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RESEARCH ARTICLE

Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry

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Aims To describe the characteristics and assess the 1-year outcomes of hospitalized (HHF) and chronic (CHF) heart failure patients with chronic obstructive pulmonary disease (COPD) enrolled in a large European registry between May 2011 and April 2013.

Methods and results Overall, 1334/6920 (19.3%) HHF patients and 1322/9409 (14.1%) CHF patients were diagnosed with COPD. In both groups, patients with COPD were older, more frequently men, had a worse clinical presentation and a higher prevalence of co-morbidities. In HHF, the increase in the use of heart failure (HF) medications at hospital discharge was greater in non-COPD than in COPD for angiotensin-converting enzyme inhibitors (+13.7% vs. +7.2%), beta-blockers (+20.6% vs. +11.8%) and mineralocorticoid receptor antagonists (+20.9% vs. +17.3%), thus widening the gap in HF treatment already existing between the two groups at admission. In CHF patients, there was a similar increase in the use of these medications after enrollment visit in the two groups, leaving a significant difference of 8.2% for beta-blockers in favour of non-COPD patients (89.8% vs. 81.6%, $P < 0.001$). At 1-year follow-up, the hazard ratios for COPD in multivariable analysis confirmed its independent association with hospitalizations both in HHF [all-cause: 1.16 (1.04–1.29), for HF: 1.22 (1.05–1.42)] and CHF patients [all-cause: 1.26 (1.13–1.41), for HF: 1.37 (1.17–1.60)]. The association between COPD and all-cause mortality was not confirmed in both groups after adjustments.

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Conclusions COPD frequently coexists in HHF and CHF, worsens the clinical course of the disease, and significantly impacts its therapeutic management and prognosis. The matter should deserve greater attention from the cardiology community.

Keywords Heart failure • Chronic obstructive pulmonary disease • Registry • Hospitalization • Mortality • Beta-blockers

Introduction

Chronic obstructive pulmonary disease (COPD) is a common co-morbidity that worsens the clinical course of heart failure (HF), both in the acute and chronic phases of the disease.[1] Several publications to date have investigated the prevalence of COPD in HF[2] and its impact on HF clinical presentation, treatment and outcomes.[1,3] Some contrasting findings have been reported, primarily due to the design of the study (i.e. clinical trial vs. observational study), the clinical setting (i.e. acute vs. chronic HF), the length of follow-up (i.e. months vs. years) and the outcomes considered (i.e. hospitalizations and mortality for cardiovascular and non-cardiovascular reasons).[1,3] More importantly, the majority of the data were from populations enrolled 10 or more years ago, when the importance of neurohormonal inhibition of the sympathetic nervous and renin–angiotensin–aldosterone systems in HF was less recognized.

The HF Long-Term Registry promoted by the European Society of Cardiology in the years 2011–13 offers a unique opportunity to investigate this topic of COPD and HF from a larger, contemporary and multinational perspective. The present analysis aims to describe characteristics, treatments and 1-year outcomes of hospitalized HF (HHF) and chronic HF (CHF) patients with and without COPD enrolled in the abovementioned registry. The results of both HHF and CHF patients with COPD are discussed in a single paper by considering that, in a transversal enrollment, such as that undertaken in the present study, each patient is casually found in a fluctuating state of stability or instability, but in fact all the population investigated is affected by the same progressing condition which is HF.

Methods

Study design and clinical setting

This prospective observational registry enrolled HHF and CHF patients presenting to participating European centres from May 2011 to April 2013, on a one-day-per-week basis for 12 consecutive months. Further details have been previously reported.[4,5] The only exclusion criterion was age < 18 years. CHF patients were enrolled during an ambulatory visit, whereas HHF patients had to be admitted to hospital because of acute, pre-existing, or new-onset HF, and were enrolled only if treated with intravenous therapy for HF (i.e. inotropes, vasodilators, or diuretics). Each local Institutional Review Board approved the registry, and all patients enrolled in the study signed an informed consent.

Clinical characteristics and treatments were recorded in all HHF and CHF patients at study entry, and some variables were collected both at hospital admission and discharge, and before and after ambulatory study visit, respectively. Some laboratory blood tests were available for only part of the whole sample (see *Table 1* for details). Diagnosis of COPD was based on the clinical judgment of each investigator, taking into account the patient's medical history, treatment and/or spirometric data. Patients were followed up in accordance with the usual practice of each centre, but a mandatory follow-up visit at 12 months was requested to collect information on morbidity and mortality. Owing to between-country differences in the starting date of enrollment, there were varying follow-up times in the entire study group, with a median follow-up time of 373 days, and 9.7% of patients having more than 2 years' follow-up.[4]

Statistical analysis

Statistical analysis was performed for HHF and CHF, comparing patients with and without COPD in each population. Continuous variables were reported as mean ± standard deviation or as median and interquartile range (IQR). Between-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages (without missing values if applicable). Between-group comparisons were made using χ^2 test or Fisher's exact test. For qualitative variables with more than two possibilities, the Monte Carlo estimates of the exact *P*-values were used.

Plots of the Kaplan–Meier curves for all-cause and HF hospitalizations in HHF and CHF patients according to COPD status were performed, and survival distributions compared using the log-rank test.

A stepwise multiple Cox regression was used to determine the predictors of all-cause mortality, cardiovascular mortality, all-cause hospitalization, HF hospitalization and all-cause mortality or HF hospitalization, including into the model all the variables with a *P*-value of <0.10 in univariate analysis. In multivariable analysis, a significance level of 0.05 was required for a variable to enter the model (SLENTRY = 0.05) and a significance level of 0.05 was required for a variable to stay into the final model (SLSTAY = 0.05). No interaction was tested.

A two-sided *P*-value of <0.05 was considered as statistically significant. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Prevalence and clinical characteristics

The registry included 16 329 HF patients (mean age 66.7 ± 13.4 years, 67.9% men), of whom 6920 were HHF (mean age 69.0 ± 13.1 years, 63.0% men) and 9409 were seen during an ambulatory visit for CHF (mean age 65.0 ± 13.4 years, 71.5% men). Physician-reported COPD prevalence was 16.3% in the overall study population, 19.3% in HHF and 14.1% in CHF patients.

Table 1 Clinical characteristics of hospitalized and chronic heart failure patients according to the presence or absence of chronic obstructive pulmonary disease at study entry

	Hospitalized heart failure			Chronic heart failure		
	COPD ($n=1334$)	No COPD ($n=5586$)	*P*-value	COPD ($n=1322$)	No COPD ($n=8087$)	*P*-value
Age (years), mean ± SD	70.8 ± 11.5	68.6 ± 13.4	<0.001	67.8 ± 11.4	64.5 ± 13.6	<0.001
Age ≥ 70 years (%)	58.6	50.3	<0.001	46.2	38.9	<0.001
Female sex (%)	31.0	38.5	<0.001	17.5	30.2	<0.001
BMI (kg/m^2), mean ± SD	29.1 ± 6.1	28.4 ± 5.2	<0.001	28.6 ± 5.6	28.0 ± 5.1	<0.001
Former smoking (%)	46.4	30.4	<0.001	57.4	37.5	<0.001
Current smoking (%)	22.8	15.7	<0.001	17.4	10.4	<0.001
SBP (Ent, mmHg), mean ± SD	132.0 ± 27.2	132.7 ± 28.9	0.493	125.2 ± 20.5	124.3 ± 21.1	0.093
SBP (Disch, mmHg), mean ± SD	119.7 ± 16.5	118.6 ± 16.3	0.036	–	–	–
HR (Ent, b.p.m.), mean ± SD	91.9 ± 25.1	91.1 ± 25.6	0.182	74.8 ± 15.7	72.8 ± 15.6	<0.001
HR (Disch, b.p.m.), mean ± SD	75.5 ± 13.0	74.6 ± 13.8	0.010	–	–	–
LVEF (%), mean ± SD	41.6 ± 15.8 ($n=861$)	39.7 ± 14.7 ($n=3457$)	0.006	36.6 ± 14.1 ($n=1211$)	37.2 ± 13.6 ($n=7192$)	0.066
LVEF >45% (%)	37.5	31.6	<0.001	22.5	23.1	0.673
NYHA class III–IV (%)	90.3	83.6	<0.001	33.0	24.9	<0.001
Pulmonary rales (%)	82.1	71.7	<0.001	22.9	13.5	<0.001
Hepatomegaly (%)	33.6	23.5	<0.001	13.9	8.3	<0.001
Peripheral oedema (%)	64.6	53.3	<0.001	27.4	19.2	<0.001
S3 gallop (%)	36.5	29.1	<0.001	6.6	5.9	0.296
Mitral regurgitation (%)	46.7	45.7	0.533	30.4	25.9	<0.001
Aortic stenosis (%)	12.0	9.0	0.001	4.6	4.0	0.278
HF history (%)						
New-onset HF	22.3	31.9	<0.001	7.7	10.4	0.002
Known HF with previous hospitalization	36.7	32.2	0.002	48.4	41.4	<0.001
Known HF without previous hospitalization	41.0	35.9	<0.001	43.9	48.2	0.003
HF diagnosis more than 12 months before	52.1	49.7	0.203	56.2	62.9	<0.001
HF primary aetiology (%)						
Ischaemic heart disease	56.2	56.2	0.992	45.5	42.5	0.043
Dilated cardiomyopathy	14.3	13.1	0.261	28.5	29.4	0.514
Valve disease	8.3	12.6	<0.001	7.1	8.5	0.091
Hypertension	8.3	8.6	0.702	9.7	8.0	0.030
HFpEF syndrome	3.9	1.9	<0.001	1.6	1.4	0.660
Tachycardia-related cardiomyopathy	1.7	2.3	0.181	1.0	1.6	0.116
Other	7.3	5.2	0.002	6.6	8.7	0.011
Atrial fibrillation (%)						
Paroxysmal	10.9	9.6	0.137	8.6	9.8	0.195
Persistent	5.6	6.2	0.419	4.2	4.5	0.578
Permanent	31.3	26.8	<0.001	28.8	22.6	<0.001
Prior stroke/TIA (%)	17.2	10.9	<0.001	10.2	9.2	0.247
Diabetes mellitus (%)	44.3	37.5	<0.001	36.7	30.3	<0.001
Hypertension treatment (%)	70.9	62.9	<0.001	66.3	57.6	<0.001
Peripheral arterial disease (%)	25.0	11.3	<0.001	20.5	10.7	<0.001
Renal dysfunction (%)	34.5	24.0	<0.001	24.0	17.9	<0.001
Hepatic dysfunction (%)	14.2	6.3	<0.001	4.9	3.3	0.004
Sleep apnoea (%)	7.7	1.9	<0.001	12.1	4.0	<0.001
Depression (%)	12.9	5.9	<0.001	9.3	7.0	0.003
Current cancer (%)	6.2	4.3	0.003	4.0	4.2	0.679
ICD (%)	5.3	5.0	0.666	13.7	16.0	0.032
CRT-P/D (%)	3.5	3.9	0.520	13.2	13.1	0.991
Laboratory tests (median, IQR)						
White blood cells (Ent, g/L)	8540 (6730–11 000) ($n=1243$)	8100 (6420–10 500) ($n=5173$)	<0.001	7690 (6400–9170) ($n=1051$)	7200 (6000–8700) ($n=5992$)	<0.001
White blood cells (Disch, g/L)	7885 (6300–9400) ($n=986$)	7400 (6000–9000) ($n=3935$)	<0.001	–	–	–
Creatinine (Ent, μmol/L)	1.21 (0.99–1.60) ($n=1261$)	1.15 (0.90–1.50) ($n=5266$)	<0.001	1.15 (0.92–1.44) ($n=1236$)	1.09 (0.90–1.36) ($n=7289$)	<0.001
Creatinine (Disch, μmol/L)	1.24 (1.00–1.61) ($n=1141$)	1.18 (0.93–1.50) ($n=4596$)	<0.001	–	–	–
Uric acid (Ent, mg/dL)	7.46 (5.80–9.35) ($n=774$)	6.90 (5.50–8.70) ($n=2834$)	<0.001	7.00 (5.69–8.40) ($n=756$)	6.50 (5.28–7.98) ($n=4177$)	<0.001
Uric acid (Disch, mg/dL)	7.26 (5.70–9.18) ($n=573$)	6.70 (5.40–8.36) ($n=1995$)	<0.001	–	–	–

Table 1 Continued

	Hospitalized heart failure			Chronic heart failure		
	COPD (*n* = 1334)	**No COPD (*n* = 5586)**	***P*-value**	**COPD (*n* = 1322)**	**No COPD (*n* = 8087)**	***P*-value**
hs-CRP (Ent, mg/dL)	11.30 (4.60–20.00) (*n* = 499)	7.84 (3.00–20.00) (*n* = 1439)	<0.001	3.18 (1.30–6.30) (*n* = 109)	3.00 (1.00–7.70) (*n* = 545)	0.860
hs-CRP (Disch, mg/dL)	8.50 (4.00–19.00) (*n* = 171)	7.40 (3.00–22.00) (*n* = 437)	0.340	–	–	–
BNP (Ent, pg/dL)	725 (306–1229) (*n* = 145)	785 (379–1432) (*n* = 554)	0.15	463 (169–899) (*n* = 201)	283 (116–686) (*n* = 940)	<0.001
BNP (Disch, pg/dL)	496 (242–870) (*n* = 78)	516 (226–1009) (*n* = 300)	0.41	–	–	–
NT-proBNP (Ent, pg/dL)	3701 (1575–8518) (*n* = 244)	3828 (1695–9077) (*n* = 1253)	0.75	1466 (640–3559) (*n* = 491)	1246 (470–3360) (*n* = 2663)	0.07
NT-proBNP (Disch, pg/dL)	2501 (1105–6040) (*n* = 117)	2328 (1097–5926) (*n* = 521)	0.88			

BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT-P/D, cardiac resynchronization therapy with pacemaker/defibrillation; DBP, diastolic blood pressure; Disch, at hospital discharge or after study visit; Ent, at hospital admission or before study visit; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack.

Table 1 shows the main clinical characteristics of the HHF and CHF cohorts with and without COPD. Both HHF and CHF patients with COPD as compared to their counterparts without COPD were older, more frequently men, had a higher body mass index, were more frequently smokers, and had worse symptoms and signs of congestion. In addition, in both HHF and CHF patients, a diagnosis of COPD was associated with a higher prevalence of co-morbidities. HHF but not CHF patients with COPD had more frequently a concurrent diagnosis of cancer than those without COPD. Similarly to the CHF population, HHF patients with COPD had higher systolic blood pressure and heart rate than those without COPD at the time of hospital discharge, but not of hospital admission.

At least one evaluation of left ventricular ejection fraction (LVEF) was available in 77.9% of the overall population (in 62.4% of HHF patients and in 89.3% of CHF patients). LVEF was >45% in 26.3% of the overall population (in 32.8% of HHF and in 23.0% of CHF patients). HHF patients with COPD had a significantly higher LVEF and more frequently were found with a preserved LVEF than those without COPD. The opposite was found in CHF patients, with COPD patients being less likely to have a cardioverter-defibrillator implanted than those without COPD.

In both HHF and CHF cohorts, blood tests showed a more activated inflammatory state (i.e. elevated white blood cell count, uric acid, high-sensitivity C-reactive protein) and worse renal function in COPD compared to non-COPD patients (*Table 1*). In particular, in HHF patients, this difference was confirmed both at hospital admission and at discharge. There were no statistically significant differences in natriuretic peptide measurements between COPD and non-COPD HHF patients both at hospital admission and discharge, though dosages were available in only a minority of these patients (*Table 1*). On the contrary, natriuretic peptide levels were significantly higher in COPD than non-COPD CHF patients (*Table 1*).

Hospitalized patients

The Supplemental *Table S1* contains details on the HHF population. The principal reasons for the index hospitalization that were more frequent in COPD than in non-COPD patients were worsening HF, infection, renal dysfunction, uncontrolled hypertension, anaemia and ventricular arrhythmias ($P < 0.05$ for all). At hospital admission, COPD patients presented more frequently with right HF than non-COPD ones, whereas decompensated HF, pulmonary oedema, acute coronary syndrome, hypertensive HF and cardiogenic shock were similarly prevalent ($P \geq 0.05$ for all). COPD patients were more frequently treated with intravenous diuretics and inotropic agents than those without COPD, whereas nitrates were similarly used (see the Supplementary material online, *Table S1*).

Treatments

Table 2 shows the cardiovascular treatments of HHF and CHF patients according to the diagnosis of COPD, before and after hospitalization or the ambulatory visit, respectively. *Figure 1* demonstrates a significant gap in the use of several HF recommended treatments between COPD and non-COPD patients, both in the acute and chronic setting, which was in part modified by hospitalization or the ambulatory visit (see the Supplementary material online, *Figure S1*, for details).

Among HHF patients (*Figure 1*), COPD vs. non-COPD patients were less likely to receive a beta-blocker (BB) and

Table 2 Cardiovascular treatments of hospitalized and chronic heart failure patients according to the presence or absence of chronic obstructive pulmonary disease at study entry

	Hospitalized heart failure			Chronic heart failure		
	COPD ($n = 1334$)	No COPD ($n = 5586$)	*P*-value	COPD ($n = 1322$)	No COPD ($n = 8087$)	*P*-value
ACEi (Ent, %)	49.4	51.1	0.281	62.7	64.4	0.239
ACEi (Disch, %)	56.6	64.7	<0.001	65.4	67.0	0.246
ARB (Ent, %)	15.2	13.0	0.044	23.6	22.2	0.246
ARB (Disch, %)	17.0	14.3	0.012	26.1	23.7	0.053
BB (Ent, %)	51.0	56.3	<0.001	77.0	85.3	<0.001
BB (Disch, %)	62.8	76.9	<0.001	81.6	89.8	<0.001
MRA (Ent, %)	38.1	33.5	0.001	57.0	52.3	0.002
MRA (Disch, %)	55.4	54.4	0.53	62.9	58.2	0.001
Diuretics (Ent, %)	72.8	61.9	<0.001	87.7	78.1	<0.001
Diuretics (Disch, %)	84.5	83.0	0.199	90.6	81.5	<0.001
2nd Diuretic (Ent, %)	7.9	5.5	<0.001	13.3	9.6	<0.001
2nd Diuretic (Disch, %)	10.8	9.2	0.095	15.9	10.8	<0.001
Ivabradine (Ent, %)	1.2	1.3	0.803	8.5	5.4	<0.001
Ivabradine (Disch, %)	3.9	3.0	0.096	11.9	7.8	<0.001
Digitalis (Ent, %)	22.8	18.1	<0.001	27.9	20.2	<0.001
Digitalis (Disch, %)	27.4	23.9	0.008	28.6	21.9	<0.001
Statins (Ent, %)	42.3	42.0	0.835	58.9	57.0	0.207
Statins (Disch, %)	54.4	59.3	0.001	62.2	60.1	0.142
Amiodarone (Ent, %)	10.0	9.4	0.483	13.8	13.6	0.854
Amiodarone (Disch, %)	13.4	14.3	0.403	14.6	13.8	0.444
CCB (Ent, %)	18.9	14.5	<0.001	12.9	11.1	0.052
CCB (Disch, %)	18.1	14.7	0.003	12.6	11.2	0.161

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; Disch, at hospital discharge or after study visit; Ent, at hospital admission or before study visit; MRA, mineralocorticoid receptor antagonists.

an angiotensin-converting enzyme inhibitor (ACEi), and this difference widened after hospitalization. Angiotensin receptor blockers (ARBs) were more frequently used in COPD than non-COPD HHF patients, and a similar trend was noticed for ivabradine at hospital discharge. COPD HHF patients were more frequently given symptomatic medications, including diuretics and digitalis.

Among CHF patients (*Figure 1*), there was a very significant gap in the use of BB with lower rates in COPD patients, which did not modify after the recruitment visit and which was partly counterbalanced by a more frequent use of ivabradine in the same group. Digitalis and diuretics, including mineralocorticoid receptor antagonists, were more frequently used in COPD patients, and the gap in the use of these medications between the two groups did not modify after study visit. A significantly greater prescription of ARBs was noticed in patients with COPD after study visit.

After restricting our sample to the subset of patients with LVEF ≤45%, patients with COPD remained less likely to have been prescribed a BB and an ACEi at the time of hospital discharge (BB: 70.0% vs. 80.2%, $P < 0.001$; ACEi: 61.2% vs. 70.7%, $P < 0.001$) or after study visit (BB: 87.7% vs. 93.5%, $P < 0.001$; ACEi: 67.8% vs. 70.2%, $P = 0.128$) than patients without COPD. The opposite was true for ARBs, digitalis and diuretics, being more prescribed in COPD than non-COPD HHF and CHF patients with LVEF ≤45% (data not shown).

Among those not prescribed a BB after hospitalization or ambulatory visit, the primary reason in patients with vs. without COPD was asthma/bronchospasm (HHF 44.1% vs. 9.9%; CHF: 50.0% vs. 8.7%), whereas bradyarrhythmia (HHF: 5.7% vs. 12.0%; CHF: 7.5% vs. 16.1%), symptomatic hypotension (HHF: 6.4% vs. 12.4%; CHF: 5.7% vs. 12.6%) and worsening HF (HHF: 3.0% vs. 9.3%; CHF: 2.6% vs. 9.4%) were more frequently reported in non-COPD ($P < 0.05$ for all). Other reasons, including peripheral arterial disease and sexual dysfunction, were equally distributed in the two groups (data not shown). Among those not prescribed an ACEi after hospitalization or ambulatory visit, the primary reason in patients with vs. without COPD was cough (HHF: 14.7% vs. 7.5%, $P < 0.001$; CHF: 24.1% vs. 20.1%, $P = 0.071$). Other reasons, including renal dysfunction, hyperkalaemia, symptomatic hypotension and angioedema, were equally distributed in the two groups (data not shown).

Among HHF patients, bisoprolol was used more than any other BB in both COPD and non-COPD (see the Supplementary material online, *Figure S2*, for details). At hospital admission, COPD patients were taking more carvedilol and nebivolol and less metoprolol than non-COPD ones. Five per cent of HHF with COPD were

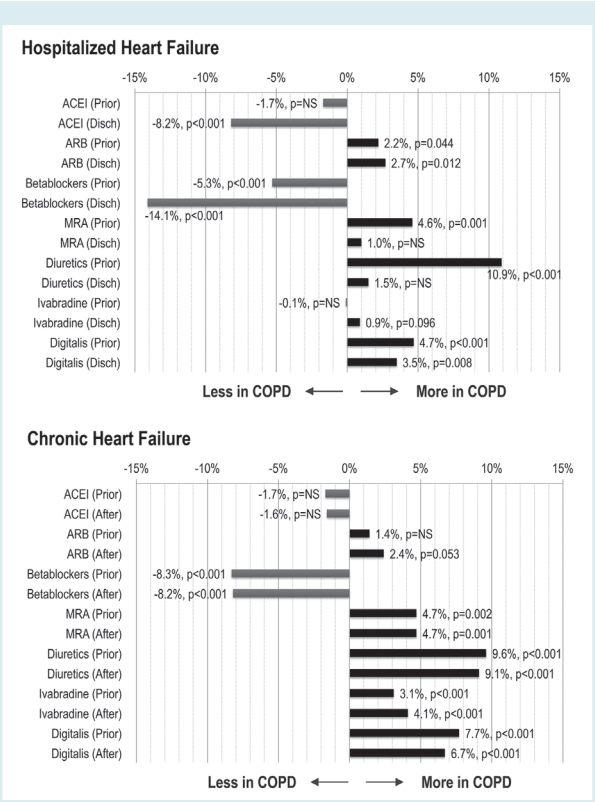

Figure 1 Gap in heart failure therapy between chronic obstructive pulmonary disease (COPD) and non-COPD patients before and after hospitalization (hospitalized heart failure) or ambulatory study visit (chronic heart failure). ACEI, angiotensin-converting enzyme inhibitors; After, after ambulatory visit; ARB, angiotensin receptor blockers; Disch, hospital discharge; MRA, mineralocorticoid receptor antagonists; Prior, before hospitalization/ambulatory visit.

shifted from carvedilol to either bisoprolol or nebivolol at hospital discharge. Among CHF patients, both before and after study visit, bisoprolol and nebivolol were preferentially used in COPD vs. non-COPD patients, whereas the opposite was true for carvedilol and metoprolol (*Figure S2*).

Spirometric data were available in only 16.9% of HHF and 30.6% of CHF patients with COPD, and a GOLD stage III–IV was found in 30.1% of HHF and 23.4% of CHF patients who performed a spirometric test. Overall, 44.7% of HHF and 52.0% of CHF patients with COPD were treated with at least one COPD medication at hospital admission and before enrollment visit, respectively. These percentages increased to 50.8% at hospital discharge and to 54.1% after study visit. Detailed COPD treatment in the two study groups are presented in the Supplementary material online, *Table S2*.

Prognosis

In-hospital mortality of HHF patients was higher in COPD than non-COPD (8.1% vs. 5.0%, $P < 0.001$), but reasons for death were similar in the two groups (cardiovascular in 80.4% vs. 84.6%, $P = 0.202$).

A total of 421 HHF patients (6.1%) and 229 CHF patients (2.4%) were lost to 1-year follow-up, leaving a final sample of 6499 HHF patients [1262 (19.4%) with COPD] and 9180 CHF patients [1290 (14.1%) with COPD]. During the 1-year follow-up, 1781 HHF (27.4%) and 754 CHF patients (8.2%) died, and 2383 HHF (36.7%) and 2361 CHF patients (25.7%) had at least one hospital admission. In both HHF and CHF cohorts, over the course of follow-up all clinical outcomes occurred more frequently in COPD than in non-COPD patients (*Table 3* and *Figure 2*). However, after performing multivariable analysis to adjust for potential confounding factors, the univariate association in all-cause mortality between COPD and non-COPD patients became statistically not significant, whereas a significantly higher cardiovascular mortality was found only in the HHF population with COPD (*Table 3*). Multivariable analysis confirmed a significantly higher risk of both all-cause and HF hospitalizations in COPD vs. non-COPD patients in both groups (*Table 3*).

Discussion

The results of the present analysis indicate that COPD frequently coexists in HHF and CHF, worsens the clinical course of the disease, and significantly impacts its therapeutic management. A concomitant diagnosis of COPD at the time of HF hospitalization or ambulatory visit determined an almost 30% increase in the risk of new hospitalization in the subsequent year, but had no significant independent impact on 1-year total mortality.

Prevalence and clinical characteristics

The finding of a higher prevalence of COPD in the HHF than in the CHF population (19.3% vs. 14.1% in the present analysis) is recurrent in the literature, with a prevalence of ~10–20% in ambulatory HF studies[3,6,7] vs. 20–30% in HHF studies.[8–10] This is likely due, at least in part, to some diagnostic overestimation in the acute HF setting, when signs and symptoms of COPD may be more easily misinterpreted[11] and a confirmatory spirometric evaluation being less frequently performed. Nonetheless, the interpretation of spirometry is challenging in HF patients, particularly during acute decompensation, as HF by itself (even in the absence of true COPD) may exert restrictive as well as obstructive alterations in pulmonary function testing. Thus, this test is often postponed to months after hospitalization, as the current guidelines of both the European Society of Cardiology[12] and the GOLD group[13] recommend, and even when used during stable HF conditions, it increases the prevalence of COPD in HF above 30%.[14] Only a minority of patients diagnosed by their responsible physicians as COPD underwent a spirometric confirmation of the diagnosis in this large European registry (i.e. 19.6% of HHF and 30.6% of CHF patients). This is in sharp contrast with the stringent requirement of spirometric examination as fundamental criterion of COPD diagnosis by all pulmonologists' scientific societies. The present paper reports observational findings, which illustrate current medical practice, where most HF patients are diagnosed with COPD regardless of having or not spirometric documentation of bronchial obstruction.

Table 3 One-year event rate by chronic obstructive pulmonary disease (COPD) status and Cox multivariable analysis of the association between COPD and clinical outcomes

	Hospitalized heart failure				Chronic heart failure			
	COPD ($n = 1262$)	No COPD ($n = 5237$)	Adjusted HR (95% CI)	*P*-value	COPD ($n = 1290$)	No COPD ($n = 7890$)	Adjusted HR (95% CI)	*P*-value
All-cause mortality (%)	34.7	25.6	1.12 (0.97–1.29)	0.109	11.2	7.7	1.04 (0.82–1.30)	0.755
CV mortality (%)	22.5	15.6	1.24 (1.07–1.45)	0.005	5.7	4.1	1.04 (0.77–1.42)	0.783
All-cause hospitalization (%)	49.7	43.1	1.16 (1.04–1.29)	0.008	36.4	26.6	1.26 (1.13–1.41)	<0.001
HF hospitalization (%)	31.5	24.6	1.22 (1.05–1.42)	0.009	17.0	11.5	1.37 (1.17–1.60)	<0.001
All-cause mortality or HF hospitalization (%)	54.5	44.2	1.12 (1.00–1.26)	0.046	25.1	17.6	1.06 (0.90–1.25)	0.489

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.
All models were adjusted for age, sex, systolic blood pressure, body mass index, aortic stenosis, mitral regurgitation, S3 gallop, New York Association class III–IV, pulmonary or peripheral congestion, atrial fibrillation, peripheral vascular disease, prior stroke/transient ischaemic attack, renal dysfunction, depression, hepatic dysfunction, diabetes mellitus, ischaemic aetiology, left ventricular ejection fraction, implantable cardioverter-defibrillator, cardiac resynchronization therapy with defibrillation, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, beta-blockers.

In fact, the recent HF guidelines of the European Society of Cardiology pragmatically read: 'Both correctly and incorrectly labelled COPD are associated with worse functional status and a worse prognosis in HF with reduced LVEF'.[12] It is important that scientists, including cardiologists and pulmonologists, are aware of what happens in the real world, characterized by patients with multiple co-morbidities but managed with a healthcare approach oriented towards the treatment of individual diseases in isolation.

To date, all HF studies reported a worse clinical presentation and a higher prevalence of co-morbidities in patients with COPD, both in the acute and chronic setting.[1,3] These findings were confirmed in our large European population, where about one-third of both HHF and CHF patients with COPD also had atrial fibrillation, diabetes mellitus or renal dysfunction, or a combination of them. HHF but not CHF patients with COPD were more likely to have a LVEF >45%, as previously shown in a large American HHF database.[9] This is in agreement with the hypothesis of a stronger relationship between non-cardiac co-morbidities, such as COPD, and HF with preserved vs. reduced LVEF.[15,16] Interestingly, the higher prevalence of cancer observed only among HHF patients with vs. without COPD may have determined a greater fragility, which in turn may have contributed to the index hospitalization.[17]

HHF COPD patients were discharged with significantly higher heart rate and systolic blood pressure than their non-COPD counterparts, and these differences were also confirmed in the ambulatory CHF population. Higher heart rate is independently associated with greater morbidity and mortality both in COPD[18] and HF patients.[19] The association between blood pressure and outcomes is less clear,[20,21] as a higher systolic blood pressure has been shown to convey some prognostic benefit in large HF populations with mainly reduced LVEF, including ours.[4] Inflammation may potentially explain these differences in haemodynamics, as suggested by the higher values of white blood cells, uric acid and high-sensitivity C-reactive protein in COPD patients. These data are in agreement with several previous works[3,22] and confirm the inflammatory burden imposed by COPD on the HF syndrome. In addition, infection, a recognized precipitant of HF decompensation,[23] was more frequently seen among the reasons for hospitalization in COPD vs. non-COPD patients (32.6% vs. 17.1%, $P < 0.001$). COPD and its associated co-morbidities may also be responsible for some additional chronic haemodynamic overload of the heart,[24] as suggested by the significantly higher natriuretic peptide levels found in ambulatory HF patients with COPD vs. non-COPD. This could partly explain and support the greater use of symptomatic medications and particularly diuretics in this group of patients, as discussed next, though definite conclusions regarding appropriateness cannot be drawn from these data.

Treatments

The most striking differences between COPD and non-COPD patients were noticed in HF medications, particularly BB and ACEi. We demonstrated, first, that a significant gap existed in the use of several HF treatments between COPD and non-COPD patients at the time of hospital admission and enrollment visit (*Figure 1*). Second, that a diagnosis of COPD was responsible for a significantly lower increase in the rates of prescription of HF treatments at hospital discharge, with respect to the period preceding admission (particularly BB, +11.8% in COPD vs. +20.6% in non-COPD, and ACEi, +7.2% in COPD vs. +13.7% in non-COPD). Rates of prescription of HF treatments after ambulatory visit were similar, and only slightly higher for ivabradine and ARBs in COPD vs. non-COPD (see the Supplementary material online, *Figure S1*). Third, as a consequence of previous points, the gap in several HF

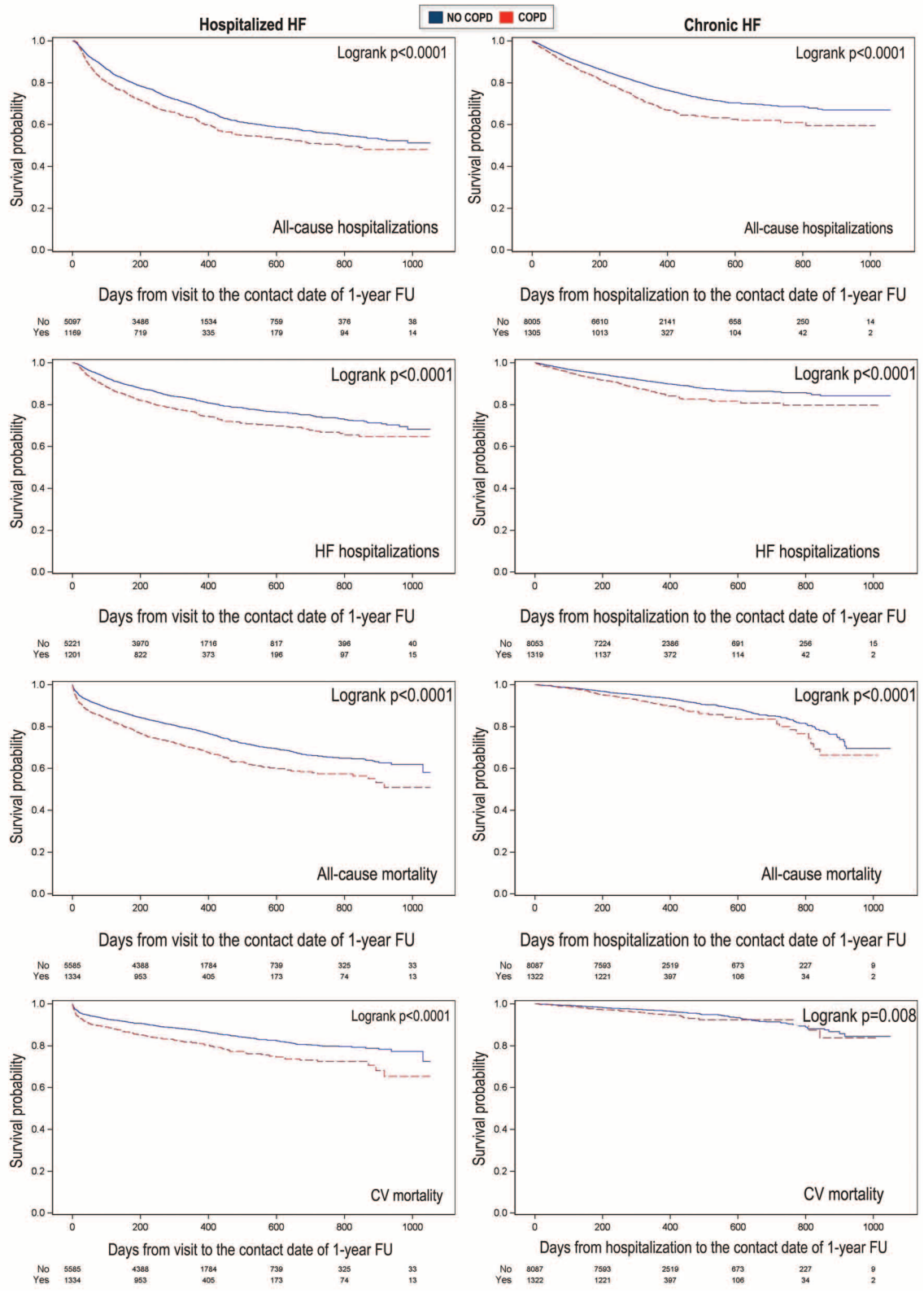

Figure 2 Kaplan–Meier curves for all clinical outcomes in hospitalized and chronic heart failure (HF) patients with and without chronic obstructive pulmonary disease (COPD). CV, cardiovascular; FU, follow-up.

treatments between COPD and non-COPD patients widened after hospitalization in the HHF population, and remained unchanged after study visit in the CHF population (*Figure 1*).

A previous publication from this same registry concluded that the treatment of CHF patients could be considered largely adherent to recommendations of guidelines, and observed a significant increase in the use of disease-modifying medications in HHF patients at discharge.[5] However, our present work highlights the significant gap in HF treatments that still exists between COPD and non-COPD patients, particularly after a hospitalization for HF. These differences in treatment are in agreement with those found in the OPTIMIZE-HF registry.[8] The alarming evidence reported here is that in the years 2011–13 still half of patients with HF and COPD were not taking any BB at the time of hospital admission, and one-third of them was not prescribed a BB at hospital discharge, with a trend in the opposite direction for ivabradine. These data highlight a continuing important issue of the appropriate treatment of HF patients with COPD that would deserve greater attention in the cardiology community.

Among those receiving a BB, we noticed a preference for more selective beta-1-adrenoceptor antagonists (particularly bisoprolol and nebivolol) in CHF patients with COPD, and curiously a greater prevalence of carvedilol in COPD vs. non-COPD patients at the time of hospital admission (33.9% vs. 28.1%, $P < 0.001$), which was counteracted at hospital discharge (29.3% vs. 28.7%, $P = 0.730$) (see the Supplementary material online, *Figure S2*). Carvedilol (a non-selective agent) has been suggested to be associated with a greater reduction of forced expiratory volume in 1 s (FEV_1) when compared with cardioselective BB in patients with HF.[14] However, a formal interaction between COPD status and BB selectivity for mortality/hospitalization has never been shown.[25] The 2017 GOLD recommendations are substantially silent on the COPD/HF co-morbidity care, just recommending the use of selective beta-1 blocker drugs in stable patients, and referring to the HF guidelines for other decisions.[13] Actually two points remain open in the field of adrenergic modulation in COPD/HF co-morbid patients from both cardiology and pulmonology fronts: the association of beta-1 blockers and beta-2 agonists (with diametrically opposed action on both heart and lungs) in bronchoreactive patients, and how to manage beta-blockade in case of COPD exacerbations.[26] Unfortunately our data cannot be of help for these clinically important issues.

The greater use of ARBs in COPD patients, paired with a lesser use of ACEi, is a new finding, considering that most analyses investigating the role of COPD in HF either combined these two categories of drugs in one[9] or were completed before the first ARB was approved for HF.[2] Their subsequent increased employment has been in part favoured by the perception of a greater safety profile in comparison with ACEi, particularly in HF patients with co-morbidities, such as COPD and chronic kidney disease. Interestingly, cough was more frequently reported as a side effect motivating the non-use of ACEi in our COPD than non-COPD population. No evidence exists in the literature suggesting that the ACEi-dependent cough rate is different in HF patients with and without COPD,[27] and the latest HF guidelines still recommend ARBs 'only as an alternative in patients intolerant of an ACEi'.[12]

Finally, we believe that the greater use of mineralocorticoid receptor antagonists in HF patients with COPD may be more due to their ability to prevent hypokalaemia induced by loop diuretics (which were also more frequently prescribed in the same group) than to a greater adherence to HF guidelines (which recommend their use in all symptomatic patients despite treatment with an ACEi and a BB[12]).

Prognosis

Several studies have investigated the independent prognostic impact of COPD in HF patients, which has been acknowledged in the recent European HF guidelines.[12] The present analysis confirmed an independent relationship between COPD and morbidity but not mortality. About half of HHF and one-third of CHF patients with COPD were hospitalized within 1 year after enrollment in the registry, and a diagnosis of COPD was independently associated with a 20% to 30% greater risk of all-cause and HF hospitalizations. Previous HF registries mainly reported on the impact of COPD on survival, but analyses from clinical trials that included morbidity endpoints generally agreed on the larger proportion of hospitalizations in this group of patients.[3,6,22] Reasons for these findings may be several, and in part related to the greater co-morbidities, the worse haemodynamics, the greater inflammation burden, and the poorer HF treatment in COPD vs. non-COPD discussed before. However, our findings did not materially change when these potential explanatory variables were included in the regression models. Maybe the available variables included in our dataset were not strong enough to be representative of such complex pathophysiological components. However, the excessive residual risk imposed by COPD warrants further investigation.

On the contrary, both all-cause and cardiovascular mortality appeared less affected by COPD if co-morbidities (e.g. chronic kidney disease and atrial fibrillation) and HF medication underuse (e.g. BB and ACEi) in patients with COPD were taken into account, as shown in previous work.[6,8,22] Post-hospitalization risk of death associated with COPD is known to increase over time in patients with HF,[9] and our 1-year follow-up may have been not sufficiently long to allow us to observe this relationship. The excessive cardiovascular mortality related to COPD, found in our HHF population only, may simply be due to the greater number of events in this subgroup of patients; however, the significantly lower rate of prescription of BB in HHF vs. CHF with COPD (62.8% vs. 81.6%) may have likely contributed to this finding.

Strengths and limitations

Our analysis has some strengths and limitations that should be acknowledged.

The present results come from a large contemporary multinational prospective registry with no particular exclusion criteria, and specifically designed to collect detailed 1-year outcomes in hospitalized and ambulatory HF patients across Europe. Several variables were collected before and after hospitalization or ambulatory visit, allowing the exploration of changes in HF medications that occurred with the enrollment in the registry.

Among the limitations, we investigated the independent impact of COPD using multivariable analysis and accounting for potential confounders, including HF medications, but other measured and unmeasured factors may have influenced our findings. Cause–effect relationships should not be drawn outside the context of clinical trials. However, patients with severe COPD are generally excluded from HF clinical trials (and vice versa),[28] and a large randomized outcome trial testing HF disease-modifying medications such as BB and ACEi in patients with COPD would be unethical today, and will likely never be undertaken. Although LVEF data were available in the majority of our patients, only about a quarter of them had a preserved LVEF (a third in the HHF population), thus we were not able to test the interaction between COPD and LVEF. The same was true for the interaction between COPD and gender, due to the low prevalence of female patients in our sample (~30%). Finally, although less than 5% of patients were lost to follow-up—a proportion that can be considered acceptable in a multinational voluntary registry—the possibility that this has somehow affected the results cannot be ruled out.

Conclusion

The present analysis confirms the considerable burden imposed by the co-existence of COPD in patients with HF, both in the acute and chronic phases of the disease, which translates into less HF drug usage and increased hospitalization rates. There is an urgent need for integrated care in patients with HF and COPD,[26] and further clinical investigations and educational initiatives from both the cardiology and pulmonology communities will be essential to enhance the quality of treatment and improve the outcomes of these patients.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Registry committees and investigators.

Table S1. Reasons of hospitalization, clinical profiles at admission and intravenous treatments in hospitalized heart failure patients.

Table S2. COPD treatments in hospitalized and chronic heart failure patients.

Figure S1. Increase in the use of heart failure medications after hospitalization in HHF patients and after study visit in CHF patients.

Figure S2. Use of different beta-blockers in hospitalized and chronic heart failure patients.

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