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ORIGINAL RESEARCH

Clinical Characteristics and Outcomes of Patients With Heart Failure With Reduced Ejection Fraction and Chronic Obstructive Pulmonary Disease: Insights From PARADIGM-HF

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BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common comorbidity in heart failure with reduced ejection fraction, associated with undertreatment and worse outcomes. New treatments for heart failure with reduced ejection fraction may be particularly important in patients with concomitant COPD.

METHODS AND RESULTS: We examined outcomes in 8399 patients with heart failure with reduced ejection fraction, according to COPD status, in the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor Blocker–Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. Cox regression models were used to compare COPD versus non-COPD subgroups and the effects of sacubitril/valsartan versus enalapril. Patients with COPD (n=1080, 12.9%) were older than patients without COPD (mean 67 versus 63 years; $P<0.001$), with similar left ventricular ejection fraction (29.9% versus 29.4%), but higher NT-proBNP (N-terminal pro-B-type natriuretic peptide; median, 1741 pg/mL versus 1591 pg/mL; P=0.01), worse functional class (New York Heart Association III/IV 37% versus 23%; $P<0.001$) and Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score (73 versus 81; $P<0.001$), and more congestion and comorbidity. Medical therapy was similar in patients with and without COPD except for beta-blockade (87% versus 94%; $P<0.001$) and diuretics (85% versus 80%; $P<0.001$). After multivariable adjustment, COPD was associated with higher risks of heart failure hospitalization (hazard ratio [HR], 1.32; 95% CI, 1.13–1.54), and the composite of cardiovascular death or heart failure hospitalization (HR, 1.18; 95% CI, 1.05–1.34), but not cardiovascular death (HR, 1.10; 95% CI, 0.94–1.30), or all-cause mortality (HR, 1.14; 95% CI, 0.99–1.31). COPD was also associated with higher risk of all cardiovascular hospitalization (HR, 1.17; 95% CI, 1.05–1.31) and noncardiovascular hospitalization (HR, 1.45; 95% CI, 1.29–1.64). The benefit of sacubitril/valsartan over enalapril was consistent in patients with and without COPD for all end points.

CONCLUSIONS: In PARADIGM-HF, COPD was associated with lower use of beta-blockers and worse health status and was an independent predictor of cardiovascular and noncardiovascular hospitalization. Sacubitril/valsartan was beneficial in this high-risk subgroup.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01035255.

Key Words: chronic obstructive pulmonary disease ■ ejection fraction ■ heart failure ■ hospitalization ■ mortality ■ neprilysin ■ right ventricle

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CLINICAL PERSPECTIVE

What Is New?

- Patients with chronic obstructive pulmonary disease (COPD) had a higher risk of cardiovascular (including heart failure) and noncardiovascular hospitalization than patients without COPD.
- COPD was associated with a lower (worse) baseline Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score, and at 8 months, patients with COPD were more likely to experience a clinically important deterioration in Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score than patients without COPD.
- Overall, the uptake of influenza vaccination was low, which is a major cause for concern.

What Are the Clinical Implications?

- As the benefit of sacubitril/valsartan over enalapril was consistent in patients with and without COPD for all end points, patients with COPD obtained a large absolute benefit from angiotensin receptor–neprilysin inhibition because of their high baseline risk.
- The low rates of influenza vaccination and high prevalence of continuing smoking in patients with heart failure and COPD represent targets for public health initiatives and quality improvement.

Nonstandard Abbreviations and Acronyms

HFrEF	heart failure with reduced ejection fraction
IRR	incidence rate ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score

The quest to improve outcomes for patients with heart failure (HF) has recently focused not only on the underlying disease but also on the associated comorbidities. Chronic obstructive pulmonary disease (COPD) is increasing in prevalence, has few effective therapies, and is predicted to be the third leading cause of death worldwide by 2030.[1] Up to one-third of unselected patients with stable HF have concurrent COPD, largely because of the shared risk factor of smoking.[2] Cumulative smoking exposure has been associated with incident HF and ventricular remodeling, but the effect of COPD as an independent contributor to HF outcomes is less well understood.[3–7]

One potential contributor to the higher rates of death and hospitalization in patients with HF with reduced ejection fraction (HFrEF) who have COPD, compared with patients with HFrEF who do not have COPD, is underuse of beta-blockers because of perceived or actual intolerance of these drugs in people with COPD. This highlights the importance of alternative therapies in these particularly high-risk patients with the combination of HFrEF and COPD. A recent therapeutic advance in HFrEF has been the introduction of neprilysin inhibition (used in conjunction with an angiotensin receptor blocker). However, the potential effects of neprilysin inhibition in HFrEF patients with COPD, especially those with concomitant pulmonary hypertension, is uncertain, with conflicting experimental and other data. Mice genetically deficient in neprilysin develop exaggerated pulmonary vascular remodeling in response to chronic hypoxia and in another study, lung tissue from patients with severe COPD showed reduced neprilysin activity and protein expression, and more pulmonary vascular remodeling.[8,9] These observations gave rise to a hypothesis that decreased neprilysin activity contributes to the adverse pulmonary vascular remodeling in COPD. On the other hand, neprilysin inhibition has been shown to acutely reduce pulmonary artery pressure in patients with pulmonary hypertension and there are recent reports that sacubitril/valsartan reduces pulmonary artery pressure and improves right ventricular function in experimental models and case series.[10–14] The PARADIGM-HF (Prospective Comparison of Angiotensin Receptor Blocker–Neprilysin Inhibitor With Angiotensin-Converting Enzyme to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial provides a large, contemporary cohort to further characterize the interaction between HF and COPD, assess the effect of sacubitril/valsartan in patients with COPD, and identify areas for improvement in management of these 2 important diseases.[15,16]

METHODS

PARADIGM-HF was a randomized, double blind trial comparing the long-term efficacy and safety of enalapril and sacubitril/valsartan in patients with chronic symptomatic HF and reduced left ventricular ejection fraction (LVEF). The study design and primary results have been described previously.[15–17] The trial was approved by the ethics committee at each study center, and all patients provided written informed consent. The data that support the findings of this study are

available from the corresponding author upon reasonable request.

Study Design and Population

The trial enrolled patients with New York Heart Association class II–IV symptoms, LVEF ≤40% (amended to ≤35% during study), and plasma BNP (B-type natriuretic peptide) ≥150 pg/mL or NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≥600 pg/mL. Patients hospitalized for HF within the preceding 12 months were enrolled with a lower natriuretic peptide concentration (BNP ≥100 pg/mL or NTpro-BNP ≥400 pg/mL). Patients tolerating enalapril and sacubitril/valsartan at target doses during a run-in period were randomly assigned to double-blind treatment with either enalapril 10 mg twice daily or sacubitril/valsartan 97/103 mg twice daily. Participants were followed for a median duration of 27 months. Exclusion criteria included symptomatic hypotension, estimated glomerular filtration rate <30 mL/min per 1.73 m^2; serum potassium concentration >5.2 mmol/L at screening; history of angioedema; and recent acute coronary syndrome, cardiovascular procedure, or surgery.

COPD or asthma was not an exclusion criterion. The presence of COPD was recorded using a yes/no check box by individual site investigators at study entry. Two particular aspects of the COPD history were uniquely recorded in PARADIGM-HF compared with other contemporary clinical trials: smoking history and vaccination record.

Study End Points

The primary outcome was the composite of cardiovascular death or first hospitalization for HF. Secondary outcomes were cardiovascular death, HF hospitalization, and all-cause mortality. We analyzed the primary outcome, heart failure hospitalization, and deaths (all-cause, noncardiovascular and cardiovascular, with cardiovascular further subclassified as sudden or attributable to worsening heart failure). In PARADIGM-HF, deaths that could be classified were presumed to be cardiovascular. We have also analyzed recurrent hospitalizations for HF, any cardiovascular, noncardiovascular, and all causes. Analyses of other specific cardiovascular end points for example, new-onset atrial fibrillation were precluded by small numbers.

Statistical Analysis

Baseline characteristics are presented as mean with SD or median with interquartile range for continuous variables, and frequencies and percentages for categorical variables. Means were compared using the Wilcoxon rank-sum test or Student's *t*-test, depending on the distribution of the data and proportions using the chi-square test. All analyses were performed on an intention-to-treat basis. Unadjusted event rates are reported per 100 patient-years of follow-up according to COPD status. Cumulative event rates were estimated using the Kaplan–Meier method and were compared using log-rank test. A 2-tailed *P*-value of <0.05 was considered statistically significant.

The prognostic significance of COPD was evaluated for the predefined outcomes. The estimated hazard ratios (HRs) were adjusted for all the important predictors of mortality and morbidity using Cox proportional hazards models. Models were adjusted for region, treatment, age, sex, race, systolic blood pressure, heart rate, body mass index, serum creatinine, clinical features of heart failure (LVEF, NT-proBNP [log]), New York Heart Association class, hypertension, diabetes mellitus, atrial fibrillation, hospitalization for HF, myocardial infarction, stroke, and duration of HF.

Recurrent hospitalizations (for HF, cardiovascular, noncardiovascular, and all causes) were analyzed using a negative binomial regression model.[18] Both crude incidence rate ratios (IRRs) and IRRs adjusted for the variables mentioned previously are reported. All analyses were conducted using STATA version 16 (StataCorp LLC, College Station, TX).

RESULTS

Clinical Characteristics

Demographics and Comorbidity

COPD was present in 1080 of the 8399 enrolled patients (12.9%), with most patients having been diagnosed with COPD for over a year (879/1080). Given the large sample size, many differences were statistically significant but not necessarily clinically significant. However, compared with those without COPD, patients with COPD were older, more often male, White, and had a higher body mass index (Table 1). They also had more cardiovascular and noncardiovascular comorbidity: atrial fibrillation (44.8% in patients with COPD versus 35.6% in those without COPD), myocardial infarction (48.1% versus 42.5%), diabetes mellitus (39.2% versus 33.8%), and hypertension (80.2% versus 69.3%) (all comparisons *P*<0.001). Current smoking (28.2% versus 12.3%) was more common in patients with COPD than in those without (both *P*<0.001).

HF Characteristics

Patients with COPD had worse functional class (New York Heart Association III, 35.9% versus 22.3%) and a more frequent history of HF hospitalization (70.3% versus 61.7%; both *P*<0.001). They displayed more signs of congestion including more frequent peripheral edema

Table 1. Baseline Characteristics of Patients With and Without COPD

	No COPD n=7319	COPD n=1080	*P* Value
Age, y	63.3±11.6	67.4±9.5	<0.001
Female sex, n (%)	1680 (23.0)	152 (14.1)	<0.001
Race, n (%)			<0.001
White	4655 (63.6)	889 (82.3)	
Black	385 (5.3)	43 (4.0)	
Asian	1421 (19.4)	88 (8.1)	
Other*	858 (11.7)	60 (5.6)	
Region, n (%)			<0.001
North America	461 (6.3)	141 (13.1)	
Latin America	1343 (18.3)	90 (8.3)	
Western Europe	1742 (23.8)	309 (28.6)	
Central Europe	2374 (32.4)	452 (41.9)	
Asia/Pacific and other	1399 (19.1)	88 (8.1)	
Date of COPD diagnosis			N/A
0–3 mo	N/A	58 (5.4)	
3–6 mo	N/A	61 (5.6)	
6–12 mo	N/A	82 (7.6)	
1–2 y	N/A	142 (13.1)	
2–5 y	N/A	261 (24.2)	
>5 y	N/A	476 (44.1)	
Physiological measures			
Systolic BP, mm Hg	121.2±15.4	122.8±14.8	<0.001
Heart rate, bpm	72.2±11.9	73.3±12.4	0.008
Body mass index, kg/m^2	28.1±5.4	28.7±6.0	0.001
Laboratory investigations			
Hemoglobin, g/L	139.2±15.9	140.6±16.6	0.007
White blood cells, 10^9/L	6.9±2.0	7.3±2.0	<0.001
Neutrophil count, 10^9/L	4.3±1.5	4.7±1.7	<0.001
Lymphocyte count,10^9/L	1.9±0.9	1.9±0.7	0.540
Neutrophil/lymphocyte ratio (%)	2.6±1.6	2.9±1.6	<0.001
Creatinine, µmol/L	98.7±26.1	103.5±27.1	<0.001
Sodium, mmol/L	141.4±3.0	141.8±3.1	<0.001
Potassium, mmol/L	4.5±0.5	4.5±0.5	0.043
Current smoking, n (%)	903 (12.3)	305 (28.2)	<0.001
Medical history, n (%)			
Hypertension	5074 (69.3)	866 (80.2)	<0.001
Atrial fibrillation	2607 (35.6)	484 (44.8)	<0.001
Myocardial infarction	3114 (42.5)	520 (48.1)	<0.001
Prior CABG	1111 (15.2)	192 (17.8)	0.028
Prior PCI	1521 (20.8)	280 (25.9)	<0.001
Prior stable angina	1484 (20.3)	310 (28.7)	<0.001
Prior unstable angina	812 (11.1)	158 (14.6)	<0.001
Diabetes mellitus	2473 (33.8)	423 (39.2)	<0.001
Stroke	620 (8.5)	105 (9.7)	0.170
Cardiovascular treatments at randomization, n (%)			
Other antiplatelet	335 (4.6)	52 (4.8)	0.730
Aspirin	3751 (51.3)	598 (55.4)	0.011

(*Continued*)

Table 1. Continued

	No COPD n=7319	COPD n=1080	*P* Value
Anticoagulants	2301 (31.4)	384 (35.6)	0.007
Statins	4085 (55.8)	638 (59.1)	0.044
Calcium channel blocker	719 (9.8)	115 (10.6)	0.400

Values are mean±SD, n (%), or median (interquartile range), for continuous measures and number (%) for categorical measures. BP indicates blood pressure; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.
*"Other" refers to Native American, Pacific Islander and Other.

(26.5% versus 20.0%) and rales (11.2 versus 7.4%) than participants without COPD (all *P*<0.001). Patients with COPD also had more evidence of coronary heart disease than patients without COPD (Table 1). They also had a lower (worse) Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score (KCCQ-CSS; 73.4 versus 81.2; *P*<0.001) and higher median NT-proBNP level (1741 pg/mL versus 1591 pg/mL; *P*=0.01) (Table 2). Left bundle-branch block, was more prevalent in patients with COPD than in participants without COPD (22.2% versus 19.7% *P*=0.05, respectively).

Standard Laboratory Measures and Cardiovascular Biomarkers

Patients with COPD had a higher serum creatinine (103.5±27.1 µmol/L versus 98.7±26.1 µmol/L), white blood cell count (7.3±2.0×10^9/L versus 6.9±2.0×10^9/L), neutrophil count (4.7±1.7×10^9/L versus 4.3±1.5×10^9/L), and neutrophil/lymphocyte ratio (2.9±1.6% versus 2.6±1.6%; *P*<0.001 for all comparisons). Levels of high-sensitivity troponin T, kidney injury molecule-1 and growth differentiating factor 15 were all significantly higher in patients with COPD compared with those without COPD (Table 2).

Baseline Cardiovascular Treatment

Medical therapy was similar in patients with and without COPD, with 3 exceptions (Table 2). Beta-blockers were prescribed less often to patients with COPD compared with those without (86.5% versus 94.0%; *P*<0.001). Conversely, use of diuretics and anticoagulants was more common in patients with COPD (84.6% versus 79.6%; *P*<0.001; and 35.6% versus 31.4%; *P*=0.01, respectively). Influenza vaccination rate was low overall but more frequent in patients with COPD compared with those without COPD (27.8% versus 20.1%; *P*<0.001; Table 2). Patients with COPD were also more frequently enrolled in structured disease management program, n (%) (19.7% versus 14.6%; *P*<0.001; Table 2).

Baseline Respiratory Treatment

Overall, 23% of patients with COPD received 1 respiratory medication, 15% received 2, and 8% received 3 drugs. The most commonly used treatments were a muscarinic antagonist (24%), a beta-2 adrenoceptor agonist (16%), a corticosteroid (11%), and a theophylline (8%) and other agents, including combination products (16%).

Outcomes: COPD Versus No COPD

Time-to-First-Event Analyses

COPD was associated with significantly higher risk of the primary and all secondary end points: unadjusted HR for the primary end point, 1.33 (95% CI, 1.18–1.50); cardiovascular death, 1.29 (95% CI, 1.10–1.51); HF hospitalization, 1.48 (95% CI, 1.27–1.72); and all-cause death, 1.33 (95% CI, 1.16–1.53). After adjustment, the risk of the primary end point and HF hospitalization remained significantly higher in patients with COPD (18% and 32% higher, respectively), while the associated risk of cardiovascular and total mortality was attenuated and no longer significant (Table 3).

Cause of Hospitalization and Death

COPD was associated with a significantly higher risk of cardiovascular and noncardiovascular hospitalization: unadjusted HR, 1.29 (95% CI, 1.16–1.44) and 1.63 (95% CI, 1.45–1.84), respectively. After adjustment for other predictive variables, the risk of cardiovascular and noncardiovascular hospitalization remained significantly higher in patients with COPD (17% and 45% higher, respectively, for cardiovascular and noncardiovascular hospitalization). The risk of death caused by worsening HF and sudden death was not statistically different between patients with and without COPD. However, the risk of noncardiovascular death was higher in patients with COPD: unadjusted HR, 1.51 (95% CI, 1.12–2.03); adjusted HR, 1.27 (95% CI, 0.94–1.71; Table 3).

Total HF Hospitalizations

During a median follow-up of 27 months, 216 of 1080 people (20.0%) with COPD were admitted to the hospital for HF (and experienced a total of 377 admissions). Among the 7319 patients without COPD, 979 (13.4%) were admitted to the hospital for HF (and experienced a total of 1553 admissions). The adjusted IRR for all HF hospitalizations was 1.35 (95% CI, 1.12–1.63; Table 4).

Table 2. HF Characteristics of Patients With and Without COPD

	No COPD n=7319	COPD n=1080	*P* Value
Ejection fraction (%)	29.4±6.2	29.9±6.2	0.018
Previous HF hospitalization	4515 (61.7)	759 (70.3)	<0.001
NYHA class, n (%)			<0.001
I	353 (4.8)	36 (3.3)	
II	5273 (72.1)	646 (60.0)	
III	1631 (22.3)	387 (35.9)	
IV	52 (0.7)	8 (0.7)	
KCCQ-CSS	81.2 (64.6–92.7)	73.4 (56.1–87.5)	<0.001
Etiology of HF, n (%)			<0.001
Ischemic, n (%)	4322 (59.1)	714 (66.1)	
Nonischemic, n (%)	2997 (40.9)	366 (33.9)	
Signs and symptoms, n (%)			
Dyspnea at rest	251 (3.4)	58 (5.4)	0.002
Dyspnea on effort	6243 (85.5)	964 (89.5)	<0.001
Orthopnea	509 (7.0)	99 (9.2)	0.009
PND	325 (4.4)	74 (6.9)	<0.001
Jugular venous distention	713 (9.8)	105 (9.7)	0.99
Peripheral edema	1463 (20.0)	285 (26.5)	<0.001
Third heart sound	707 (9.7)	89 (8.3)	0.14
Rales			<0.001
Basilar only	525 (7.2)	112 (10.4)	
Greater than third of lung field	17 (0.2)	9 (0.8)	
ECG			
LBBB	1416 (19.7)	237 (22.2)	0.053
RBBB	536 (7.3)	91 (8.4)	0.200
QRS duration	117.0±35.8	119.9±35.6	0.012
Left ventricular hypertrophy	1319 (18.0)	174 (16.1)	0.130
Biomarkers			
NT-proBNP, pg/mL	1591 (882–3171)	1741 (949–3503)	0.011
NT-proBNP, pg/mL with ECG atrial fibrillation/flutter	1995 (1177–3823)	1995 (1123–4003)	0.920
NT-proBNP, pg/mL without ECG atrial fibrillation/flutter	1468 (817–2965)	1670 (851–3368)	0.011
Galectin-3, ng/mL	17 (13.8–21.1)	16.9 (14.4–20.9)	0.510
hsTropT, ng/L	16.0 (10.0–25.0)	19.0 (13.0–28.0)	<0.001
KIM-1, pg/mL	127.0 (85.4–191.0)	143.5 (96.8–209.0)	<0.001
MMP-2, ng/mL	134.1 (115.4–155.8)	136.8 (119.7–162.0)	0.110
MMP-9, ng/mL	630.6 (387.5–1269.8)	668.9 (370.4–1238.5)	0.650
ST2, ng/mL	32.0 (25.5–41.4)	33.7 (25.9–42.0)	0.150
TIMP-1, ng/mL	122.6 (104.2–149.6)	130.9 (10.5.7–156.6)	0.053
GDF-15, ng/L	1613 (1142–2335)	1913 (1365–2721)	<0.001
Treatment at randomization, n (%)			
Diuretic	5824 (79.6)	914 (84.6)	<0.001
Digitalis	2216 (30.3)	323 (29.9)	0.800
Beta-blocker	6877 (94.0)	934 (86.5)	<0.001
MRA	4086 (55.8)	585 (54.2)	0.310
ICD	1039 (14.2)	204 (18.9)	<0.001
CRT	486 (6.6)	88 (8.1)	0.067

(*Continued*)

Table 2. Continued

	No COPD n=7319	COPD n=1080	*P* Value
Immunization and lifestyle management			
Influenza vaccination in past 12 mo, n (%)	1469 (20.1)	300 (27.8)	<0.001
Prescribed exercise regime, n (%)	1258 (17.2)	206 (19.1)	0.130
Enrolled in structured disease management program, n (%)	1071 (14.6)	213 (19.7)	<0.001

Values are mean±SD, n (%), or median (interquartile range), for continuous measures and number (%) for categorical measures.

CRT indicates cardiac resynchronization therapy (including CRT-pacemaker and CRT-defibrillator); GDF-15, growth differentiating factor 15; HF, heart failure; hsTropT, high-sensitivity troponin T; ICD, implantable cardiac defibrillator (including CRT-D); KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; KIM-1, Kidney injury molecule-1; LBBB, left bundle-branch block; MMP, matrix metalloproteinase; MRA, mineralocorticoid receptor antagonist; NT pro-BNP, N-terminal pro hormone B-type natriuretic peptide; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnea; RBBB, right bundle-branch block; ST2, suppression of tumorigenicity 2; and TIMP, tissue inhibitor metalloproteinase.

Among patients with COPD, 132 (12.2%) had 1 HF hospitalization, 54 (5.0%) had 2 hospitalizations (total 108 admissions), and 30 (2.8%) had 3 or more hospitalizations (total 137 admissions). Among those without COPD, 653 (8.9%) had 1 HF hospitalization, 199 (2.7%) had 2 hospitalizations (total 398 admissions), and 127 (1.7%) had 3 or more hospitalizations (total 502 admissions). A full breakdown of repeat HF admissions is given in Table S1, with the distribution shown in Figure S1.

Analyses of Total Cardiovascular and Total Hospitalizations

During a median follow-up of 27 months, there were 1523 total hospitalizations for any cause in participants with COPD and a total of 6094 hospitalizations for any cause in patients without COPD (Table 4). There were 632 (41.5%) noncardiovascular hospitalizations in participants with COPD and 2110 (34.6%) in those without COPD. The adjusted IRR for cardiovascular hospitalization in patients with COPD, compared with those without, was 1.30 (95% CI, 1.14–1.48). The adjusted IRR for noncardiovascular hospitalization for patients with COPD, compared with those without, was 1.67 (95% CI, 1.44–1.92) and for all-cause hospitalization the IRR was 1.43 (95% CI, 1.29–1.59; Table 4).

Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score

On average, the KCCQ-CSS decreased (deteriorated) between baseline and 8 months. The mean decrease was significantly larger in patients with COPD (–6.26±0.26 points) than in those without COPD (–3.43±0.25;, *P*<0.001). A significantly greater proportion of patients reported a clinically meaningful deterioration (ie, ≥5-point decrease) in KCCQ–Total Symptom Score in the COPD group (32.6%) than in the no-COPD group (28.1%; unadjusted odds ratio, 1.16; 95% CI, 1.01–1.34); fewer COPD patients had a clinically meaningful increase (improvement) in KCCQ-CSS (25.0 versus 27.0%; unadjusted odds ratio, 0.68; 95% CI, 0.58–0.80; Table 3).

Effect of Sacubitril/Valsartan Compared With Enalapril

Although the benefit of sacubitril/valsartan compared with enalapril appeared somewhat attenuated, especially for fatal outcomes, formal statistical testing did not show an interaction between COPD status and effect of randomized therapy on hospitalization or mortality (Table 5). There was no interaction between COPD status and effect of study treatment on KCCQ-CSS (Table 5) or mean NT-proBNP at 8 months.

DISCUSSION

This analysis has several key findings. Patients with COPD had notably worse symptoms and quality of life despite an overall similar LVEF. Inequalities in treatment of HF were apparent only for beta-blockers, and less notable than most previous reports.[19–23] Patients with COPD had a higher risk of HF hospitalization and the primary end point but not cardiovascular or all-cause mortality, in contrast with previous studies. Additionally, patients with COPD had a greater risk of noncardiovascular hospitalization and, as a result, all-cause hospitalization. Finally, the benefit of sacubitril/valsartan compared with enalapril was consistent across all end points in patients with and without COPD.

The prevalence of COPD in PARADIGM-HF was consistent with other HF clinical trials,[21,22,24,25] and lower than in epidemiological studies and registries.[2] Patients with COPD had a greater burden of cardiovascular and noncardiovascular comorbidities as previously reported.[21,26,27] Of interest, both renal impairment and hyperkalemia were more common in COPD, despite the potassium-lowering action of

Table 3. Clinical Outcomes in Patients With and Without COPD

	Without COPD n=7319	With COPD n=1080	*P* Value
Primary outcome			
Event number	1711	320	
Event rate per 100 patient-years	11.33 (10.81–11.88)	15.16 (13.58–16.91)	
Unadjusted HR	1.0 (ref)	1.33 (1.18–1.50)	<0.001
Adjusted HR	1.0 (ref)	1.18 (1.05–1.34)	0.007
Heart failure hospitalisation			
Event number	979	216	
Event rate per 100 patient-years	6.48 (6.09–6.90)	10.23 (8.95–11.69)	
Unadjusted HR	1.0 (ref)	1.48 (1.27–1.72)	<0.001
Adjusted HR	1.0 (ref)	1.32 (1.13–1.54)	<0.001
Cardiovascular hospitalisation			
Event number	2145	409	
Event rate per 100 patient-years	15.75 (15.10–16.43)	22.25 (20.20–24.52)	
Unadjusted HR	1.0 (ref)	1.29 (1.16–1.44)	<0.001
Adjusted HR	1.0 (ref)	1.17 (1.05–1.31)	0.004
Non-CV hospitalisation			
Event number	1427	337	
Event rate per 100 patient-years	9.87 (9.37–10.40)	17.64 (15.86–19.63)	
Unadjusted HR	1.0 (ref)	1.63 (1.45–1.84)	<0.001
Adjusted HR	1.0 (ref)	1.45 (1.29–1.64)	<0.001
All cause hospitalisation			
Event number	6094	1523	
Event rate per 100 patient-years	37.66 (36.72–38.61)	64.55 (61.39–67.88)	
Unadjusted HR	1.0 (ref)	1.57 (1.48–1.66)	<0.001
Adjusted HR	1.0 (ref)	1.40 (1.32–1.49)	<0.001
Cardiovascular death			
Event number	1065	186	
Event rate per 100 patient-years	6.58 (6.20–6.99)	7.88 (6.83–9.10)	
Unadjusted HR	1.0 (ref)	1.29 (1.10–1.51)	0.002
Adjusted HR	1.0 (ref)	1.10 (0.94–1.30)	0.227
Death due to worsening HF			
Event number	282	49	
Event rate per 100 patient-years	1.74 (1.55–1.96)	2.08 (1.57–2.75)	
Unadjusted HR	1.0 (ref)	1.24 (0.91–1.69)	0.174
Adjusted HR	1.0 (ref)	0.98 (0.72–1.35)	0.923
Sudden death			
Event number	486	75	
Event rate per 100 patient-years	3.00 (2.75–3.28)	3.18 (2.54–3.99)	
Unadjusted HR	1.0 (ref)	1.19 (0.93–1.52)	0.165
Adjusted HR	1.0 (ref)	1.10 (0.85–1.41)	0.476
Non-cardiovascular death			
Event number	240	55	
Event rate per 100 patient-years	1.48 (1.31–1.68)	2.33 (1.79–3.04)	
Unadjusted HR	1.0 (ref)	1.51 (1.12–2.03)	0.007
Adjusted HR	1.0 (ref)	1.27 (0.94–1.71)	0.127
All cause death			
Event number	1305	241	
Event rate per 100 patient-years	8.06 (7.64–8.51)	10.22 (9.00–11.59)	

(*Continued*)

Table 3. Continued

	Without COPD n=7319	With COPD n=1080	*P* Value
Unadjusted HR	1.0 (ref)	1.33 (1.16–1.53)	<0.001
Adjusted HR	1.0 (ref)	1.14 (0.99–1.31)	0.080
KCCQ-clinical symptom score			
Mean change in KCCQ CSS (SE)	−3.43 (0.25)	−6.26 (0.26)	
Difference	−2.84 (0.69)		<0.001
Proportion with increase in score ≥5 at 8 mo (%)	27.0	25.0	
Unadjusted OR	0.68 (0.58–0.80)		<0.001
Adjusted OR	0.70 (0.59–0.83)		<0.001
Proportion with decrease in score ≥5 at 8 mo (%)	28.1	32.6	
Unadjusted OR	1.16 (1.01–1.34)		0.039
Adjusted OR	1.15 (0.99–1.33)		0.068

Event rate is number of events per 100 person-years. Plus-minus values are means±SE. Cox proportional hazard models were used for the clinical outcomes, and logistic regression was used for KCCQ-Clinical Summary Score. All models adjusted for treatment and region at baseline. OR additionally adjusted for KCCQ-CSS at baseline. Model 1: Adjusted for region, treatment, age, sex, race, systolic blood pressure, heart rate, body mass index, serum creatinine, clinical features of heart failure (LVEF, NT-proBNP [log]), NYHA class, hypertension, diabetes mellitus, atrial fibrillation, hospitalization for heart failure, myocardial infarction, stroke, and duration of heart failure. COPD indicates chronic obstructive pulmonary disease; HF, heart failure; HR, hazard ratio; 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 Hospital Association; and OR, odds ratio.

beta-agonist bronchodilators.[28] Also corroborating prior studies, patients with COPD had similar LVEF but worse New York Heart Association functional status compared with those without.[20,26,29,30] We explored HF status further, finding higher median NT-proBNP in those with COPD. A recent systematic review of natriuretic peptides in COPD revealed mild elevation in stable disease and more significant elevation during acute exacerbations, the causes of which may include hypoxia, pulmonary hypertension, right ventricular dysfunction, and other comorbidities including renal dysfunction.[31] Indeed, markers of renal function (kidney injury molecule-1 and creatinine) were both worse in patients with COPD, and diuretic usage was greater. High-sensitivity troponin T was also higher, and the reasons for this are likely to overlap with those contributing to higher NT-proBNP, as well as potentially reflecting the higher prevalence of ischemic heart disease in that group. Markers of systemic inflammation, including growth differentiating factor-15 and total white cell count were higher in patients with COPD, as was the ratio of neutrophil to lymphocyte count. There has been a growing interest in the latter as a marker of systemic inflammation and its correlation with poorer outcomes in a variety of conditions, including HF. COPD was not associated with differences in biomarkers of pro-fibrosis (soluble suppression of tumorigenicity 2, tissue inhibitor metalloproteinase-1 and galectin 3) nor of collagen degradation (matrix metalloproteinase-2 and -9).

Few studies have examined the impact of COPD on quality of life. The KCCQ-CSS in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) was worse in patients with COPD (61 versus 69 points).[29] We found that patients with COPD had a markedly lower KCCQ-CSS at baseline (73 versus 81, *P*<0.001) and at 8 months were less likely to improve and more likely to experience a clinically important deterioration in KCCQ-CSS, compared with patients without COPD. It is possible that even with effective HF treatment, progression of COPD may lead to worsening of symptoms and quality of life.

Patients with HF and concurrent COPD have historically been undertreated across the spectrum of care, including all neurohormonal antagonists and device therapy. However, in PARADIGM-HF, the use of evidence-based therapy was greater than in prior studies examining patients with COPD. Not only were baseline angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and aldosterone antagonist levels similar irrespective of COPD status, but those with COPD had significantly more devices, particularly implantable cardiac defibrillators. The only exception was beta-blockade (86% versus 94%). Nevertheless, overall beta-blocker uptake has improved compared with prior studies, and the treatment gap, albeit persistent, is narrowing.[19–23] Further knowledge translation work is needed, as cardioselective beta-blockers are safe and well tolerated in COPD,[28,32]associated with reduced mortality and risk of both HF and COPD exacerbation,[24,33,34] and recommended in international guidelines irrespective of pulmonary disease.[35]

The low uptake of influenza vaccination is a major cause for concern. Vaccination was associated with reduced all-cause mortality in a previous analysis from PARADIGM-HF,[36] although a causal relationship cannot be inferred because of potential confounders, including greater access and quality of health care.[37]

Table 4. Analysis of Repeat Hospitalization in Patients With and Without COPD

	Total Events		Events Per 100 Person-years		No COPD vs COPD	
	No COPD	COPD	No COPD	COPD	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
HF hospitalization	1553	377	9.60 (9.13–10.09)	15.98 (14.45–17.68)	1.60 (1.31–1.95) *P*<0.001	1.35 (1.12–1.63) *P*=0.002
Cardiovascular hospitalization	3984	891	24.62 (23.87–25.40)	37.77 (35.37–40.33)	1.46 (1.28–1.67) *P*<0.001	1.30 (1.14–1.48) *P*<0.001
Non cardiovascular hospitalization	2110	632	13.04 (12.49–13.61)	26.79 (24.78–28.96)	1.88 (1.63–2.17) *P*<0.001	1.67 (1.44–1.92) *P*<0.001
All-cause hospitalization	6094	1523	37.66 (36.72–38.61)	64.55 (61.39–67.88)	1.63 (1.46–1.82) *P*<0.001	1.43 (1.29–1.59) *P*<0.001

COPD indicates chronic obstructive pulmonary disease; HF, heart failure; IRR, incident rate ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Hospital Association. Recurrent hospitalizations were analyzed using a negative binomial regression model, which was offset for time. Adjusted for region, treatment, age, sex, race, systolic blood pressure, heart rate, body mass index, serum creatinine, clinical features of heart failure (LVEF, NT-proBNP [log]), NYHA class, hypertension, diabetes mellitus, atrial fibrillation, hospitalization for heart failure, myocardial infarction, stroke, duration of heart failure.

Nevertheless, influenza vaccination is recommended in international guidelines[38] and in multiple observational studies associated with reduced hospitalizations and mortality in HF.[37,39,40] The low rate of influenza vaccination is even more remarkable considering that the Global Initiative for Chronic Obstructive Lung Disease recommends influenza vaccine for all patients with COPD.[41]

Outcomes

Cause of death has rarely been assessed in patients with HF and COPD.[22,26,42] In those few prior studies and in the present analysis, COPD was associated with higher unadjusted but not adjusted risk of cardiovascular death. Although COPD is portrayed as a systemic inflammatory disease, this attenuation of risk with multivariable adjustment suggests that clustering of factors such as comorbidities are largely responsible for adverse outcomes (as opposed to the COPD disease state per se). The unadjusted and adjusted risk for all-cause mortality followed a similar pattern, largely because 81% of deaths were attributed to cardiovascular causes. Clinical trial data also permit more comprehensive adjustment than most population-based studies, including for LVEF and NT-proBNP. A further consideration is that recruitment bias may select patients with milder pulmonary disease. This is not to discount the importance of COPD as a comorbidity in HF—unadjusted risk is most important from a patient perspective. It simply highlights the importance of treating patients in totality.

Prior clinical trials and registries have reported a 19% to 40% higher risk of HF hospitalization associated with COPD.[22,42–44] Our findings occupy the midpoint of this range (32% higher adjusted risk). Many factors may contribute. Pulmonary infection is a common precipitant of HF decompensation.[45] Beta-blockers, a key therapy in reducing HF hospitalization, remain underprescribed. Patients with COPD also receive bronchodilators, which are associated with increased risk of HF hospitalization,[46] acknowledging that this relationship may be confounded.[28] Finally, acute exacerbation of COPD may be responsible for some hospitalizations but misdiagnosed as worsening HF. However, this is less likely in clinical trials with blinded end point adjudication, a key strength of our analysis.

Unfortunately, current smoking remained common in patients with COPD (28% versus 12% in those without COPD), and this clearly should mandate more intensive efforts to aid cessation.

Limitations

Several limitations must be acknowledged, foremost being the investigator-derived diagnosis of COPD. This was obtained from hospital records, pulmonary function if available, and questioning the patient. No prespecified criteria were defined in the investigator brochure. Furthermore, investigators were not required to document previous smoking history. Misdiagnosis is unavoidable and inherent to all clinical trials lacking spirometry.[21,22,29,42] Recruitment bias will exclude some individuals with severe pulmonary disease. However, the generalizability of results is reasonable, as severe airflow obstruction is also uncommon in the wider population.[30] The exclusion of severe COPD and misclassification of patients with undiagnosed COPD will reduce the apparent magnitude of any association. Finally, in this analysis, no adjustment was made for multiplicity.

CONCLUSIONS

In conclusion, patients with HF and concurrent COPD have greater comorbidity and higher risk of HF and noncardiovascular hospitalization but not mortality. Inequalities in the treatment of patients with COPD were apparent only for beta-blockers, and of lesser magnitude than previous studies. Low rates of

Table 5. Clinical Outcomes According to Randomized Treatment in Patients With and Without COPD

	Without COPD		With COPD		
	Enalapril n= 3682	Sacubitril/Valsartan n=3637	Enalapril n=530	Sacubitril/Valsartan n=550	*P* Value for interaction
Primary outcome					
Event number	953	758	164	156	0.171
Event rate per 100 patient-years	12.79 (12.00–13.63)	9.91 (9.23–10.64)	15.77 (13.53–18.38)	14.56 (12.45–17.04)	
Unadjusted HR	0.78 (0.71–0.85)		0.92 (0.74–1.15)		
HF Hospitalisation					
Event number	545	434	113	103	0.430
Event rate per 100 patient-years	7.31 (6.72–7.95)	5.67 (5.16–6.23)	10.86 (9.03–13.06)	9.62 (7.93–11.66)	
Unadjusted HR	0.78 (0.69–0.88)		0.88 (0.67–1.15)		
CV hospitalisation					
Event number	1146	999	198	211	0.055
Event rate per 100 patient-years	17.10 (16.14–18.12)	14.44 (13.57–15.37)	21.69 (18.87–24.93)	22.81 (19.93–26.10)	
Unadjusted HR	0.85 (0.78–0.92)		1.05 (0.86–1.27)		
Non CV hospitalisation					
Event number	767	660	164	173	0.098
Event rate per 100 patient-years	10.74 (10.01–11.53)	9.03 (8.37–9.74)	17.29 (14.84–20.15)	17.99 (15.50–20.88)	
Unadjusted HR	0.84 (0.76–0.93)		1.02 (0.82–1.26)		
CV death					
Event number	598	467	95	91	0.241
Event rate per 100 patient-years	7.41 (6.84–8.03)	5.75 (5.25–6.30)	8.13 (6.65–9.95)	7.64 (6.22–9.38)	
Unadjusted HR	0.78 (0.69–0.88)		0.94 (0.71–1.26)		
Non CV death					
Event number	111	129	31	24	0.168
Event rate per 100 patient-years	1.38 (1.14–1.66)	1.59 (1.34–1.89)	2.65 (1.87–3.77)	2.01 (1.35–3.01)	
Unadjusted HR	1.15 (0.89–1.48)		0.76 (0.44–1.29)		
All cause death					
Event number	709	596	126	115	
Event rate per 100 patient-years	8.79 (8.17–9.46)	7.34 (6.78–7.96)	10.79 (9.06–12.85)	9.65 (8.04–11.59)	0.638
Unadjusted HR	0.84 (0.75–0.93)		0.90 (0.70–1.16)		
KCCQ CSS					
Mean change in KCCQ at 8 mo (SE)	−4.50 (0.35)	−2.74 (0.35)	−5.63 (0.91)	−4.47 (0.89)	
Between treatment difference	1.76 (0.5)		1.16 (1.27)		0.449
Proportion with increase in score ≥5 at 8 mo, n (%)	978 (26.6)	997 (27.4)	135 (25.5)	135 (24.5)	0.377
Proportion with decrease in score ≥5 at 8 mo, n (%)	1104 (30.0)	951 (26.1)	179 (33.8)	173 (31.5)	0.580
NT–proBNP					
Mean change in NT-proBNP at 8 mo (pg/ml)	−536±2888	−990±2697	−593±2235	1058±2454	0.971
Between treatment difference	454 (171–736)		466 (−53–985)		

All models adjusted for treatment and region at baseline. Event rate is number of events per 100 person-years. Plus-minus values are means±SE. Cox proportional hazard models were used for the clinical outcomes.

CV indicates cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; and Sac/val, sacubitril/valsartan.

influenza vaccination and high prevalence of continuing smoking in patients with HF and COPD represent ongoing targets for public health initiatives and quality improvement.

ARTICLE INFORMATION

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Supplementary Material

Table S1
Figure S1

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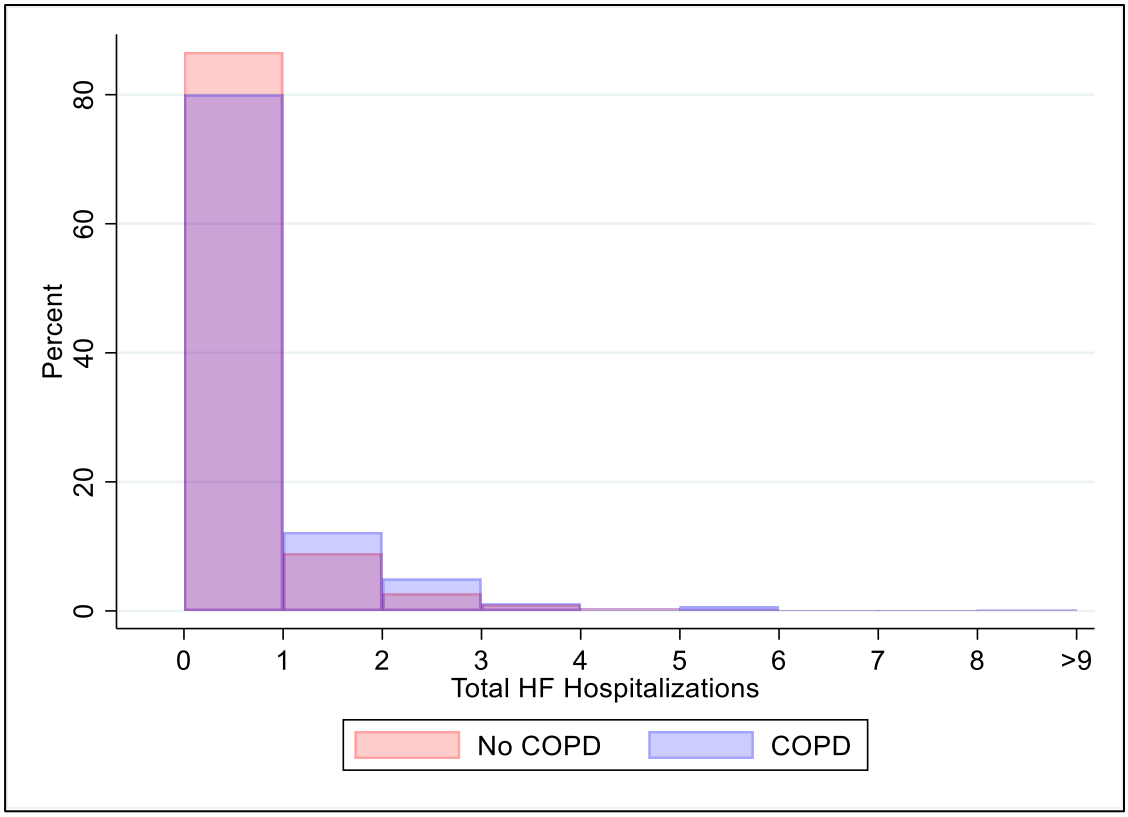
SUPPLEMENTAL MATERIAL

Table S1. Number of patients admitted to hospital one or more times with heart failure and number of admissions.

Number of Heart Failure Hospitalizations	Total Number (%) of patients without COPD admitted	Total number of admissions for patients without COPD, n	Total Number (%) of patients with COPD admitted	Total number of admissions for patients with COPD, n
1	653 (8.92)	653	132 (12.22)	132
2	199 (2.72)	398	54 (5.00)	108
3	73 (1.00)	219	13 (1.20)	39
4	27 (0.37)	108	4 (0.37)	16
5	13 (0.18)	65	8 (0.74)	40
6	4 (0.05)	24	1 (0.09)	6
7	6 (0.08)	42	1 (0.09)	7
8	1 (0.01)	8	0 (0.00)	0
9	2 (0.03)	18	2 (0.19)	18
11	0 (0.00)	0	1 (0.09)	11
18	1 (0.01)	18	0 (0.00)	0

COPD: chronic obstructive pulmonary disease

Figure S1. Frequency distribution of heart hospitalizations in patients with and without COPD.



HF, heart failure; COPD, chronic obstructive pulmonary disease