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, 1.32; 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
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–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

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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**

| Abbreviation | Definition |
|--------------|------------|
| 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 |
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 NT-pro-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 m²; 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. 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                | 481 (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/m²       | 28.1±5.4       | 28.7±6.0    | 0.001   |
| Laboratory investigations    |                |             |         |
| Hemoglobin, g/L              | 139.2±15.9     | 140.8±16.6  | 0.007   |
| White blood cells, 10⁹/L     | 6.9±2.0        | 7.3±2.0     | <0.001  |
| Neutrophil count, 10⁹/L      | 4.3±1.5        | 4.7±1.7     | <0.001  |
| Lymphocyte count, 10⁹/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 antplatelet             | 335 (4.6)      | 52 (4.8)    | 0.730   |
| Aspirin                       | 3751 (51.3)    | 598 (55.4)  | 0.011   |
(Continued)
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(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±2.0×10⁹/L versus 6.9±2.0×10⁹/L), neutrophil count (4.7±1.7×10⁹/L versus 4.3±1.5×10⁹/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).

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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.

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**Table 1. Continued**

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**Table 2.**

|                  | 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     |
## 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±35.8  | 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) | 666.9 (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 (10.5–156.6) | 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)
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 participants 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**

| Outcome                                         | 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                | 188              |         |
| 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)
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.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
Nevertheless, influenza vaccination is recommended in international guidelines and in multiple observational studies associated with reduced hospitalizations and mortality in HF. 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.

Outcomes

Cause of death has rarely been assessed in patients with HF and COPD. 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. 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. 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, acknowledging that this relationship may be confounded. 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. 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. 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

| Total Events | Events Per 100 Person-years | Unadjusted IRR (95% CI) | Adjusted IRR (95% CI) |
|----------------|-----------------------------|-------------------------|-----------------------|
| No COPD | COPD | No COPD | COPD | No COPD | COPD | No COPD | COPD |
| HF hospitalization | 1553 | 377 | 9.60 (9.13–10.09) | 15.98 (14.45–17.68) | 1.60 (1.31–1.95) | 1.35 (1.12–1.63) | P<0.001 | 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) | 1.30 (1.14–1.48) | P<0.001 | 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) | 1.67 (1.44–1.92) | P<0.001 | 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) | 1.43 (1.29–1.59) | P<0.001 | 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.
## Table 5. Clinical Outcomes According to Randomized Treatment in Patients With and Without COPD

|                                | Without COPD | With COPD | P Value for interaction |
|--------------------------------|--------------|-----------|-------------------------|
|                                | Enalapril    | Sacubitril/Valsartan | Enalapril | Sacubitril/Valsartan |
|                                | n= 3682      | n=3637    | n=530                   | n=550      |
| Primary outcome                |              |           |                         |            |
| Event number                   | 953          | 785       | 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                     | 105        | 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 (8.84–8.03) | 5.75 (5.25–6.30) | 8.13 (6.65–9.95) | 7.64 (8.22–9.38) |
| 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        | 0.638 |
| 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) |
| 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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SUPPLEMENTAL MATERIAL
| 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