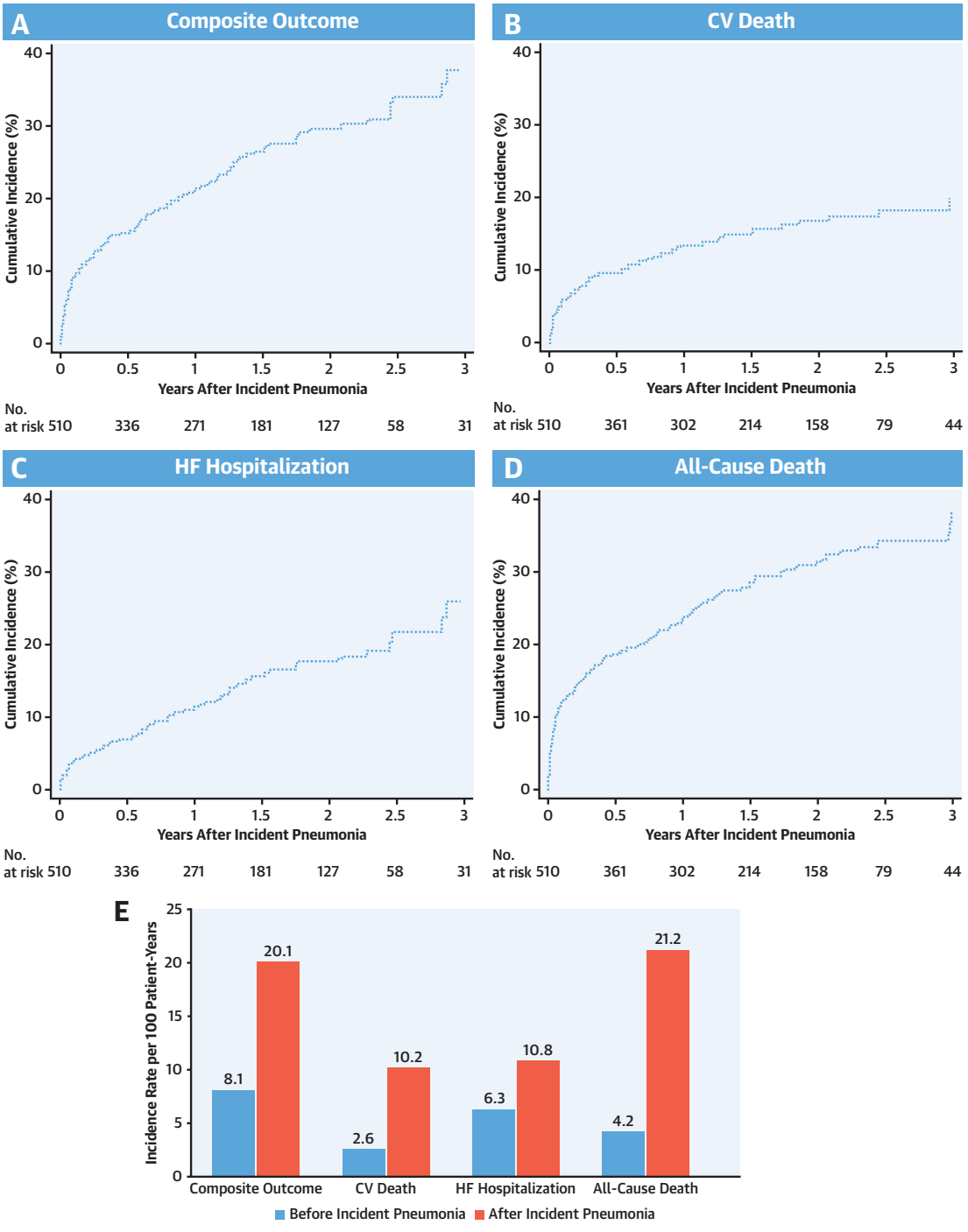
PARAGON-HF. For all outcomes of interest, the incidence rates before and after the occurrence of pneumonia are shown in Figure 2. The subsequent risks of all outcomes were elevated 2- to 5-fold after the occurrence of pneumonia, and, as in PARADIGM-HF, the elevated risk remained significant after extensive adjustment for other prognostic variables (Central Illustration, Table 2). The adjusted HR for the risk of death from any cause was 3.76 (95% CI: 3.09 to 4.58).

Sensitivity analyses. The excess risk observed in each trial remained significantly elevated in the sensitivity analyses. There was little attenuation of the excess risk in the sensitivity analysis excluding episodes of pneumonia that coincided with a HF hospitalization; the number of those cases was 98 in PARADIGM-HF (19% of pneumonia cases) and 77 in PARAGON-HF (15% of pneumonia cases) (Supplemental Table 1). There was somewhat more attenuation in the analyses excluding patients who died during an acute episode of pneumonia or those who died during an episode of pneumonia or within 4 weeks of such an event (Supplemental Tables 2 and 3).

TIME COURSE OF FATAL AND NONFATAL HF OUTCOMES AFTER OCCURRENCE OF PNEUMONIA. In both PARADIGM-HF and PARAGON-HF, the elevated risk of all events examined was extremely high in the first month following an episode of pneumonia, remained elevated 2- to 4-fold from months 1 to 3 and stabilized thereafter, with the elevation in risk remaining 1.5- to 2-fold higher than before the episode pneumonia (Tables 3 and 4, Figures 1 and 2).

COMPARATOR GROUP (URINARY TRACT INFECTION). Urinary tract infection was reported in 395 patients (4.7%) in PARADIGM-HF and 579 patients (12.1%) in PARAGON-HF, giving rates of 22 (95% CI: 20 to 24)

FIGURE 2 **Risk of Clinical Outcomes After Occurrence of Pneumonia in PARAGON-HF**



The **line graphs** show the cumulative incidence risks of **(A)** the composite of the first HF hospitalization or CV death, **(B)** CV death, **(C)** the first HF hospitalization, and **(D)** all-cause death after the occurrence of pneumonia. **(E)** The **bar graph** shows the incidence rates (per 100 patient-years) for the composite outcome of the first HF hospitalization or CV death, CV death, HF hospitalization and all-cause death. The **blue bars** are the rates before the occurrence of pneumonia, and the **red bars** are the rates after the occurrence of pneumonia. Abbreviations as in Figure 1.

TABLE 3 Subsequent Risk of Clinical Outcomes Various Time Intervals After Occurrence of Pneumonia in PARADIGM-HF

	Unadjusted HR* (95% CI)	p Value	Adjusted HR*† (95% CI)	p Value
All-cause death				
Within 1 month	21.69 (16.79–28.02)	<0.001	17.78 (13.73–23.03)	<0.001
>1 to 3 months	4.69 (3.38–6.51)	<0.001	3.87 (2.78–5.38)	<0.001
>3 months	2.68 (2.20–3.27)	<0.001	2.21 (1.81–2.71)	<0.001
CV death				
Within 1 month	15.22 (10.88–21.28)	<0.001	12.18 (8.69–17.08)	<0.001
>1 to 3 months	3.11 (2.00–4.85)	<0.001	2.54 (1.63–3.97)	<0.001
>3 months	2.66 (2.13–3.33)	<0.001	2.17 (1.73–2.72)	<0.001
HF hospitalization				
Within 1 month	10.34 (6.69–15.98)	<0.001	8.32 (5.37–12.88)	<0.001
>1 to 3 months	2.88 (1.70–4.89)	<0.001	2.31 (1.36–3.92)	0.002
>3 months	1.62 (1.15–2.29)	0.006	1.31 (0.92–1.85)	0.13
CV death or HF hospitalization				
Within 1 month	11.62 (8.40–16.06)	<0.001	9.48 (6.85–13.12)	<0.001
>1 to 3 months	2.64 (1.73–4.03)	<0.001	2.15 (1.41–3.28)	<0.001
>3 months	1.96 (1.54–2.48)	<0.001	1.59 (1.25–2.01)	<0.001

*Hazard ratios were estimated with stratification by geographic region. †Adjusted variables included randomized treatment, age, sex, left ventricular ejection fraction, NYHA functional class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log-transformed NT-proBNP.

Abbreviations as in Tables 1 and 2.

and 45 (95% CI: 41 to 49) per 1,000 person-years, respectively. The baseline characteristics of patients who did or did not develop a urinary tract infection are presented in Supplemental Table 4. Interestingly, many of the variables associated with developing pneumonia were also associated with higher risk of urinary tract infection, including older age, longer duration or more symptomatic HF, and more comorbidity (especially diabetes, but also chronic obstructive pulmonary disease); the one difference was sex, with more women than men developing urinary tract infection.

The subsequent risks of the primary composite outcome and death (either cardiovascular or from any cause) were higher after urinary tract infection, but the elevation in risk was substantially less than with pneumonia: Unadjusted HRs for the analyzed outcomes ranged from 1.31 to 2.23, compared with 2.19 to 5.19 associated with pneumonia (Supplemental Table 5).

EFFECT OF SACUBITRIL/VALSARTAN ON RISK OF PNEUMONIA. Sacubitril/valsartan did not reduce the risk of pneumonia in either trial. In PARADIGM-HF, the HR for sacubitril/valsartan versus enalapril was 0.99 (95% CI: 0.83 to 1.17; p = 0.88). In PARAGON-HF, the HR for sacubitril/valsartan versus valsartan was 0.97 (95% CI: 0.81 to 1.15; p = 0.69).

DISCUSSION

We found that patients with both HFrEF and HFpEF had a much higher incidence of pneumonia than is usually reported in age- and sex-matched individuals in the population. Patients developing pneumonia were older and more comorbid than those not and the occurrence of pneumonia was associated with substantially higher rates of fatal and nonfatal adverse outcomes, even after adjustment for other prognostic variables. The risk was greatest around the time of the episode of pneumonia but remained elevated beyond 3 months after the event.

In adults in the general population, there is a marked age dependency in the incidence of community-acquired pneumonia. For example, in the Cardiovascular Health Study, the rate of pneumonia in participants aged 65 to 79 years was 10 per 1,000 person-years (95% CI: 9 to 11 per 1,000 person-years), rising steeply to 27 per 1,000 person-years (95% CI: 22 to 32 per 1,000 person-years) in those aged ≥80 years. In PARADIGM-HF (mean age 64 years) the incidence of pneumonia was 29 per 1,000 person-years (95% CI: 27 to 32 per 1,000-person years) and in PARAGON-HF, where patients were on average about a decade older (mean age 73 years), the incidence rate was 39 per 1,000 person-years (95% CI: 36 to 42 per 1,000-person years). The higher than expected rates of pneumonia are consistent with previous epidemiologic analyses, although those studies were unable to specify HF phenotype (24-34). The reasons why patients with HF are more susceptible to pneumonia than other people are manifold and are both nonspecific and specific in nature. Nonspecific predisposing factors include comorbidities such as chronic obstructive pulmonary disease and chronic kidney disease and other diverse contributors related to older age, ranging from poor oral health through undernutrition to reduced cell-mediated immunity. However, accumulation of alveolar fluid may be a specific mechanism in patients with HF, both impairing bacterial clearance and disrupting the local defense against infection (35,36). In keeping with this, we found that patients who developed pneumonia generally exhibited more symptoms and signs, and had higher NT-proBNP levels, than those who did not develop pneumonia in the 2 trials we studied.

Pneumonia was associated with an elevated subsequent risk of all outcomes of interest. This was especially true for mortality, with an overall 3- to 4-fold higher risk of cardiovascular and all-cause death after the occurrence of pneumonia. The risk of HF hospitalization was also elevated, albeit not as much

as the risk of death. The risk was also "front-loaded," with extremely high mortality rates in the first month after an event with a steep decline in risk to around 3 months, after which it stabilized at 1.5- to 2.0-fold higher than before the occurrence of pneumonia. While it is tempting to attribute these raised risks to the worse overall health profile of patients developing pneumonia, along with severity of HF, they persisted in multivariable analyses adjusting for an extensive range of other prognostic factors. The finding of continued elevation of risk beyond the acute episode is also of interest given the observation in epidemiologic studies that acute pneumococcal infection appears to lead to a sustained subsequent elevation in risk of myocardial infarction and stroke (1–3,37). Persistence of systemic inflammatory and procoagulant states are suggested mechanisms explaining this observation and organ injury (e.g., kidney and myocardial injury) at the time of acute infection may also have longer term consequences (37–39).

Although our findings show only an association between pneumonia and worse outcomes and do not prove cause and effect, there seems little doubt that prevention of pneumonia is important in patients with HF. The most common pathogen causing pneumonia is *Streptococcus pneumoniae*, for which 2 vaccines are available (12,40). Although pneumonia (and influenza) vaccination is advocated for older adults in the general population and in all major HF guidelines, it is consistently found to be underutilized. In a recent review, the estimated vaccination coverage in immunocompetent adults ≥65 years in the USA was only 47%, and similarly low levels have been reported in European countries with a national health service (5,10). Although higher in a large U.S. heart failure registry, pneumococcal vaccination rates were reported to have decreased from 71% in 2013 to 60% in 2016 (13). This missed opportunity may be relatively more important in patients with HFpEF, given their older average age, higher rate of pneumonia, and absence of other treatment options.

As with any study of this type, there are limitations. The analyses were retrospective and had not been prespecified. The patients included in both trials were selected and likely less comorbid than in the "real world." Cases of pneumonia were reported by investigators as serious adverse events and were not adjudicated, and it is possible that different criteria for pneumonia diagnosis may have been used by different investigators, although any hospitalization with any feature raising a possibility of worsening HF was reported. The lack of effect of sacubitril/valsartan on these events suggests that they were not missed HF events. Our approach to pneumonia definition was also at least as robust as used in epidemiologic and registry studies, and the rates of pneumonia that we observed are consistent with those expected in an older high-risk population (5,40). We had no information on the specific cause of pneumonia (38).

TABLE 4 Subsequent Risk of Clinical Outcomes at Various Time Intervals After Incident Pneumonia in PARAGON-HF

	Unadjusted HR* (95% CI)	p Value	Adjusted HR*† (95% CI)	p Value
All-cause death				
Within 1 month	36.34 (27.06–48.82)	<0.001	31.29 (23.18–42.25)	<0.001
>1 to 3 months	3.92 (2.44–6.29)	<0.001	3.22 (2.00–5.18)	<0.001
>3 months	2.19 (1.70–2.83)	<0.001	1.79 (1.38–2.32)	<0.001
CV death				
Within 1 month	26.59 (17.48–40.44)	<0.001	23.42 (15.30–35.84)	<0.001
>1 to 3 months	3.98 (2.23–7.11)	<0.001	3.26 (1.82–5.84)	<0.001
>3 months	1.64 (1.13–2.37)	0.008	1.36 (0.94–1.97)	0.102
HF hospitalization				
Within 1 month	8.18 (4.97–13.47)	<0.001	7.39 (4.48–12.20)	<0.001
>1 to 3 months	1.87 (0.93–3.77)	0.079	1.67 (0.83–3.36)	0.152
>3 months	1.64 (1.19–2.26)	0.002	1.47 (1.06–2.03)	0.022
CV death or HF hospitalization				
Within 1 month	11.56 (7.91–16.90)	<0.001	10.50 (7.16–15.39)	<0.001
>1 to 3 months	2.12 (1.20–3.76)	0.01	1.88 (1.06–3.33)	0.032
>3 months	1.56 (1.18–2.07)	0.002	1.40 (1.05–1.86)	0.024

*Hazard ratios were estimated with stratification by geographic region. †Adjusted variables included randomized treatment, age, sex, left ventricular ejection fraction, NYHA functional class, systolic blood pressure, HF duration, previous HF hospitalization, history of myocardial infarction, hypertension, diabetes, and atrial fibrillation, eGFR, and log transformed NT-proBNP.

Abbreviations as in Tables 1 and 2.

CONCLUSIONS

We found that incidence of investigator-reported pneumonia was high in patients with HF, especially HFpEF. An episode of pneumonia was of considerable prognostic importance, as it was associated with an approximately 4-fold elevation in risk of death.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Pneumonia is common in patients with either HFrEF or HFpEF and is associated with high short-term mortality and worse longer-term outcomes.

TRANSLATIONAL OUTLOOK: The mechanisms underlying the sustained risk after pneumonia warrant further investigation and more aggressive use of pneumococcal and influenza vaccinations is encouraged in patients with heart failure.

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KEY WORDS heart failure, incidence, pneumonia, risk, vaccination

APPENDIX For supplemental tables, please see the online version of this paper.