ESC European Society of Cardiology

European Journal of Heart Failure (2025) **27**, 2858–2868
doi:10.1002/ejhf.70046

RESEARCH ARTICLE

Beta-blockers in patients with heart failure with reduced ejection fraction and concomitant chronic obstructive pulmonary disease: Cardiovascular and respiratory outcomes

Benedikt N. Beer[1,2,3], Lina Benson[1], Christian Basile[1], Benedikt Schrage[2,3], Peter Moritz Becher[1,2,3], Stefan Blankenberg[2,3,4], Paulus Kirchhof[2,3,5], Barna Szabó-Söderberg[6], Marco Metra[7], Anne Lindberg[8], Egidio Imbalzano[9], Giuseppe M.C. Rosano[10,11], Patric Karlström[12,13], Peter G.M. Mol[14], Raffaele Scorza[1], Lars H. Lund[6], Felix Lindberg[1†], and Gianluigi Savarese[1*†]

[1]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [2]Department of Cardiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]German Centre for Cardiovascular Research (DZHK), partner site Hamburg/Luebeck/Kiel, Hamburg, Germany; [4]Center for Population Health Innovation (POINT), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [6]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [7]Cardiology, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [8]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [9]Department of Internal Medicine, University of Messina, Messina, Italy; [10]San Raffaele Open University of Rome, Rome, Italy; [11]IRCCS San Raffaele Roma, Rome, Italy; [12]Department of Internal Medicine, Ryhov County Hospital, Region Jönköping County, Jönköping, Sweden; [13]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; and [14]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Received 2 May 2025; revised 19 August 2025; accepted 26 August 2025; online publish-ahead-of-print 11 September 2025

Aims Patients with heart failure (HF) with reduced ejection fraction (HFrEF) and chronic obstructive pulmonary disease (COPD) are poorly represented in HFrEF trials testing beta-blockers. We assessed cardiovascular effectiveness and respiratory safety of beta-blockers in these patients.

Methods and results Patients with HFrEF and COPD in the Swedish HF Registry (2006–2023) were included. Overlap-weighted models were used to assess associations between beta-blocker use and 5-year risk of outcomes, with cardiovascular death/total hospitalizations for HF (HHF) representing the primary cardiovascular effectiveness outcome, and total severe COPD exacerbations being the primary respiratory safety outcome. Of 5084 patients with HFrEF and COPD, median age was 75 years (interquartile range [IQR] 69–81), 68.3% were male, 36.9% were in GOLD group E, 91.5% used beta-blockers. Over a median follow-up of 2.5 years (IQR 1.0–4.8), beta-blocker users had lower crude risk of cardiovascular death/total HHF (rate ratio [RR] 0.66, 95% confidence interval [CI] 0.56–0.78) and total severe COPD exacerbations (RR 0.75, 95% CI 0.60–0.93). After overlap weighting, beta-blocker use was independently associated with lower risk of cardiovascular death/total HHF (RR 0.74, 95% CI 0.58–0.96) but not total severe

*Corresponding author. Department of Clinical Science and Education, Södersjukhuset – Karolinska Institutet, Sjukhusbacken 10, 118 83 Stockholm, Sweden.
Email: gianluigi.savarese@ki.se

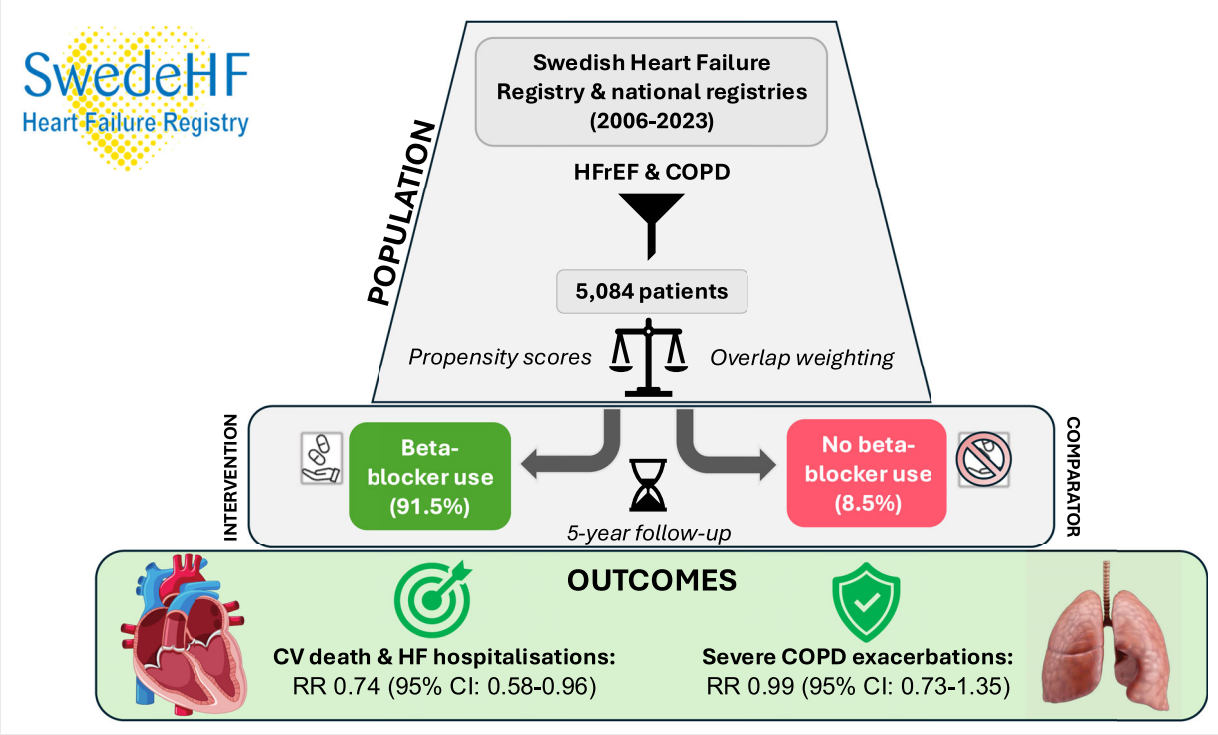
†Contributed equally as co-last authors.

[Correction added on 10 November 2025, after first online publication: Giuseppe M. C. Rosano's affiliation has been corrected in this version.]

COPD exacerbations (RR 0.99, 95% CI 0.73–1.35). These associations were consistent across subgroups (including GOLD groups), except for the greater magnitude of the association with lower risk of cardiovascular death/total HHF in patients with left ventricular ejection fraction <30% (p for interaction = 0.004). Falsification analyses suggested no influence from residual confounding.

Conclusions In patients with HFrEF and COPD, beta-blocker use was associated with lower risk of cardiovascular death/total HHF, without evidence of safety concerns for COPD exacerbations.

Graphical Abstract



In total, 5084 patients from Swedish registries with both heart failure (HF) with reduced ejection fraction (HFrEF) and chronic obstructive pulmonary disease (COPD) were included. Confounding was handled by overlap weighting based on propensity scores for beta-blocker use. Patients were followed up for 5 years, or until death, emigration from Sweden or registry censoring on 31 December 2023. Beta-blocker use in these patients was effective (reduced risk of cardiovascular [CV] death and HF hospitalizations) and safe (no difference for severe COPD exacerbations). CI, confidence interval; RR, rate ratio.

Keywords Heart failure • HFrEF • Chronic obstructive pulmonary disease • Beta-blocker • Safety • Effectiveness

Introduction

International heart failure (HF) guidelines provide a class IA recommendation for the use of beta-blockers in patients with HF with reduced ejection fraction (HFrEF),[1,2] based on the results of multiple randomized controlled trials (RCTs) clearly demonstrating the efficacy of beta-blockers on mortality and morbidity.[3–6]

In the airways, blockade of beta-2 adrenoceptors mediates bronchoconstriction. This has contributed to the historical controversy on the safety of beta-blocker use in patients with HFrEF and chronic obstructive pulmonary disease (COPD), representing 15%–36% of

the total HFrEF population, and potentially leading to beta-blocker underuse and underdosing in this large subgroup.[7,8] The BLOCK COPD trial, randomizing patients with COPD and high exacerbation risk to metoprolol versus placebo, was stopped early due to futility and safety concerns, i.e. higher rates of severe COPD exacerbations with metoprolol.[9] However, BLOCK COPD excluded patients with clear indications for beta-blockers, such as HFrEF.

In patients with comorbid HFrEF and COPD, the substantial cardiovascular benefits of beta-blockers are generally considered to outweigh potential concerns for respiratory safety, but direct evidence is lacking. Most major RCTs on beta-blockers in HFrEF explicitly excluded patients with documented COPD or bronchodilator therapy.[3–5] MERIT-HF is an exception as it formally allowed their inclusion, but COPD was then reported only in a minority (5.3%) and not assessed as a potential source of treatment heterogeneity.[6,10] RCTs testing beta-blocker use in patients with HFrEF and COPD were small, targeting surrogate endpoints, and could not assess hard outcomes for either cardiovascular efficacy or respiratory safety.[11] Existing observational studies exploring these questions lacked left ventricular ejection fraction (LVEF) and/or respiratory outcomes.[12] It is unlikely that this research question will be assessed in future large RCTs due to ethical concerns of randomizing patients with HFrEF to non-use of beta-blocker therapy. Whether the presence of concomitant COPD – or COPD severity – should influence the choice of beta-blocker dosage and cardioselectivity is also not well-established.

Therefore, we aimed to assess cardiovascular effectiveness and respiratory safety of beta-blocker use in patients with HFrEF and concomitant COPD in a large and well-characterized real-world population.

Methods

Data sources

Data from five different Swedish registries were used. The study population was derived from the Swedish Heart Failure Registry (SwedeHF), managed by the Uppsala Clinical Research Center (Uppsala, Sweden), which was founded in 2000 and implemented nationwide in 2003.[13] Until April 2017, physician-judged HF was the only inclusion criterion. Thereafter, inclusion criterion is a diagnosis of HF according to the International Statistical Classification of Diseases, 10th revision, Swedish version (ICD-10-SE) codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.6–7 or I50. Approximately 80 variables are recorded at hospital discharge or outpatient visit that prompts a registration, i.e. the index date. As of December 2023, 129 240 unique patients were registered in SwedeHF, with 59% coverage of prevalent HF in Sweden in 2023.[14] The Swedish personal identification number enables linkage between SwedeHF and other national registries.

For the current analysis, the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) managed by Statistics Sweden provided socioeconomic variables.[15] The National Patient Register (NPR), containing data on diagnoses and procedures from inpatient stays since 1964 (nationwide 1987) and from specialist outpatient care (but not primary care) since 2001, was used to supplement comorbidity variables and to obtain cause-specific hospitalization outcomes according to ICD-10-SE.[16] The National Prescribed Drug Register (NPDR) was implemented in July 2005, and provided information according to Anatomical Therapeutic Chemical (ATC) classification codes on prescribed drugs that were dispensed in pharmacies.[17] Information on cause-specific death was collected through the National Cause of Death Register.[18] The NPR, NPDR and National Cause of Death Register are all managed by the National Board of Health and Welfare.

Study population and definitions

We included all patients enrolled in SwedeHF between 1 July 2006 (allowing 1 year lookback for drug dispensations in the NPDR) and 31 December 2023 with a LVEF <40% and concomitant COPD. For patients with ≥1 eligible registrations in SwedeHF, the first was selected to allow for longer follow-up. Patient selection flowcharts are presented in online supplementary *Figures S1* and *S2*.

The validity of COPD as main or secondary diagnosis in the NPR has been reported to have acceptable validity, with only 9.1% of patients having uncertain or unlikely COPD against chart review.[19] To further strengthen this validity, we defined COPD as ≥2 specialty outpatient visits or hospitalizations (separated by >14 days) recording COPD as diagnosis in any position (ICD-10-SE codes J40-44) in the past 5 years. Patients receiving beta-blockers other than those recommended for HF (metoprolol, bisoprolol, carvedilol, or nebivolol) were excluded.[1] Patients with HFrEF and no COPD diagnosis were included as a positive control population.

Moderate COPD exacerbations were defined based on previously validated methods, i.e. as the presence of a dispensation of oral glucocorticoids (ATC code H02AB) in the prior year retrieved from the NPDR.[20] A new dispensation of oral corticosteroids <4 weeks after any prior exacerbation did not count as a new event as it was deemed to be a continuation of the prior exacerbation. Dispensations via ApoDos (a Swedish one-dose package system) were excluded as they are likely to represent chronic use rather than prescriptions for acute exacerbations. Severe COPD exacerbations were defined as hospitalization for ICD-10-SE codes J12-18, J20-22, J40-44 or J96 as main diagnosis.[21]

Based on exacerbation history, COPD patients were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria into groups A or B if they experienced <2 moderate COPD exacerbations and no severe COPD exacerbation in the past year, and as GOLD group E if they experienced ≥2 moderate COPD exacerbations or ≥1 severe COPD exacerbations in the past year.[22] Differentiation between groups A and B was not feasible since COPD symptoms are not recorded in our data sources.

Beta-blocker use/non-use and dosage at index date were recorded through the electronic case report form of SwedeHF. Dosage was quantified as a percentage of the target dose according to the prescribed substance (online supplementary *Table S1*).[1]

A full list of the definitions used for all baseline characteristics is available in online supplementary *Table S2*.

Outcomes

The primary cardiovascular effectiveness outcome was the composite of cardiovascular death and total number of hospitalizations for HF (HHF). Secondary effectiveness outcomes were (i) time to the composite of cardiovascular death or first HHF, (ii) time to cardiovascular death, (iii) time to first HHF, (iv) total number of HHFs, (v) time to all-cause death, (vi) time to first all-cause hospitalization, and (vii) total

number of all-cause hospitalizations. The primary safety outcome was the total number of severe COPD exacerbations. The secondary safety outcome was time to first severe COPD exacerbation.

Time to first cancer hospitalization was used as a negative control outcome.

ICD-10-SE codes used to define cause-specific outcomes are described in online supplementary *Table S3*.

Patients were censored at the first occurrence of emigration from Sweden, death, 5 years after index date, or end of follow-up period (31 December 2023).

Statistical analysis

Baseline characteristics were reported as median (interquartile range [IQR]) for continuous variables and as frequency (percent) for categorical variables. Comparisons across beta-blocker users versus non-users were performed by the Mann–Whitney U test for continuous and by the χ^2 test for categorical variables.

Missing data for covariates considered for adjustments were handled by multiple imputation using chained equations (20 imputed datasets, R-package *mice*), including variables labelled 'a' in *Table 1* along with all-cause death as the Nelson–Aalen estimator in the imputation model.

We used overlap weighting based on propensity scores to balance patient characteristics across beta-blocker users and non-users and handle confounding. A detailed description and rationale of this method is available in online supplementary *Methods*. First, a propensity score for beta-blocker treatment was calculated for each patient by Balance Super Learner with 45 covariates as independent variables (labelled 'b' in *Table 1*). Propensity scores were calculated separately in each imputed dataset and then averaged per patient by the 'across' method. Based on the propensity score, each patient was assigned a weight proportional to the probability of receiving the opposite treatment. Sufficient balance in the overlap weighted sample was considered as a standardized mean difference (SMD) <10%.

The associations between beta-blocker use and outcomes were estimated by unweighted (crude) and overlap weighted models. Negative binomial regression with log of time as an offset was used for repeated events and Cox proportional hazards models for time-to-event outcomes. The proportional hazards assumption was met according to visual assessment of Schoenfeld residuals. Results were presented as hazard ratios (HR) or rate ratios (RR) with 95% confidence intervals (CI). Event-free survival was depicted by unweighted and overlap weighted Kaplan–Meier curves.

As a positive control analysis, we assessed the association between beta-blocker use and the primary outcome in patients with HFrEF without COPD, as a beneficial treatment effect is well-established in these patients.

As a negative control outcome analysis to detect potential residual confounding, we assessed the association between beta-blocker use and hospitalization for cancer in the main study population (patients with HFrEF and concomitant COPD), since the finding of a significant association with this outcome would be deemed biologically implausible and indicative of residual confounding.

Potential heterogeneity in the weighted association between beta-blocker use and the primary cardiovascular effectiveness and respiratory safety outcomes was explored across pre-defined subgroups (age, sex, LVEF, atrial fibrillation, GOLD group, New York Heart Association [NYHA] class, HF cardiac devices, mean blood pressure, heart rate, bronchial asthma, N-terminal pro-B-type natriuretic peptide [NT-proBNP] and inpatient vs. outpatient status) and a post-hoc defined subgroup analysis according to background guideline-directed medical therapy (excluding sodium–glucose co-transporter 2 inhibitors [SGLT2i] as this drug class was not available or approved for HF during most of the study period). Within the beta-blocker arm, we also explored outcomes according to beta-blocker dosage (as percentage of target dose) and cardioselectivity (carvedilol vs. bisoprolol), with confounding handled by separate overlap weighting procedures.

Patients with incident HF (i.e. first HF diagnosis ≤30 days before SwedeHF registration) were evaluated in a sensitivity analysis, as they are more likely to have been newly prescribed beta-blockers rather than representing prevalent beta-blocker use.

All statistical analyses were performed in the statistical software R. Two-sided *p*-values <0.05 denote statistical significance. Standardized reporting of the study plan (HARmonized Protocol Template to Enhance Reproducibility [HARPER]) is provided online in the Heads of Medicines Agencies – European Medicines Agency (HMA-EMA) Catalogues of real-world data sources and studies (Study ID: 1000000462; https://catalogues.ema.europa.eu/catalogue-rwd-studies).

Ethics approval and patient consent

The study was performed in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Swedish Ethical Review Authority. Individual patient consent is not required to be enrolled in SwedeHF, but patients are informed of entry and may opt out.

Results

Patient characteristics

Of 5084 patients with HFrEF and concomitant COPD, 91.5% were treated with a beta-blocker at index visit (63.7% with bisoprolol, 33.1% with metoprolol, 3.2% with carvedilol). The median age was 75 years (IQR 69–81), the majority (68.3%) were male, 60.9% had NYHA class III or IV, median NT-proBNP was 2853 pg/ml (IQR 1190-6496), and 44.7% had LVEF <30% (*Table 1*). Approximately 75.6% used any COPD inhalation therapy, 36.9% were in COPD GOLD group E, and 26.1% were current smokers and 62.5% former smokers. The most common comorbidities were ischaemic heart disease (66.2%), hypertension (63.4%) and atrial fibrillation/flutter (52.2%).

Patients treated versus not treated with a beta-blocker at baseline were similar for most characteristics, although those treated with a beta-blocker were slightly younger, had more likely atrial fibrillation/flutter, higher body weight, lower heart rate, more likely used renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, SGLT2i, anticoagulants and statins, were less likely enrolled prior to 2009 and as inpatients, and more likely received follow-up in specialty care or in HF nurse-led units.

After overlap weighting, all measured baseline variables were well-balanced between beta-blocker users versus non-users (*Table 1*, online supplementary *Figure S3* and *Table S4*). The overlap weighted analytic sample consisted of 3142 patients with HFrEF and COPD, of whom 2717 (86.5%) were treated with beta-blockers.

Table 1 Baseline characteristics of the study population

Patients, *n* (%)	Overall unweighted population (*n* = 5084)	Unweighted (*n* = 5084)			Weighted (*n* = 3142)			Missing data, *n* (%)
		BBL Yes (*n* = 4650, (91.5%)	BBL No (*n* = 434, 8.5%)	SMD (%)	BBL Yes (*n* = 2717, 86.5%)	BBL No (*n* = 425, 13.5%)	SMD (%)	
Sociodemographics								
Age (years), median [IQR][a,b]	75 [69–81]	75 [69–80]	77 [70–82]	18.85	76 [69–82]	76 [69–82]	0.02	0 (0.0)
>75 years, *n* (%)	2651 (52.1)	2383 (51.2)	268 (61.8)	10.50	1590 (59.4)	256 (60.4)	0.98	0 (0.0)
Male sex, *n* (%)[a,b]	3472 (68.3)	3182 (68.4)	290 (66.8)	1.61	1799 (67.2)	285 (67.2)	0.00	0 (0.0)
Disposable income > median, *n* (%)	2542 (50.0)	2342 (50.4)	200 (46.1)	4.32	1226 (45.8)	198 (46.8)	0.99	3 (0.1)
Education, *n* (%)	–	–	–	–	–	–	–	92 (1.8)
Compulsory school	2338 (46.8)	2129 (46.6)	209 (48.8)	2.18	1339 (50.0)	204 (48.1)	1.87	–
Secondary school	2070 (41.5)	1898 (41.6)	172 (40.2)	1.40	1031 (38.5)	172 (40.5)	1.99	–
University	584 (11.7)	537 (11.8)	47 (11.0)	0.78	308 (11.5)	48 (11.4)	0.12	–
Single/widowed/divorced, *n* (%)	2841 (55.9)	2612 (56.2)	229 (52.8)	3.44	1550 (57.9)	220 (51.9)	5.96	3 (0.1)
Living alone, *n* (%)	2662 (52.4)	2441 (52.5)	221 (50.9)	1.61	1456 (54.4)	212 (50.1)	4.32	3 (0.1)
Clinical variables								
COPD GOLD E, *n* (%)[a,b]	1876 (36.9)	1704 (36.6)	172 (39.6)	2.99	1039 (38.8)	165 (38.8)	0.00	0 (0.0)
LVEF <30%, *n* (%)[a,b]	2272 (44.7)	2097 (45.1)	175 (40.3)	4.77	1092 (40.8)	173 (40.8)	0.00	0 (0.0)
Duration of heart failure (years), median [IQR][a,b]	2.3 [0.2–7.1]	2.2 [0.2–7.0]	2.4 [0.2–8.5]	7.40	2.6 [0.2–8.3]	2.4 [0.1–8.5]	0.01	0 (0.0)
NYHA class, *n* (%)[a,b]	–	–	–	–	–	–	–	1303 (25.6)
I	132 (3.5)	117 (3.4)	15 (4.8)	1.40	126 (4.7)	19 (4.4)	0.28	–
II	1349 (35.7)	1245 (35.9)	104 (33.1)	2.79	921 (34.4)	145 (34.2)	0.25	–
III	2105 (55.7)	1936 (55.8)	169 (53.8)	2.02	1443 (53.9)	229 (54.1)	0.18	–
IV	195 (5.2)	169 (4.9)	26 (8.3)	3.41	187 (7.0)	31 (7.3)	0.35	–
Dyspnoea, *n* (%)	–	–	–	–	–	–	–	2784 (54.8)
Unaffected	132 (5.7)	118 (5.5)	14 (8.2)	2.64	174 (6.5)	33 (7.9)	1.40	–
At moderate effort	1096 (47.7)	1017 (47.8)	79 (46.2)	1.57	1266 (47.3)	196 (46.2)	1.07	–
At more than moderate effort	955 (41.5)	886 (41.6)	69 (40.4)	1.26	1065 (39.8)	175 (41.2)	1.39	–
At rest	117 (5.1)	108 (5.1)	9 (5.3)	0.19	174 (6.5)	20 (4.7)	1.71	–
Weight (kg), median [IQR]	76 [65–89]	76 [65–90]	72 [61–86]	22.50	73 [62–85]	72 [61–86]	0.54	410 (8.1)
BMI (kg/m^2), median [IQR][a,b]	26 [22–30]	26 [23–30]	24 [21–28]	25.56	25 [22–29]	24 [21–28]	0.47	1371 (27)
Obese (≥30 kg/m^2), *n* (%)	926 (24.9)	878 (25.6)	48 (17.1)	8.42	517 (19.3)	75 (17.6)	1.68	–
Comorbidities and cardiovascular risk factors, *n* (%)								
Valvular disease[a,b]	1021 (20.1)	914 (19.7)	107 (24.7)	5.00	648 (24.2)	103 (24.2)	0.00	0 (0.0)
Liver disease[a,b]	182 (3.6)	165 (3.5)	17 (3.9)	0.37	104 (3.9)	17 (3.9)	0.00	0 (0.0)
Cancer (past 3 years)[a,b]	724 (14.2)	649 (14.0)	75 (17.3)	3.32	447 (16.7)	71 (16.7)	0.00	0 (0.0)
Arterial hypertension[a,b]	3221 (63.4)	2965 (63.8)	256 (59.0)	4.78	1612 (60.2)	255 (60.2)	0.00	0 (0.0)
Atrial fibrillation/flutter[a,b]	2652 (52.2)	2461 (52.9)	191 (44.0)	8.92	1221 (45.6)	193 (45.6)	0.01	0 (0.0)
Diabetes mellitus[a,b]	1557 (30.6)	1449 (31.2)	108 (24.9)	6.28	691 (25.8)	109 (25.8)	0.01	0 (0.0)
Bronchial asthma[a,b]	778 (15.3)	706 (15.2)	72 (16.6)	1.41	439 (16.4)	70 (16.4)	0.00	0 (0.0)
Smoking, *n* (%)[a,b]	–	–	–	–	–	–	–	886 (17.4)
Current smoker	1094 (26.1)	1007 (26.2)	87 (24.2)	2.00	667 (24.9)	106 (24.9)	0.06	–
Former smoker	2624 (62.5)	2403 (62.6)	221 (61.6)	1.03	1652 (61.7)	261 (61.6)	0.04	–
Never smoked	480 (11.4)	429 (11.2)	51 (14.2)	3.03	359 (13.4)	57 (13.5)	0.10	–
Ischaemic heart disease, *n* (%)[a,b]	3364 (66.2)	3096 (66.6)	268 (61.8)	4.83	1676 (62.6)	265 (62.5)	0.00	0 (0.0)
History of stroke/TIA, *n* (%)[a,b]	946 (18.6)	862 (18.5)	84 (19.4)	0.82	522 (19.5)	83 (19.5)	0.00	0 (0.0)
Anaemia, *n* (%)[a,b]	1817 (37.9)	1640 (37.6)	177 (41.9)	4.39	1111 (41.5)	176 (41.5)	0.00	295 (5.8)
Charlson comorbidity index, median [IQR]	4.0 [3.0–6.0]	4.0 [3.0–6.0]	4.0 [3.0–6.0]	0.37	3.5 [2.3–5.1]	3.5 [2.3–5.1]	0.23	0 (0.0)
Vital signs								
Systolic blood pressure (mmHg), median [IQR]	120 [108–133]	120 [108–132]	120 [110–135]	9.29	119 [106–133]	120 [109–135]	9.81	110 (2.2)
Diastolic blood pressure (mmHg), median [IQR]	70 [60–80]	70 [60–80]	70 [60–80]	9.67	69 [60–79]	69 [60–79]	7.63	106 (2.1)
Mean arterial pressure (mmHg), median [IQR][a,b]	87 [79–96]	87 [79–96]	87 [78–97]	0.96	86 [78–96]	87 [78–96]	0.60	106 (2.1)
≤90 mmHg, *n* (%)	3068 (61.6)	2809 (61.7)	259 (61.2)	0.44	1665 (62.2)	257 (60.6)	1.56	–
Heart rate (bpm), median [IQR][a,b]	73 [65–84]	73 [65–83]	78 [66–90]	19.00	76 [66–88]	76 [65–88]	0.38	144 (2.8)
>70 bpm, *n* (%)	2821 (57.1)	2550 (56.3)	271 (65.6)	9.29	1703 (63.6)	271 (63.9)	0.27	–
Laboratory parameters								
Haemoglobin (g/L), median [IQR]	132 [119–144]	132 [120–144]	130 [117–144]	8.38	130 [117–142]	130 [116–144]	0.61	295 (5.8)
Potassium (mmol/L), median [IQR][a,b]	4.2 [3.9–4.5]	4.2 [3.9–4.6]	4.2 [3.9–4.5]	10.50	4.1 [3.8–4.5]	4.1 [3.9–4.4]	0.08	680 (13.4)
Normokalaemia (3.5–5.0 mmol/L), *n* (%)	4011 (91.1)	3693 (91.3)	318 (88.6)	2.72	2417 (90.3)	377 (88.9)	1.39	–
Hyperkalaemia (>5.0 mmol/L), *n* (%)	205 (4.7)	187 (4.6)	18 (5.0)	0.39	131 (4.9)	21 (4.9)	0.02	–
Hypokalaemia (<3.5 mmol/L), *n* (%)	188 (4.3)	165 (4.1)	23 (6.4)	2.33	128 (4.8)	26 (6.2)	1.37	–
Sodium (mmol/l), median (IQR)[a,b]	140 [138–142]	140 [138–142]	139 [137–141]	5.09	139 [137–141]	139 [137–141]	2.85	1519 (29.9)
Normonatraemia (135–145 mmol/L), *n* (%)	3211 (90.1)	2977 (90.1)	234 (89.3)	0.82	2377 (88.8)	381 (89.9)	1.11	–
Hypernatraemia (>145 mmol/L), *n* (%)	83 (2.3)	75 (2.3)	8 (3.1)	0.78	80 (3.0)	10.6 (2.5)	0.52	–
Hyponatraemia (<135 mmol/L), *n* (%)	271 (7.6)	251 (7.6)	20 (7.6)	0.03	220 (8.2)	32 (7.6)	0.58	–
eGFR (ml/min/1.73 m^2), median [IQR][a,b]	64.0 [47.0–84.3]	64.0 [46.9–84.0]	65.6 [47.8–85.7]	3.70	64.4 [46.4–86.2]	64.7 [47.4–85.5]	1.01	88 (1.7)
>60 ml/min/1.73 m^2, *n* (%)	2709 (54.2)	2473 (54.1)	236 (55.3)	1.14	1464 (54.7)	232 (54.8)	0.09	–
30-60 ml/min/1.73 m^2, *n* (%)	1955 (39.1)	1796 (39.3)	159 (37.2)	2.07	1007 (37.6)	160 (37.8)	0.20	–
<30 ml/min/1.73 m^2, *n* (%)	332 (6.6)	300 (6.6)	32 (7.5)	0.93	206 (7.7)	31 (7.4)	0.29	–
NT-proBNP (pg/ml), median [IQR][a,b]	2853 [1190–6496]	2880 [1224–6610]	2640 [955–5851]	5.02	2673 [1069–5933]	2639 [980–5838]	3.49	1988 (39.1)
> median, *n* (%)	1548 (50.0)	1426 (50.1)	122 (48.6)	1.52	1314 (49.1)	206 (48.7)	0.40	–

Table 1 (Continued)

Patients, *n* (%)	Overall unweighted population (*n* = 5084)	Unweighted (*n* = 5084)			Weighted (*n* = 3142)			Missing data, *n* (%)
		BBL Yes (*n* = 4650, (91.5%)	BBL No (*n* = 434, 8.5%)	SMD (%)	BBL Yes (*n* = 2717, 86.5%)	BBL No (*n* = 425, 13.5%)	SMD (%)	
Cardio-circulatory treatment								
Beta-blocker, *n* (%)[a]	4650 (91.5)	4650 (100.0)	0 (0.0)	–	2677 (100.0)	0 (0.0)	–	0 (0.0)
Beta-blocker agent	–	–	–	–	–	–	–	434 (8.5)
Bisoprolol, *n* (%)	2963 (63.7)	2963 (63.7)	0 (0.0)	–	1732 (64.7)	0 (0.0)	–	–
Carvedilol, *n* (%)	150 (3.2)	150 (3.2)	0 (0.0)	–	94 (3.5)	0 (0.0)	–	–
Metoprolol, *n* (%)	1537 (33.1)	1537 (33.1)	0 (0.0)	–	851 (31.8)	0 (0.0)	–	–
Nebivolol, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0)	0 (0.0)	–	–
Beta-blocker dose (% of target dose), median [IQR]	50 [25–100]	50 [25–100]	–	–	43 [23–88]	–	–	455 (8.9)
≥100%, *n* (%)	1499 (32.4)	1499 (32.4)	–	–	707 (26.4)	–	–	–
50%-99%, *n* (%)	1664 (35.9)	1664 (35.9)	–	–	972 (36.3)	–	–	–
<50%, *n* (%)	1466 (31.7)	1466 (31.7)	–	–	1001 (37.4)	–	–	–
ACEi/ARB/ARNi, *n* (%)[a,b]	4455 (88.5)	4129 (89.7)	326 (76.0)	13.69	2128 (79.5)	337 (79.4)	0.10	51 (1.0)
MRA, *n* (%)[a,b]	2276 (45.0)	2112 (45.6)	164 (38.0)	7.64	1041 (38.9)	165 (38.9)	0.03	21 (0.4)
SGLT2i, *n* (%)[a,b]	467 (18.5)	445 (19.5)	22 (9.0)	10.49	262 (9.8)	43 (10.2)	0.47	4321 (85.0)
Diuretic, *n* (%)[a,b]	4222 (83.4)	3876 (83.7)	346 (80.1)	3.59	2155 (80.5)	342 (80.7)	0.14	20 (0.4)
Digoxin, *n* (%)[a,b]	661 (13.0)	605 (13.1)	56 (12.9)	0.15	343 (12.8)	54 (12.7)	0.03	16 (0.3)
Nitrate, *n* (%)[a,b]	819 (16.1)	760 (16.4)	59 (13.6)	2.79	369 (13.8)	59 (13.8)	0.04	12 (0.2)
Anticoagulant, *n* (%)[a,b]	2359 (46.5)	2213 (47.7)	146 (33.7)	14.00	964 (36.0)	153 (36.0)	0.03	13 (0.3)
Platelet inhibitor, *n* (%)[a,b]	2299 (45.4)	2106 (45.5)	193 (44.5)	0.99	1210 (45.2)	192 (45.2)	0.04	17 (0.3)
Statin, *n* (%)[a,b]	2900 (57.2)	2713 (58.5)	187 (43.1)	15.41	1221 (45.6)	193 (45.5)	0.01	12 (0.2)
Cardiac devices[a,b], *n* (%)	–	–	–	–	–	–	–	51 (1.0)
No device	4006 (79.6)	3647 (79.2)	359 (83.9)	4.68	2230 (83.3)	353 (83.2)	0.04	–
Pacemaker	450 (8.9)	406 (8.8)	44 (10.3)	1.46	276 (10.3)	44 (10.3)	0.01	–
CRT-P	138 (2.7)	130 (2.8)	8 (1.9)	0.95	54 (2.0)	8 (2.0)	0.02	–
CRT-D	221 (4.4)	211 (4.6)	10 (2.3)	2.25	70 (2.6)	11 (2.6)	0.01	–
ICD	218 (4.3)	211 (4.6)	7 (1.6)	2.95	48 (1.8)	8 (1.8)	0.02	–
COPD inhalation therapy, *n* (%)								
SABA and/or SAMA[a,b]	2002 (39.4)	1808 (38.9)	194 (44.7)	5.82	1151 (43.0)	182 (43.0)	0.01	0 (0.0)
LAMA[a,b]	2391 (47.0)	2191 (47.1)	200 (46.1)	1.04	1245 (46.5)	197 (46.5)	0.00	0 (0.0)
LABA[a,b]	389 (7.7)	350 (7.5)	39 (9.0)	1.46	236 (8.8)	37 (8.8)	0.00	0 (0.0)
ICS[a,b]	12 (0.2)	11 (0.2)	1 (0.2)	0.01	5 (0.2)	1 (0.2)	0.00	0 (0.0)
LABA/LAMA[a,b]	355 (7.0)	333 (7.2)	22 (5.1)	2.09	142 (5.3)	22 (5.3)	0.00	0 (0.0)
LABA/ICS[a,b]	1933 (38.0)	1776 (38.2)	157 (36.2)	2.02	972 (36.3)	154 (36.3)	0.00	0 (0.0)
LABA/LAMA/ICS[a,b]	192 (3.8)	174 (3.7)	18 (4.1)	0.41	112 (4.2)	18 (4.2)	0.00	0 (0.0)
Any COPD inhalation therapy	3846 (75.6)	3522 (75.7)	324 (74.7)	1.09	2351 (75.8)	2307 (74.4)	1.38	0 (0.0)
Index visit and follow-up								
Year of index visit, median [IQR][a,b]	2015 [2011–2019]	2015 [2011–2019]	2014 [2009–2018]	24.51	2013 [2009–2018]	2013 [2009–2018]	0.02	0 (0.0)
2005-2009, *n* (%)	945 (18.6)	821 (17.7)	124 (28.6)	10.92	672 (25.1)	113 (26.7)	1.61	–
2010-2014, *n* (%)	1428 (28.1)	1312 (28.2)	116 (26.7)	1.49	803 (30.0)	114 (26.9)	3.16	–
2015-2019, *n* (%)	1614 (31.7)	1490 (32.0)	124 (28.6)	3.47	712 (26.6)	125 (29.5)	2.95	–
2020-2023, *n* (%)	1097 (21.6)	1027 (22.1)	70 (16.1)	5.96	493 (18.4)	72 (16.9)	1.41	–
In-patient index visit, *n* (%)[a,b]	1999 (39.3)	1792 (38.5)	207 (47.7)	9.16	1226 (45.8)	194 (45.8)	0.01	0 (0.0)
Planned follow-up in specialty care, *n* (%)[a,b]	3560 (73.3)	3312 (74.2)	248 (62.5)	11.76	1732 (64.7)	275 (64.9)	0.18	225 (4.4)
Planned follow-up in a heart failure nurse clinic, *n* (%)[a,b]	3200 (66.7)	2980 (67.8)	220 (55.3)	12.50	1550 (57.9)	247 (58.2)	0.35	289 (5.7)

ACEi, angiotensin-converting enzyme inhibitor; Anaemia, defined by haemoglobin <120 g/L for women and <130 g/L for men; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BBL, use of beta-blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD, implantable cardioverter-defibrillator; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting beta-adrenergic agonist; LAMA, long-acting muscarinic antagonist; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SABA, short-acting beta-adrenergic agonist; SAMA, short-acting muscarinic antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SMD, standardized mean difference; TIA, transient ischaemic attack.

[a]Included in imputation model.

[b]Used for propensity score calculation/displayed baseline characteristics without imputed data/frequency of missing data given for unweighted population.

Cardiovascular effectiveness outcomes according to beta-blocker treatment

During a median follow-up of 2.5 years (IQR 1.0–4.8), 58 cardiovascular deaths or total number of HHFs occurred per 100 patient-years overall, with lower crude risk among beta-blocker users versus non-users (RR 0.66 [95% CI 0.56–0.78], $p < 0.001$). Beta-blocker treatment was associated with a lower risk of all secondary cardiovascular effectiveness outcomes except time to first HHF (*Figure 1*).

In the overlap weighted analyses, beta-blocker treatment was associated with lower risk of the primary cardiovascular effectiveness outcome, i.e. cardiovascular death and total number of HHF (RR 0.74 [95% CI 0.58–0.96]) (*Figure 1*). There were no statistically significant associations between beta-blocker use and time to cardiovascular death or first HHF (HR 0.93 [95% CI 0.81–1.06]), time to cardiovascular death (HR 0.91 [95% CI 0.77–1.09]), time to first HHF (HR 0.96 [95% CI 0.82–1.13]), total number of HHFs (RR 0.75 [95% CI 0.55–1.01]), time to all-cause death (HR 0.92 [95% CI 0.81–1.05]), time to first all-cause hospitalization (HR

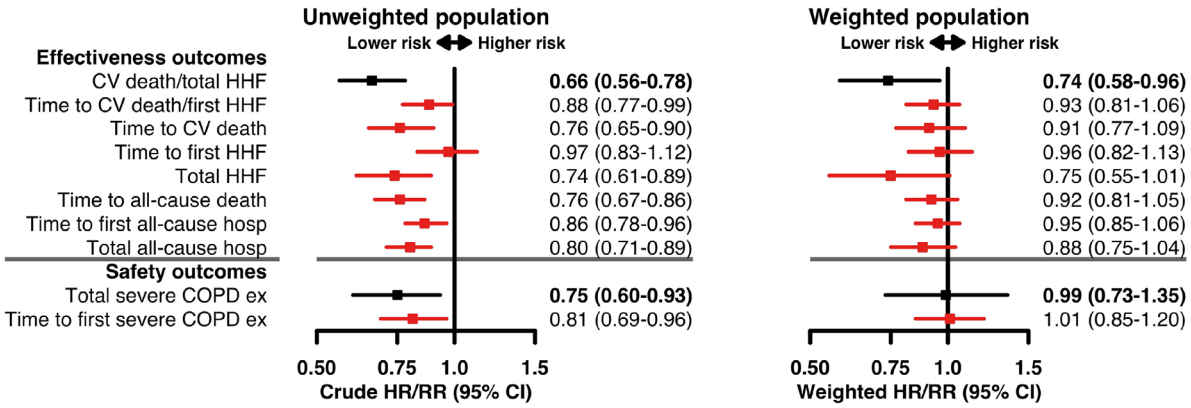


Figure 1 Association of beta-blocker treatment with clinical outcomes in patients with heart failure with reduced ejection fraction and concomitant chronic obstructive pulmonary disease (COPD). CI, confidence interval; CV, cardiovascular; ex, exacerbation; HHF, hospitalization for heart failure; HR, hazard ratio; RR, rate ratio. The primary outcomes are highlighted in black and bold, secondary outcomes are displayed in red.

0.95 [95% CI 0.85–1.06]) or total number of all-cause hospitalizations (RR 0.88 [95% CI 0.75–1.04]) (*Figure 1*, online supplementary *Figures S4–S8*).

Respiratory safety outcomes according to beta-blocker treatment

There were 32 severe COPD exacerbations per 100 patient-years overall, with lower crude risk among beta-blocker users versus non-users (RR 0.75 [95% CI 0.60–0.93]). Beta-blocker treatment was also associated with a lower crude risk of all respiratory safety outcomes (*Figure 1*).

In the overlap weighted analyses, there was no association between beta-blocker use and the primary safety outcome, i.e. total number of severe COPD exacerbations (RR 0.99 [95% CI 0.73–1.35]), nor with time to first severe COPD exacerbation (HR 1.01 [95% CI 0.85–1.20]) (*Figure 1*, online supplementary *Figure S9*).

Subgroup analyses

The overlap-weighted associations between beta-blocker use and lower risk for the primary cardiovascular effectiveness outcome had greater magnitude in patients with a LVEF <30% versus 30%–39% (RR 0.52 vs. RR 1.08, *p*-interaction = 0.004). No other significant heterogeneity was observed for the association with the primary cardiovascular effectiveness outcome across subgroups, e.g. age, sex, NYHA class and COPD GOLD group (*Figure 2*, online supplementary *Table S5*).

For the primary safety outcome analysis, no heterogeneity was observed across subgroups (*Figure 2*, online supplementary *Table S6*).

No significant differences in the primary effectiveness nor primary safety outcomes were detected according to beta-blocker dosage or cardioselectivity of agents among beta-blocker users (online supplementary *Tables S7–S9*, *Figures S10* and *S11*).

Sensitivity analysis: incident heart failure

Of 961 patients with incident HF, 865 (90.0%) were treated with beta-blockers at SwedeHF registration. Beta-blocker use did neither show significant associations with the primary effectiveness outcome (unweighted: RR 0.88 [95% CI 0.60–1.30]; weighted: RR 0.90 [95% CI 0.45–1.80]), nor with the primary safety outcome (unweighted: RR 0.81 [95% CI 0.51–1.26]; weighted: RR 0.95 [95% CI 0.45–2.00]).

Positive control analysis

In the unweighted positive control population consisting of 57 580 patients with HFrEF without COPD, differences in patient characteristics across beta-blocker users versus non-users were similar as in the main study population (online supplementary *Tables S10* and *S11*). Overlap weighting achieved balance in all assessed baseline parameters (online supplementary *Figure S12* and *Table S10*). The overlap weighted sample consisted of 36 101 patients (31 702 [87.8%] beta-blocker users and 4399 [12.2%] non-users). Beta-blocker treatment was associated with a lower total number of cardiovascular deaths and HHFs both before (RR 0.58 [95% CI 0.54–0.61]) and after overlap weighting (RR 0.74 [95% CI 0.68–0.80]). In addition, beta-blocker use did correlate with the total number of severe COPD exacerbations before (RR 0.64 [95% CI 0.57–0.72]) but not after overlap weighting (RR 0.88 [95% CI 0.75–1.04]).

Negative control analysis

In the negative control outcome analysis, beta-blocker treatment was not associated with time to first cancer hospitalization (unweighted: HR 0.84 [95% CI 0.58–1.22], $p = 0.357$; overlap weighted: HR 1.02 [95% CI 0.69–1.52]; $p = 0.902$) (online supplementary *Figure S13*).

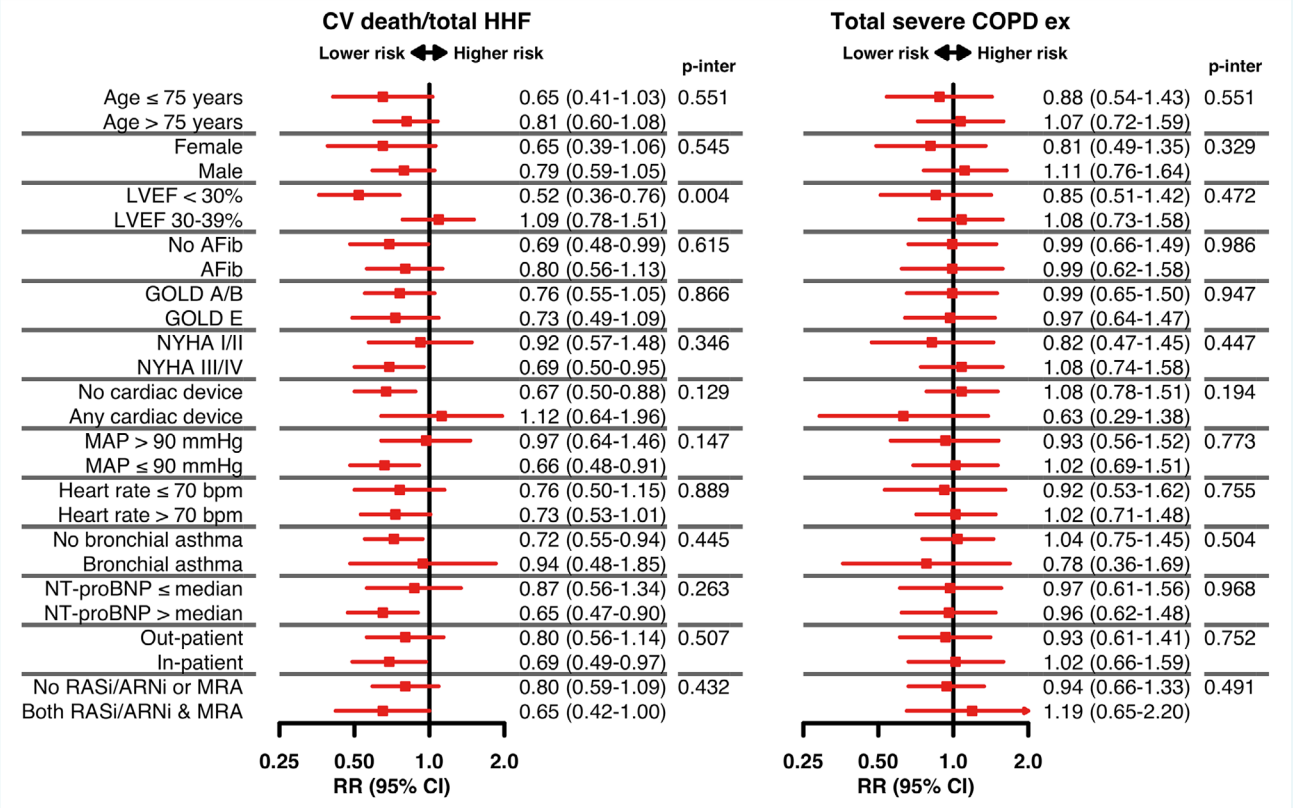


Figure 2 Association of the primary effectiveness (cardiovascular [CV] death/total hospitalizations for heart failure [HHF]) and safety (total severe chronic obstructive pulmonary disease exacerbations [COPD ex]) outcomes across pre-defined subgroups in the overlap weighted population. AFib, atrial fibrillation; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association classification; RASi, renin–angiotensin system inhibitor (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker); RR, rate ratio.

Discussion

In the present observational study enrolling a well-characterized cohort of 5084 patients with HFrEF and concomitant COPD, beta-blocker use was associated with lower risk of the primary effectiveness outcome of cardiovascular death and total HHFs. There were no signals for safety concerns in terms of respiratory outcomes, regardless of GOLD grouping based on exacerbation history. These findings support that concomitant COPD should not constitute an obstacle to cardioselective beta-blocker therapy in patients with HFrEF.

Beta-blocker therapy in patients with heart failure with reduced ejection fraction and chronic obstructive pulmonary disease

Increased sympathetic drive is a key mechanism in HF. Beta-blockers shield the heart from excessive sympathetic activation which results in well-documented clinical benefit in patients with HFrEF.[3–5] European and American guidelines on HF provide a class IA recommendation on beta-blocker use in these patients.[1,2] This recommendation does not differentiate regarding the presence of COPD, based on a statement by GOLD that cardioselective beta-blockers can be used in patients with COPD with a cardiovascular indication.[22] However, existing *de facto* evidence supporting these recommendations is scarce.

To our knowledge, the only RCT that compared a beta-blocker (bisoprolol) to placebo in patients with HFrEF and COPD enrolled only 27 patients.[11] The primary endpoint of forced expiratory volume at 1 s (FEV_1) was reduced after 4 months in the bisoprolol arm as compared with placebo, although no adverse effects were observed in terms of health-related quality of life or functional status. The study was not powered to assess hard outcomes.

Several observational studies exist on this topic, but most did not report on LVEF or the number of patients with HFrEF.[23–27] A US multicentre study showed that beta-blocker use was independently associated with lower risk of the composite of mortality and all-cause rehospitalization in 722 patients with HFrEF and COPD.[12] However, cause-specific respiratory or cardiovascular outcomes were not reported.

The present study expands on these previous data, showing that beta-blocker use was associated with cardiovascular effectiveness without any signal for more adverse respiratory events in a large and well-characterized patient population with HFrEF and COPD. Notably, more than one third of patients in our study population were in GOLD group E and neither cardiovascular effectiveness nor respiratory safety appeared to interact with GOLD grouping based on exacerbation history. Nonetheless, patients with advanced COPD or frequent exacerbations should be closely monitored through an interdisciplinary approach that includes pulmonology care. Our findings are supported by a negative control analysis that did not detect influence from residual confounding after overlap weighting. In addition, a positive control analysis in patients with HFrEF but without COPD showed that the weighted association between beta-blockers and outcomes was highly consistent with existing randomized evidence as well as the main study results on the primary effectiveness outcome (total number of cardiovascular death and HHF).

Beta-blocker cardioselectivity

The present study lacked power to assess whether the associations between beta-blocker therapy and outcomes differed according to beta-blocker cardioselectivity. This assessment would be of particular interest as beta-blockers in HF and bronchodilators in COPD have opposing effects on the adrenoceptors, and a high selectivity towards beta-1 adrenoceptors (i.e. high cardioselectivity) might mitigate the potential bronchoconstrictive effect of beta-blockers. It should be noted that the majority of beta-blocker users were treated with cardioselective substances (metoprolol or bisoprolol), preventing generalizability to less cardioselective beta-blockers such as carvedilol. Exploratory and subgroup analyses did not detect any differences according to cardioselectivity or dosage, although they might have lacked sufficient power to draw definitive conclusions. Randomized data support that cardioselective agents should be preferred in patients with HFrEF and COPD. In an open-label RCT including 63 patients with HFrEF and COPD, FEV_1 increased in patients randomized to bisoprolol but not carvedilol.[28] In a randomized crossover trial comparing beta-blocker agents in 51 patients, FEV_1 was highest with bisoprolol followed by metoprolol, and lowest with carvedilol among the 35 patients with HF and concomitant COPD.[29] Nebivolol, a cardioselective beta-blocker which might have negligible effects on FEV_1, is not available in Sweden and was therefore not assessed in our study.[30] In addition, there remain doubts about the optimal dosage of beta-blockers in patients with HFrEF and COPD.[31] We note that approximately one third of beta-blocker users in our study population received the target dose.

Beta-blocker use and chronic obstructive pulmonary disease exacerbations

The BLOCK COPD trial, which enrolled patients with COPD but without HFrEF, observed higher rates of severe COPD exacerbations in the metoprolol arm.[9] In contrast, in our study on patients with HFrEF and concomitant COPD, no such association between beta-blocker use and severe exacerbations was observed. There are several potential reasons for these diverging results. First, it is possible that unsuccessful randomization and the early termination contributed to the findings of BLOCK COPD. In BLOCK COPD, patients in the metoprolol arm were more frequently active smokers (35.4% vs. 26.9%) and exhibited a higher rate of emergency department visits or hospitalizations due to COPD exacerbations in the previous year (62.7% vs. 50.4%) as compared with the placebo arm. Second, it is pathophysiologically reasonable that improving HF may also benefit non-cardiovascular outcomes like respiratory hospitalizations due to increased resilience. This aspect has recently been highlighted in a post-hoc analysis of the IRONMAN trial, where intravenous iron was found to reduce the risk of adjudicated cardiovascular and non-cardiovascular hospitalizations to a similar degree.[32] Therefore, potential respiratory adverse effects with beta-blockers (as suggested in the BLOCK COPD trial) might be conceivably attenuated when used in patients with HFrEF. However, potential residual confounding in our study limits the certainty of our conclusion. Finally, patients prone to COPD exacerbations might have stopped beta-blocker therapy before the index date of this study ('prevalent user bias'), thus being allocated to the non-user group of the analysis.

Real-world use of beta-blockers in patients with heart failure with reduced ejection fraction and chronic obstructive pulmonary disease

In this real-world population of SwedeHF, the frequency of beta-blocker use in patients with HFrEF and concomitant COPD was 91.5%, and 92.3% in those without COPD. This suggests that, in current clinical practice, these patients are already perceived to receive net benefit from beta-blocker therapy, as supported by our findings in the context of a population mainly cared for in secondary/tertiary centres. Beta-blocker non-use might have occurred for reasons that are unrelated to the presence of COPD, e.g. clinical inertia, patient adherence and other contraindications/tolerability issues (e.g. due to allergies, bronchial asthma, severe psoriatic arthritis, hypotension, bradycardia). This aligns with the high use of beta-blockers observed in recent trials such as DAPA-HF (92.3% in patients with COPD and 96.6% in those without COPD),[33] but contrasts to previous data from the CHARM programme where 31.9% of bronchodilator users with HFrEF received a beta-blocker, but 57.3% of non-users.[34]

Strengths and limitations

The main strengths of the present study stem from the large and well-characterized HF cohort of SwedeHF and linked national registries. This allowed for the inclusion of a large, well-characterized study population with HFrEF and COPD, access to LVEF data as well as to a large set of potential confounders, and near to full coverage of cause-specific death, hospitalization as well as prescription of medication.

Several limitations should also be acknowledged. Due to the observational design, we cannot exclude influence from residual confounding on the observed relationships between beta-blocker treatment and outcomes. However, measured confounders were balanced by overlap weighting and a falsification analysis did not suggest that our findings were explained by residual confounding. Although we took steps to derive valid COPD definitions and COPD severity indicators from national registries, we did not have access to important clinical COPD parameters measured through spirometry data and COPD symptom assessments, and therefore we could only rely on exacerbation history. We opted to prioritize specificity over sensitivity for COPD in the definition of our study population, which most likely exclude patients with milder COPD as many of them are treated in primary care or not even identified by healthcare.[35] However, this was deemed appropriate to achieve representativeness of patients with a valid concomitant COPD diagnosis where respiratory safety concerns for beta-blocker use might be more apparent. This approach also came at the cost of reducing the number of included patients and, consequently, we lacked statistical power to detect associations of modest strength. Crossover between the treatment groups was not assessed, as well as the switch from one to another beta-blocker agent and the overall duration of the beta-blocker therapy. However, this approach is analogous to the intention-to-treat analysis in RCTs. In addition, beta-blocker use was defined at index but did not necessarily represent new initiation, possibly resulting in less selection of unmeasured traits predisposing to discontinuation in the beta-blocker arm, such as higher risk for respiratory adverse events or symptoms ('prevalent user bias'). However, the neutral findings on the negative control analysis make this less likely. Moreover, a sensitivity analysis in patients with incident HF (deemed more likely incident beta-blocker users) showed directionally consistent results with the overall analysis, although with lower power and not statistically significant. Furthermore, cause-specific outcomes (i.e. cardiovascular death and HHF) were not adjudicated. Finally, patients enrolled in SwedeHF represent a better-treated, younger and less comorbid subset with better outcomes as compared with the broader Swedish HF population, but with still limited uptake of SGLT2i in our study population – these aspects might limit generalizability to the setting of contemporary HFrEF guideline-directed medical therapy.[36]

Conclusion

In patients with HFrEF and concomitant COPD, beta-blocker use was associated with lower risk of cardiovascular death and HHFs. No respiratory safety concerns were detected between the treatment arms (*Graphical Abstract*), regardless of COPD GOLD group. These observational findings suggest that beta-blockers should not be withheld from patients with HFrEF because of a concomitant COPD diagnosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We thank all staff members at all participating care units as well as the patients for their contribution to the SwedeHF registry.

Funding

This work was supported by the Horizon Europe programme (project number 101095479 – More-EUROPA), and the Swedish Heart and Lung Foundation (project number 20220680) to Dr. Gianluigi Savarese's institution. Dr. Benedikt Beer was supported by a grant of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; grant number 535014557).

Conflict of interest: B.N.B. reports research funding from German Research Foundation (Deutsche Forschungsgemeinschaft, DFG; grant number 535014557), connected to the submitted work. However, DFG did not participate in or have influence on any steps of this study, did not review the manuscript and does not have any commercial interest connected to this work. He also reports research funding (grant number 81X4710101) as well as travel grants from the German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK), outside of the submitted work. B.S. reports speaker fees from Abbott, Abiomed, AstraZeneca, and Inari as well as research funding from Abiomed, German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK), Else-Kröner-Fresenius Foundation, and University of Hamburg, all outside of the submitted work. P.M.B. reports speaker fees from AstraZeneca and Ingelheim Boehringer, all outside the submitted work. P.K. was partially supported by European Union MAESTRIA (grant agreement 965 286), British Heart Foundation (AA/18/2/34218), German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK, grant numbers DZHK FKZ 81X2800182, 81Z0710116, and 81Z0710110), German Research Foundation (Deutsche Forschungsgemeinschaft, DFG; Ki 509 167 694), Dutch Heart Foundation (DHF), the Accelerating Clinical Trials funding stream in Canada, and the Else-Kröner-Fresenius Foundation. He received research support for basic, translational, and clinical research projects from German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), European Union, British Heart Foundation, Leducq Foundation, Else-Kröner-Fresenius Foundation, Dutch Heart Foundation (DHF), the Accelerating Clinical Trials funding stream in Canada, Medical Research Council (UK), and German Center for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last 5 years. He is listed as inventor on two issued patents held by University of Hamburg (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783); all disclosures outside the submitted work. A.L. reports personal fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and Novartis, all outside of the submitted work. G.R. reports support from the Italian Ministry of Health (Ricerca Corrente) 20/1819. [Correction added on 10 November 2025, after first online publication: In the preceding sentence, the Italian Ministry of Health funding statement for Giuseppe Rosano has been added in this version. L.H.L. reports grants, consulting, honoraria to his institution from Alleviant, Amgen, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Edwards, Novartis, Novo Nordisk, Owkin, Pharmacosmos, and Vifor Pharma, all outside the submitted work. F.L. reports personal fees from AstraZeneca, outside the submitted work. G.S. reports grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Medtronic, Bayer, and personal fees from Roche, Abbott, Edwards Lifescience, TEVA, Menarini, INTAS, GETZ, Hikma, and grants from Boston Scientific, Merck, all outside the submitted work. All other authors have nothing to disclose.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:e263–e421. https://doi.org/10.1016/j.jacc.2021.12.012
3. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;**353**:9–13. https://doi.org/10.1016/S0140-6736(98)11181-9
4. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, *et al.*; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225. https://doi.org/10.1093/eurheartj/ehi115
5. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, *et al.*; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199. https://doi.org/10.1161/01.cir.0000035653.72855.BF
6. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007. https://doi.org/10.1016/S0140-6736(99)04440-2
7. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, *et al.* Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585. https://doi.org/10.1002/ejhf.813
8. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: Diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;**11**:130–139. https://doi.org/10.1093/eurjhf/hfn013
9. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, *et al.*; BLOCK COPD Trial Group. Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–2314. https://doi.org/10.1056/NEJMoa1908142
10. Hawkins NM, Petrie MC, MacDonald MR, Jhund PS, Fabbri LM, Wikstrand J, *et al.* Heart failure and chronic obstructive pulmonary disease: The quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol* 2011;**57**:2127–2138. https://doi.org/10.1016/j.jacc.2011.02.020
11. Hawkins NM, MacDonald MR, Petrie MC, Chalmers GW, Carter R, Dunn FG, *et al.* Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: A randomized controlled trial. *Eur J Heart Fail* 2009;**11**:684–690. https://doi.org/10.1093/eurjhf/hfp066
12. Mentz RJ, Wojdyla D, Fiuzat M, Chiswell K, Fonarow GC, O'Connor CM. Association of beta-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). *Am J Cardiol* 2013;**111**:582–587. https://doi.org/10.1016/j.amjcard.2012.10.041
13. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci* 2019;**124**:65–69. https://doi.org/10.1080/03009734.2018.1490831
14. SWEDEHEART Annual Report 2023: SwedeHF Appendix. 2024 https://www.ucr.uu.se/rikssvikt/om-rikssvikt/arsrapporter/arsrapporter/2023-swedeheart-annual-report-swedehf-appendix-nytt Accessed 13 February 2025.
15. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol* 2019;**34**:423–437. https://doi.org/10.1007/s10654-019-00511-8
16. National Patient Register. Socialstyrelsen. 2024 https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/ Accessed 16 September 2024.
17. Ohlin M, Otterdal P. *Statistical register's production and quality – National Prescribed Drug Register*. Stockholm, Sweden: National Board of Health and Welfare (Socialstyrelsen); 2021. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/production-and-quality-lmed.pdf Accessed 18 September 2024.
18. National Cause of Death Register. Socialstyrelsen. 2022 https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/production-and-quality-dors.pdf. Accessed 18 September 2024.
19. Inghammar M, Engström G, Löfdahl C-G, Egesten A. Validation of a COPD diagnosis from the Swedish Inpatient Registry. *Scand J Public Health* 2012;**40**:773–776. https://doi.org/10.1177/1403494812463172
20. Ingebrigtsen TS, Marott JL, Lange P, Hallas J, Nordestgaard BG, Vestbo J. Medically treated exacerbations in COPD by GOLD 1-4: A valid, robust, and seemingly low-biased definition. *Respir Med* 2015;**109**:1562–1568. https://doi.org/10.1016/j.rmed.2015.10.015
21. Vanfleteren LEGW, Lindberg A, Zhou C, Nyberg F, Stridsman C. Exacerbation risk and mortality in Global Initiative for Chronic Obstructive Lung Disease Group A and B patients with and without exacerbation history. *Am J Respir Crit Care Med* 2023;**208**:163–175. https://doi.org/10.1164/rccm.202209-1774OC
22. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2025 report. https://goldcopd.org/wp-content/uploads/2024/11/GOLD-2025-Report-v1.0-15Nov2024_WMV.pdf Accessed 18 September 2024.
23. Cochrane B, Quinn S, Walters H, Young I. Investigating the adverse respiratory effects of beta-blocker treatment: Six years of prospective longitudinal data in a cohort with cardiac disease. *Intern Med J* 2012;**42**:786–793. https://doi.org/10.1111/j.1445-5994.2011.02563.x
24. Kubota Y, Asai K, Furuse E, Nakamura S, Murai K, Tsukada YT, *et al.* Impact of β-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;**10**:515–523. https://doi.org/10.2147/copd.S79942
25. Liao KM, Lin TY, Huang YB, Kuo CC, Chen CY. The evaluation of β-adrenoceptor blocking agents in patients with COPD and congestive heart failure: A nationwide study. *Int J Chron Obstruct Pulmon Dis* 2017;**12**:2573–2581. https://doi.org/10.2147/copd.S141694
26. Rasmussen DB, Bodtger U, Lamberts M, Torp-Pedersen C, Gislason G, Lange P, *et al.* Beta-blocker use and acute exacerbations of COPD following myocardial infarction: A Danish nationwide cohort study. *Thorax* 2020;**75**:928–933. https://doi.org/10.1136/thoraxjnl-2019-214206
27. Karimi L, Lahousse L, de Nocker P, Stricker BH, Brusselle GG, Verhamme KMC. Effect of β-blockers on the risk of COPD exacerbations according to indication of use: The Rotterdam study. *ERJ Open Res* 2021;**7**:624–2020. https://doi.org/10.1183/23120541.00624-2020
28. Lainscak M, Podbregar M, Kovacic D, Rozman J, von Haehling S. Differences between bisoprolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: A randomized trial. *Respir Med* 2011;**105**:S44–S49. https://doi.org/10.1016/S0954-6111(11)70010-5
29. Jabbour A, Macdonald PS, Keogh AM, Kotlyar E, Mellemkjaer S, Coleman CF, *et al.* Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: A randomized crossover trial. *J Am Coll Cardiol* 2010;**55**:1780–1787. https://doi.org/10.1016/j.jacc.2010.01.024
30. Negro RWD, Tognella S, Micheletto C. Pharmacokinetics of the effect of nebivolol 5 mg on airway patency in patients with mild to moderate bronchial asthma and arterial hypertension. *Clin Drug Investig* 2002;**22**:197–204. https://doi.org/10.2165/00044011-200222030-00007
31. Canepa M, Franssen FME, Olschewski H, Lainscak M, Böhm M, Tavazzi L, *et al.* Diagnostic and therapeutic gaps in patients with heart failure and chronic obstructive pulmonary disease. *JACC Heart Fail* 2019;**7**:823–833. https://doi.org/10.1016/j.jchf.2019.05.009
32. Cleland JGF, Pellicori P, Graham FJ, Lane R, Petrie MC, Ahmed F, *et al.*; IRONMAN Study Group. Adjudication of hospitalizations and deaths in the IRONMAN trial of intravenous iron for heart failure. *J Am Coll Cardiol* 2024;**84**:1704–1717. https://doi.org/10.1016/j.jacc.2024.08.052
33. Dewan P, Docherty KF, Bengtsson O, de Boer RA, Desai AS, Drozdz J, *et al.* Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: An analysis of DAPA-HF. *Eur J Heart Fail* 2021;**23**:632–643. https://doi.org/10.1002/ejhf.2083
34. Hawkins NM, Wang D, Petrie MC, Pfeffer MA, Swedberg K, Granger CB, *et al.*; CHARM Investigators and Committees. Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. *Eur J Heart Fail* 2010;**12**:557–565. https://doi.org/10.1093/eurjhf/hfq040
35. Diab N, Gershon AS, Sin DD, Tan WC, Bourbeau J, Boulet L-P, *et al.* Underdiagnosis and overdiagnosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;**198**:1130–1139. https://doi.org/10.1164/rccm.201804-0621CI
36. Lund LH, Carrero J-J, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, *et al.* Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail* 2017;**19**:1107–1116. https://doi.org/10.1002/ejhf.762