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Original Article

Mortality associated with cardiovascular drugs in patients with chronic obstructive pulmonary disease and right-sided heart failure – A danish nationwide registry-based study

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ABSTRACT

Background: The optimal medical treatment in patients with chronic obstructive pulmonary disease (COPD) and right-sided heart failure (RHF) is unknown. We aimed to estimate the risks of all-cause mortality associated with the current clinical use of various cardiovascular drugs in this patient-group.

Methods: We followed all patients with registered COPD and RHF (defined as a diagnosis of pulmonary hypertension plus use of loop-diuretics) for the risk of all-cause mortality (Jan 1, 1995 to Dec 31, 2015) using the Danish nationwide administrative registries. The association between mortality and claimed prescriptions for cardiovascular drugs was assessed by multivariable Cox regression models.

Results: 5991 patients (mean age 74 ± standard deviation 10 years, 51% women) were included. Of these, 1440 (24%) used beta-blockers, 2149 (36%) renin-angiotensin system inhibitors [RASi], 1340 (22%) oral anticoagulants, 1376 (23%) calcium channel blockers, 1194 (20%) statins, 1824 (30%) spironolactone, and 2099 (35%) low-dose aspirin. During an average follow-up of 2.2 years (± standard deviation 2.8, min-max 0–19.6 years), 5071 (85%) died, corresponding to a mortality rate of 38 per 100 person-years (95% confidence interval 37–39). Compared to no use, beta-blockers were associated with adjusted hazards ratio 0.90 (95% confidence interval 0.84–0.98), RASi 0.92 (0.86–0.98), calcium channel blockers 0.86 (0.80–0.92), spironolactone 1.17 (1.10–1.24), statins 0.85 (0.78–0.92), oral anticoagulants 0.87 (0.79–0.95), and aspirin 0.99 (0.93–1.05). Propensity-score matched analyses and inverse-probability-weighted models yielded similar results.

Conclusion: Several cardiovascular drugs may be associated with lowered mortality in COPD and RHF. Given the grave prognosis, randomized clinical trials are warranted to test this hypothesis.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases in developed and developing countries [1]. It is associated with substantial morbidity and mortality, especially in the presence of pulmonary hypertension and right-sided heart failure (RHF) [2,3]. COPD and heart failure are both (and independent of each other) among the top causes of mortality, according to WHO statistics [4]. Despite the common coexistence of COPD and RHF (with right ventricular dysfunction being present in up to a fifth of all COPD patients) [2], very little is known about the optimal medical therapy in these patients. Similar to the adverse remodelling occurring secondary to e.g. long-standing arterial hypertension and aortic stenosis in the left ventricle, the right ventricle undergoes several maladaptive changes secondary to COPD [5]. These include an increased right ventricular end-systolic volume, right ventricular dilation, and impaired right

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ventricular ejection fraction (such adverse changes may indeed also occur in the absence of overt pulmonary hypertension) [6]. In the setting of left ventricular systolic dysfunction, the use of renin-angiotensin inhibitors (RASi) and beta-blockers are well-known for their ability to attenuate the adverse cardiac remodelling process, to improve heart failure symptoms, and to lower mortality [7–9]. Because parts of the remodelling process are similar in right and left heart failure, it may be hypothesized that these drugs may also be beneficial in COPD patients with RHF. In addition, both calcium channel blockers, statins, and anticoagulantion therapy has been suggested to improve outcomes in COPD patients with pulmonary hypertension [10–12]. In this study, we investigated the outcomes of multiple cardiovascular drugs in patients with concomitant COPD and presumed RHF, using the Danish nationwide administrative databases.

2. Methods

The Danish healthcare system is tax-funded, free of personal charge, and equally available to all citizens, irrespectively of e.g. employment status. The government keeps records of all hospitalizations (in the Danish National Patient Registry, established in 1974), claimed prescriptions of pharmacotherapy (the Danish National Prescription Registry, established in 1995), vital status (including dates of birth and death, and immigrations and emigrations in the Danish Population Registry, established in 1968), and causes of deaths (the Danish National Causes of Death Registry, established in 1970). Data is collected as part of routine clinical work and information in these registries is for most of the common diagnoses very accurate [13–15]. The hospital departments are financially reimbursed based on available discharge diagnoses, which are coded according to the ICD-10 system since 1994 (and before then by the ICD 8 system). Pulmonary hypertension and COPD have previously been validated in the Danish registries with positive predictive values [PPV] of 87% and 92–100%, respectively [16–18]. Similar, patients are partly reimbursed for drug expenses, which make a great incentive for correct registration of claimed prescriptions. Using the above-mentioned registries, we identified all patients with COPD, defined as in or out-patient diagnosis of ICD-10 J44, or ICD-8490–492. We included those patients who also had a diagnosis of pulmonary heart disease, defined as an ICD-10 code of I27 and started follow-up at the occurrence of the second condition (from now denoted as “baseline”). To further increase the likelihood that all patients had RHF, we restricted the analyses to those who also used loop diuretics within 6 months up to baseline. Due to lack of medication data before 1995, the inclusion period spanned from Jan 1, 1995 to Dec 31, 2015. Comorbidities (see online supplemental material Table 1 for ICD codes) were defined as a diagnosis available in the registry at any time before baseline. Patients were considered to be in treatment with various pharmacotherapies if they had claimed at least one prescription of the drug within 180 days prior to baseline. Codes used to identify the various medications are also available in the Online Supplemental Material Table 2. Because the COPD diagnostic criteria have changed throughout the observational period, we performed a sensitivity analysis based on only patients diagnosed after 2007. In this period, spirometry was well-established for the diagnosis of COPD (long after the first Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were published recommending spirometry for the diagnosis) [19]. To rule out any potential impact of pre-existing left sided heart failure on the associations between mortality in RHF and various medications, a subgroup analysis was also performed where patients with pre-existing heart failure, ischemic heart disease, or prior myocardial infarction were excluded.

2.1. Ethics

Registry-based analyses, using de-identifiable data, are exempted from ethical approval in Denmark. The study was approved by the Danish Data Protection Agency.

2.2. Statistic

For the baseline characteristics table, we stratified the population by its use of RASi and beta-blockers, respectively. Cox proportional regression models were used to investigate the association of various pharmacotherapies with the risk of all-cause mortality. People were censored at the first occurring of emigration, death, or at the end of follow-up (Dec 31, 2015). All models were adjusted for the a priori selected variables presented in Table 1 plus calendar year of inclusion. The proportional hazards assumption was tested for all variables by the “assess” statement in “proc phreg” and was found valid. The assumption of lack of interactions and linearity of continuous variables were also tested and fulfilled, unless otherwise specified. As sensitivity, we performed propensity-score matched subgroup analyses, where each of the treatments were matched 1:1 with untreated individuals on propensity-score (the score being derived from multivariable logistic regression models [including all variables from Table 1 plus calendar year in bins of 1995–2001, 2002–2010, and > 2010] with treatment as the outcomes; maximal allowed difference 0.05), sex, and age (maximal allowed difference 0 for sex, and 3 years for age). We also performed inverse-probability weighted Cox regression models to increase the assumption of causality. All analyses were performed in SAS version 9.4. Two-sided p-values $< 0\,05$ were considered statistically significant.

3. Results

A total of 5991 patients (mean age 74 ± [standard deviation] 10 years; min-max 24–101 years, 51% women) were included. Of these, 1440 (24%) used beta-blockers and 2149 (36%) were in treatment with RASi. Baseline characteristics, stratified by medication use, are given in Table 1. Approximately half of all individuals had a concomitant diagnosis of heart failure. More patients who used beta-blockers and RASi were included in the later calendar period compared with the earlier years, whereas the untreated individuals were more uniformly distributed throughout the period, Fig. 1. Overall, there were minor differences between the treated and untreated individuals, but the prevalence of ischemic heart disease, atrial fibrillation, and the use of oral anticoagulant therapy tended to be higher among those who used RASi and/or beta blockers.

3.1. Mortality

During an average follow-up of 2.2 years (± standard deviation 2.8 years, min-max 0–19.6 years), 5071 (85%) died, corresponding to an overall mortality rate of 38 per 100 person-years (95% confidence interval 37–39). The 1-year cumulative mortality in our sample was 44%.

The association of various treatments with mortality from the multivariable Cox regression model is shown in Fig. 2. Male sex, increasing age, chronic kidney disease, liver disease, a previous diagnosis of heart failure, prior acute myocardial infarction, and diabetes were significantly associated with mortality risk, Fig. 3. The association of inhaled COPD treatment regimen and mortality (from the multivariable Cox model) is presented in online supplemental Fig. 1.

3.2. Sensitivity analyses

The C-statistic (from the logistic regression models underlying the propensity calculations) was lowest for spironolactone (0.64) and calcium channel blockers (0.66) and highest for use of oral anticoagulants (0.88). In general, both the propensity-matched subgroup analyses and inverse-probability-weighted models yielded results consistent with the main analyses, Table 2.

Table 1
baseline characteristics.

	BB	RASi + BB	RASi	None
N	660 (11%)	780 (13%)	1369 (23%)	3182 (53%)
Age	76 (9)	75 (9)	74 (9)	72 (11)
Gender, female	357 (54%)	379 (49%)	695 (51%)	1644 (52%)
Diabetes	93 (14%)	159 (20%)	195 (14%)	213 (7%)
Acute myocardial infarction	138 (21%)	209 (27%)	197 (14%)	263 (8%)
Ischemic heart disease	314 (48%)	423 (54%)	517 (38%)	830 (26%)
Concomitant diagnosis of heart failure*	391 (59%)	530 (68%)	846 (62%)	1538 (48%)
Pulmonary embolism	73 (11%)	64 (8%)	112 (8%)	277 (9%)
Atrial fibrillation	356 (54%)	411 (53%)	364 (27%)	654 (21%)
Chronic kidney disease	106 (16%)	129 (17%)	122 (9%)	152 (5%)
Liver disease	26 (4%)	32 (4%)	31 (2%)	81 (3%)
Medications				
Thiazides	≤3 (NA)	104 (13%)	153 (11%)	27 (1%)
Angiotensin converting enzyme inhibitor	0	548 (70%)	1051 (77%)	0
Angiotensin II receptor blockers	0	257 (33%)	347 (25%)	
Calcium channel blockers	164 (25%)	233 (30%)	359 (26%)	620 (19%)
Spironolactone	202 (31%)	259 (33%)	440 (32%)	923 (29%)
Aspirin	293 (44%)	399 (51%)	561 (41%)	846 (27%)
Clopidogrel	43 (7%)	61 (8%)	46 (3%)	47 (1%)
Ticagrelor	≤3 (NA)	4 (0.5%)	≤3 (NA)	≤3 (NA)
Statins	207 (31%)	371 (48%)	329 (24%)	287 (9%)
Oral anticoagulants**	270 (41%)	330 (42%)	258 (19%)	482 (15%)
COPD treatment				
ICS, monotherapy	15 (2%)	14 (2%)	55 (4%)	147 (5%)
LABA, monotherapy	53 (8%)	62 (8%)	142 (10%)	365 (11%)
LAMA, monotherapy	24 (4%)	31 (4%)	45 (3%)	77 (2%)
LABA + ICS	100 (15%)	142 (19%)	323 (24%)	797 (25%)
LAMA + ICS	5 (1%)	5 (1%)	11 (1%)	21 (1%)
LAMA + LABA	38 (6%)	51 (7%)	62 (5%)	182 (6%)
LAMA + LABA + ICS	171 (26%)	197 (25%)	319 (23%)	702 (22%)
No inhaled long-acting treatment	255 (39%)	284 (36%)	417 (30%)	900 (28%)

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA long-acting beta2 agonists; LAMA, long-acting muscarinic antagonists.

* Concomitant diagnosis of heart failure refers to having a separate registration of heart failure in the hospitalization registry (see online supplemental material for diagnostic codes).

** Refers to both warfarin (comprising 96%) and non-vitamin K oral anticoagulants (NOAC, comprising 4%).

Restricting the analyses to patients who received a COPD diagnosis in 2008 or later (N = 2561, of whom 1764 [69%] died during follow-up), hazards ratio estimates pointed in similar directions as those from the main analyses: oral anticoagulants 0.84 (95% CI 0.75–0.95; N treated = 845 [33%]), statins 0.90 (95% CI 0.80–1.00; N treated = 925 [36%]), aspirin 1.06 (95% CI 0.96–1.18; N treated = 1045 [41%]), RASi 0.92 (95% CI 0.82–1.02; N treated = 1134 [44%]), calcium channel blockers 0.81 (95% CI 0.73–0.91, N treated = 657 [26%], beta-blockers 0.91 (95% CI 0.82–1.02; N treated = 1028 [40%]), and spironolactone 1.15 (95% CI 1.03–1.28, N treated = 715 [28%]).

In the subgroup analysis of patients without a pre-existing diagnosis of heart failure, ischemic heart disease, and prior acute myocardial infarction (N = 1978, of whom 1626 [82%] died during follow-up), hazards ratio estimates associated with various drugs were similar to those of the main models: oral anticoagulants 0.82 (95% CI 0.69–0.98; N treated = 297 [15%]), statins 0.85 (95% CI 0.71–1.03, N treated = 242 [12%]), aspirin 1.04 (95% CI 0.92–1.18, N treated = 466 [24%]), RASi 0.88 (95% CI 0.77–1.00, N treated = 518 [26%]), calcium channel blockers 0.90 (95% CI 0.79–1.03, N treated = 396 [20%]), beta-blockers 0.83 (95% CI 0.70–0.98, N treated = 298 [15%]), and spironolactone 1.25 (95% CI 1.11–1.41, N treated = 437 [22%]).

4. Discussion

A handful of observational studies of patients with COPD have previously investigated the outcomes associated with use of selected cardiovascular pharmacotherapies and mortality [11,20–26]. However, none of these have focused specifically on patients with RHF. Mortality rates of prior investigations have therefore generally been lower than what was observed in our cohort. An exception to this was study by Ekström et al. which included patients on long-term (home) oxygen therapy, where very similar mortality rates to ours were reported (36 per 100 person-years), but the number of patients with RHF was not

Table 2
results from the sensitivity analyses.

	C statistic	Propensity score matched cohort			Inverse probability weighted Cox model
		Deaths/N, treated	Deaths/N, untreated	Hazards ratio	Hazards ratio
Beta blockers	0.83	909/1186	939/1186	0.85 (0.75–0.96)	0.90 (0.86–0.93)
RAS i	0.73	1451/1741	1494/1741	0.95 (0.86–1.04)	0.91 (0.87–0.94)
Oral anticoagulants	0.88	737/908	753/908	0.80 (0.70–0.92)	0.88 (0.85–0.92)
Statins	0.86	702/953	723/953	0.84 (0.73–0.97)	0.78 (0.75–0.82)
Spironolactone	0.64	1572/1781	1499/1781	1.20 (1.09–1.33)	1.17 (1.13–1.22)
Calcium channel blockers	0.66	1102/1363	1162/1363	0.83 (0.74–0.93)	0.87 (0.83–0.90)
Aspirin	0.74	1491/1725	1420/1725	0.95 (0.86–1.05)	1.00 (0.96–1.04)

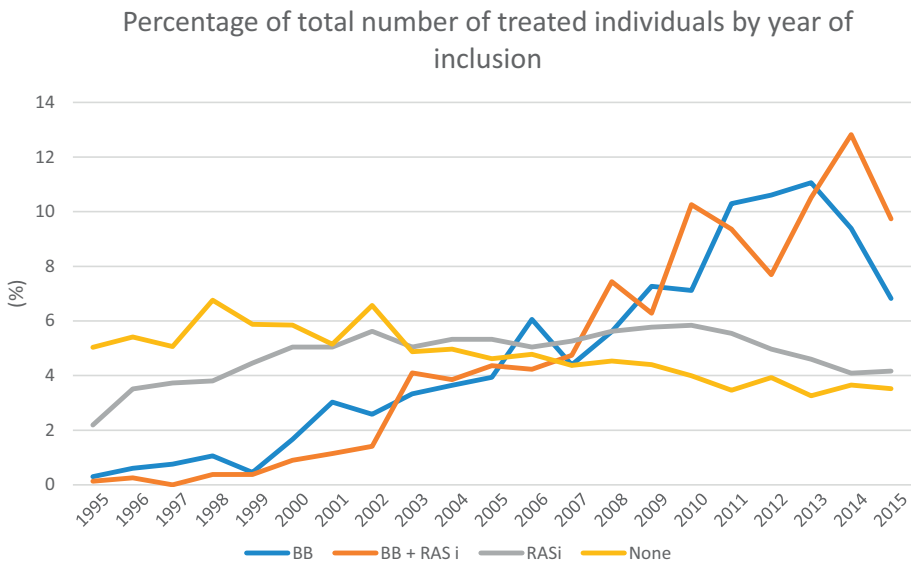

Fig. 1. Legend: Y-axis present the proportion of patients in each of the four groups who were included in the different calendar years (e.g., 6.8% of all patients who were treated with beta-blockers as monotherapy were included in 2015). BB, beta-blockers; RAS i renin-angiotensin receptor antagonists.

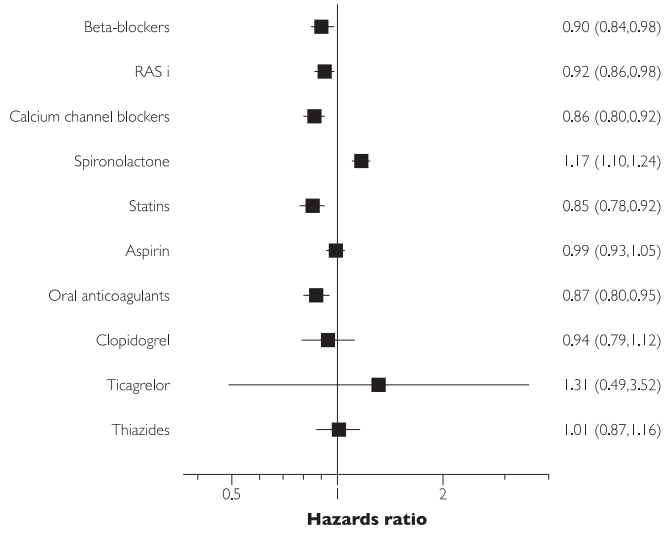

Fig. 2. association of various pharmacological treatments with all-cause mortality.
Hazards ratios associated with various pharmacological treatments with mortality. The model was additionally adjusted for age, sex, the characteristics specified in Table 1, and calendar year.

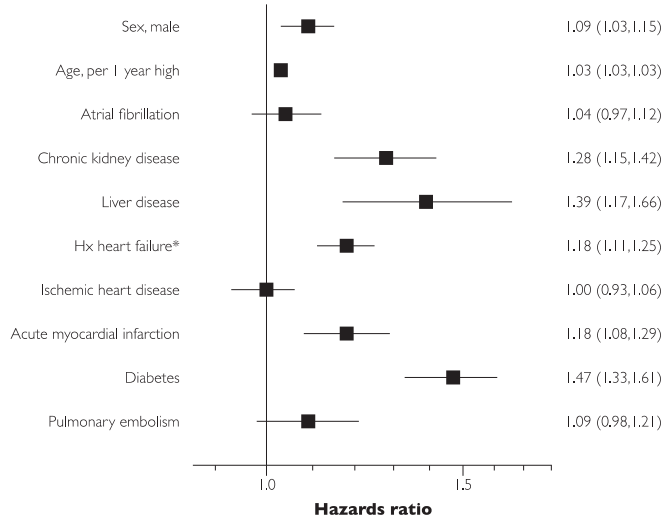

Fig. 3. association of patient comorbidities and characteristics with all-cause mortality.
Hazards ratios associated with various variables with mortality. * Hx heart failure refers a concomitant diagnosis of heart failure in the hospitalization registry. The model was additionally adjusted for age, sex, the pharmacological treatments specified in Table 1, and calendar year.

specified [20]. In contrast to our findings, however, that study reported increased hazards ratios associated with beta-blockers and lowered hazards ratios associated with antiplatelet therapy [20]. Major differences in population characteristics and the study design were present, including a time-dependent approach by Ekström et al., which may or may not have influenced the study estimates, as compared with e.g. inverse probability weighted models [27]. In contrast to the study by Ekström et al., most other available studies have suggested that beta-blockers may increase survival and lower the risk of hospitalization for COPD exacerbation [22,23,25,26], a premise that is currently being investigated in a randomized clinical trial [28].

Our data also suggested that use of RASi in COPD and RHF is associated with slightly lowered mortality. Prior studies addressing the outcomes of RASi in COPD are overall sparse, but one smaller randomized, placebo controlled studies of COPD patients have suggested that RASi may exert beneficial effects on the pulmonary hemodynamic conditions and can improve exercise capacity in COPD [29]. Another small study similarly reported favourable effects of RASi on the pulmonary circulation in a sample of COPD patients with hypoxic vasoconstriction and a third pilot study (comparing losartan with placebo) suggested a lowered tricuspid pressure gradient after a year of treatment among the subgroup of patients with pulmonary hypertension at baseline (although there was a neutral effect overall) [30,31]. Angiotensin converting enzyme gene polymorphisms have also been associated with both COPD risk in Asians and the presence of pulmonary hypertension in COPD patients, supporting a causal role of the RAS system in the pathogenesis of pulmonary hypertension and possibly RHF [32,33].

As in a plethora of prior observational studies [21], statins were associated with reduced mortality in our study. Statins have previously been investigated for its possible pleotropic effects and have been

hypothesized to possess anti-inflammatory and antihypertensive effects independent of its cholesterol-lowering effect [34]; however, this premise has never been confirmed in long-term trials of COPD patients [35]. A 6-week study randomizing 70 patients with COPD to 20 mg simvastatin or placebo similarly found no overall effect on inflammatory parameters, but drops in cholesterol levels and aortic pulse wave velocities among those with elevated aortic stiffness at baseline, who received simvastatin [36]. As large-vessel stiffness is associated with pulmonary hypertension, this may be one mechanism by which statins could be hypothesized to improve outcomes in COPD and RHF [37].

We further observed a lowered mortality risk associated with oral anticoagulants in our study. Patients with COPD and pulmonary hypertension are at increased risks of venous thromboembolisms, possibly due to altered coagulation, venous stasis (including a relative stasis in the right atria and ventricle), and immobilization [12]. To the best of our knowledge, the outcomes associated with oral anticoagulants in COPD with RHF has previously not been investigated. In the context of pulmonal arterial hypertension or pulmonary hypertension secondary to left ventricular failure, observational studies have suggested lowered mortality with oral anticoagulants, but also in these settings randomized clinical trials are lacking [38–40].

Finally, we observed neutral effects on mortality associated with aspirin and increased mortality risk associated with spironolactone. Our hazards ratio associated with aspirin treatment is in contrast to those presented in a previous meta-analysis of COPD patients from observational studies (n = 11,117 patients; 47% of whom used aspirin), where a lowered mortality risk was suggested with aspirin use in patients with COPD (odds ratio for mortality 0.81, 95% CI 0.75–0.88) [24]. However, these studies did not focus on patients with pulmonary hypertension and RHF, in whom a substantially higher baseline mortality rate is apparent and where many received oral anticoagulants. Spironolactone was associated with hazards ratio 1.17 and was used in 30% of our study population. Although we adjusted for e.g. prevalent heart failure, liver disease, and renal disease, we cannot exclude that residual confounding may have influenced the results (and given the overall rather limited C-statistic of the logistic regression model for spironolactone, the sensitivity analyses may not adequately have captured all differences between treated and non-treated patients). However, the observations could also be true, since spironolactone is associated with an increased risk of hyperkalemia, which is a very strong risk factor for mortality in various settings [41,42]. In patients with left ventricular systolic heart failure and possibly heart failure with preserved ejection fraction, spironolactone has a mortality reducing effect among those who remain symptomatic after uptitration with other heart failure medications [43–45]. Unfortunately, patients with COPD on home oxygen or hospitalized with exacerbations within the past year have not been included in prior trials [46]. Thus, more studies are warranted to address the safety and efficacy of spironolactone in RHF.

4.1. Strengths and limitations

Our data was based on a large sample of patients with COPD and presumed RHF. The sample was nationwide and unselected with respect to age, social status, geographic area, and work force. Although most of the cardiovascular and non-cardiovascular diagnoses have been validated with great to excellent positive predictive values, RHF has, to our knowledge, never been validated in the Danish administrative registries. Attempting to be conservative, we restricted the analyses to include only those who also used loop diuretics; yet, the unknown PPV of this approach must be acknowledged as a limitation.

Data were observational in nature and although the population was overall homogenous with regards to comorbidity burden (which, overall, was rather extensive) a residual confounding cannot be excluded. Especially, we lacked data on several important variables such as body-mass index, pulmonary function tests, echocardiography, long-term oxygen therapy, and functional status, which are important predictors of mortality. Our results should, therefore, be regarded as hypothesis-generating only. Given the detrimental prognosis of COPD patients with RHF, randomized clinical studies are warranted to establish if the reported associations are causal.

5. Conclusions

Several cardiovascular drugs, especially oral anticoagulants, may improve mortality in patients with advanced COPD and right-sided heart failure. Randomized clinical trials are warranted to test our hypothesis.

Conflicts of interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.02.014.

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