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Impact of pulmonary disease on the prognosis in heart failure with preserved ejection fraction: the TOPCAT trial

Chronic obstructive pulmonary disease (COPD) is highly prevalent and predictive of worse outcomes in heart failure (HF) with preserved ejection fraction (HFpEF).[1,2] Severe COPD can result in *cor pulmonale*[3] and worse outcomes in HF,[2] while less severe obstructive lung disease is associated with impaired left ventricular filling and lower cardiac output despite preserved left ventricular ejection fraction (LVEF).[4] We investigated the influence of milder obstructive lung disease – defined as the absence of use of steroids or supplemental O_2 – on cardiovascular (CV) outcomes among patients with HFpEF enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial in the Americas.

TOPCAT was a multicentre, randomized, double-blind, placebo-controlled trial that tested the efficacy of spironolactone to reduce CV morbidity and mortality in 3445 adults ≥50 years of age with HFpEF (LVEF ≥45%).[5] Key exclusion criteria relevant to this analysis included severe lung disease requiring home O_2 or systemic steroid therapy, moderate or severe pulmonary hypertension, and directed therapy or biologics for lung disease. Given the significant differences in population characteristics and outcomes by region,[6] we studied the 1767 patients recruited in the Americas. All patients provided written informed consent, and the study was approved by local institutional review boards. Outcomes included the composite of CV death, aborted sudden death, or HF hospitalization (the TOPCAT primary outcome), the individual components of this composite, all-cause mortality, non-CV mortality, and all-cause hospitalization.[5] Pulmonary disease was based on the report by the site investigator of any diagnosis of COPD or asthma at enrolment. Of 1765 patients enrolled in the Americas and with data on pulmonary disease status, 653 (37%) were included in the TOPCAT echocardiographic study.[7]

Multivariable Cox proportional hazards models were employed to relate pulmonary disease at baseline to each outcome, adjusted for age, female gender, white race, treatment group, enrolment strata, percutaneous coronary intervention, use of beta-blockers, smoking status, body mass index, and heart rate. We further adjusted for New York Heart Association (NYHA) class in separate models. Interaction between pulmonary disease and randomized treatment assignment (spironolactone vs. placebo) on clinical outcomes was assessed using a multiplicative interaction term.

The mean age was 72 ± 10 years, 50% were women, and 22% were non-white. The prevalence of COPD or asthma was 24%. Patients with prevalent lung disease were younger and more frequently non-white, had higher prevalence of current smoking, obesity, prior percutaneous coronary intervention, and NYHA III/IV functional class, and lower prevalence of beta-blocker use (online supplementary *Table S1*). At a median follow-up of 2.4 years, the primary composite outcome occurred in 522 (30%), CV death in 223 (13%), HF hospitalization in 400 (23%), all-cause mortality in 385 (22%), and all-cause hospitalization in 1059 (60%). Prevalent pulmonary disease was associated with a higher risk of the primary composite endpoint, related to higher risk of HF hospitalization but not of CV death (*Table 1*). After adjustment for demographics and co-morbidities, associations persisted with the primary composite endpoint, HF hospitalization and all-cause hospitalization (*Table 1*).

In a *post hoc* exploratory analysis, pulmonary disease at enrolment modified the relationship between treatment with spironolactone and subsequent CV mortality (interaction $P = 0.01$) and all-cause mortality (interaction $P = 0.02$), such that the risk reduction associated with spironolactone was greater among patients compared to those without pulmonary disease (*Table 1*). No significant effect modification was observed for the primary endpoint, HF hospitalization, or all-cause hospitalization. Among patients with pulmonary disease, those randomized to spironolactone demonstrated a lower prevalence of prior myocardial infarction and higher prevalence of beta-blocker use (online supplementary *Table S2*). Results remained unchanged in models adjusting for randomization strata, and further adjusting for prior myocardial infarction and beta-blocker use (online supplementary *Table S3*).

Among 653 patients in the echocardiographic study, 159 (24%) had pulmonary disease (online supplementary *Table S4*). Pulmonary disease was associated with greater left ventricular wall thickness and left ventricular hypertrophy prevalence, higher LVEF and tissue Doppler imaging s', and smaller left atrial volume index in unadjusted analysis. Only associations with LVEF, tissue Doppler imaging s', and left atrial volume index persisted after accounting for age, sex, and race (online supplementary *Table S5*).

In this analysis of HFpEF patients enrolled in TOPCAT in the Americas, obstructive lung disease was independently associated with a heightened risk of the primary composite outcome, HF hospitalization alone, and all-cause hospitalization. Despite this, pulmonary disease was associated with higher LVEF and smaller left atrial volume index, without differences in right ventricular function or pulmonary pressure, suggesting an important role for extracardiac factors in mediating the observed increase in risk. In an exploratory *post hoc* analysis, obstructive lung disease modified the relationship of randomized treatment with all-cause and CV mortality, but not with the TOPCAT primary endpoint.

Similar findings were observed in the I-PRESERVE trial, where COPD prevalence was an independent predictor of HF death or hospitalization.[8] Potential mechanisms linking COPD to increased risk of HF hospitalization in HFpEF include misdiagnosis of less severe COPD as a HF exacerbation due to overlapping signs and symptoms,[1] or to lower cardiopulmonary reserve in patients with combined HFpEF and obstructive pulmonary disease leading to a lower threshold for HF or respiratory decompensation resulting in an increased likelihood of hospitalization.

One possible explanation for the finding of effect modification of baseline pulmonary disease on treatment effect for CV and all-cause mortality is chance, given the *post hoc* nature of this analysis. However, pulmonary

Table 1 Clinical outcomes in patients without (*n* = 1349) and with (*n* = 416) concomitant pulmonary disease, and the effect of randomized treatment allocation (spironolactone vs. placebo), at a median follow-up of 2.4 (25th–75th percentile: 1.4–3.9) years

Outcomes	Risk associated with PD			Effect of randomized treatment allocation			
	Events	HR (95% CI)	Adj. HR (95% CI)[b]	Spironolactone Events	Placebo Events	HR (95% CI) (reference: placebo)	*P*-value for interaction
Primary composite outcome							
Without PD	376 (28%)	Ref.	Ref.	178 (27%)	198 (29%)	0.87 (0.72–1.08)	0.11
With PD	146 (35%)	1.37 (1.13–1.66); *P* = 0.001	1.31 (1.07–1.59); *P* = 0.001	64 (29%)	82 (41%)	0.65 (0.47–0.91)	
All-cause mortality							
Without PD	281 (21%)	Ref.	Ref.	136 (20%)	145 (21%)	0.95 (0.75–1.20)	0.02
With PD	104 (25%)	1.27 (1.01–1.59); *P* = 0.04	1.26 (1.00–1.59); *P* = 0.05	42 (19%)	62 (31%)	0.57 (0.38–0.84)	
CV mortality							
Without PD	161 (12%)	Ref.	Ref.	76 (11%)	85 (12%)	0.92 (0.67–1.25)	0.01
With PD	62 (15%)	1.30 (0.97–1.73); *P* = 0.08	1.26 (0.93–1.70); *P* = 0.13	20 (9%)	42 (21%)	0.39 (0.23–0.67)	
Non-CV mortality[a]							
Without PD	88 (6%)	Ref.	Ref.	48 (7%)	40 (6%)	1.23 (0.81–1.87)	0.61
With PD	35 (8%)	1.35 (0.91–1.99); *P* = 0.14	1.39 (0.93–2.01); *P* = 0.10	19 (9%)	16 (8%)	1.03 (0.53–2.00)	
All-cause hospitalization							
Without PD	775 (57%)	Ref.	Ref.	382 (57%)	393 (58%)	0.98 (0.85–1.13)	0.06
With PD	284 (68%)	1.38 (1.21–1.59); *P* < 0.001	1.32 (1.15–1.52); *P* < 0.001	142 (66%)	142 (72%)	0.76 (0.60–0.96)	
HF hospitalization							
Without PD	285 (21%)	Ref.	Ref.	128 (19%)	157 (23%)	0.81 (0.64–1.02)	0.96
With PD	115 (28%)	1.42 (1.14–1.76); *P* = 0.001	1.39 (1.11–1.73); *P* = 0.003	56 (26%)	59 (30%)	0.80 (0.55–1.15)	

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PD, pulmonary disease.
Aborted cardiac arrest was not individually considered because of six events only. When New York Heart Association class was added to this model, only the association of PD with HF hospitalization (HR 1.28, 95% CI 1.03–1.60; *P* = 0.03) and all-cause hospitalization (HR 1.28, 95% CI 1.11–1.47; *P* < 0.01) persisted. Randomization among patients without PD (668 spironolactone; 681 placebo) and with PD (218 spironolactone; 198 placebo).
[a]Unequivocal and documented non-CV primary cause of death; unknown causes were not considered.
[b]Adjusted for age, female gender, white race, treatment group, previous HF hospitalization strata, current smoking, percutaneous coronary intervention, use of beta-blockers, body mass index, and heart rate on electrocardiogram.

gas diffusion is reduced in HFpEF[9] and is abnormal in the majority with coexistent COPD and HFpEF.[10] This is possibly due to processes mediated by aldosterone and modifiable with mineralocorticoid receptor antagonists, including COPD-associated reduction in alveolar surface area and HF-associated proliferation of alveolar type II cells, thickening of the alveolar–capillary interstitium, and lung fibrosis. In HF with reduced ejection fraction, spironolactone improves lung diffusion capacity, potentially via aldosterone receptor inhibition on alveolar epithelium and endothelium cells.[11] Further studies are necessary to determine whether such an effect exists in patients with both HFpEF and COPD.

Limitations of this analysis include ascertainment of pulmonary disease from medical history, and not confirmed by pulmonary function testing; potential misdiagnosis of COPD exacerbation as decompensated HF resulting in overestimation of CV events among patients with obstructive lung disease; and potential limited generalizability of our results from a clinical trial sample.

We conclude that pulmonary disease independently predicts HF and all-cause hospitalizations, but not mortality, in HFpEF. Pulmonary disease is not associated with prominent alterations in cardiac structure and function, suggesting an important role for extracardiac factors in mediating this risk.

Supplementary Information

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

Table S1. Baseline clinical characteristics in the study sample overall and stratified by the presence of pulmonary disease.

Table S2. Baseline clinical characteristics, stratified by the presence of pulmonary

disease and randomization treatment assignment.

Table S3. Impact of randomized treatment allocation (spironolactone vs. placebo) on outcomes in patients without pulmonary disease (668 on spironolactone and 681 on placebo) and with pulmonary disease (218 on spironolactone and 198 on placebo).

Table S4. Baseline clinical characteristics among TOPCAT Americas patients in the echocardiographic substudy stratified by the presence of pulmonary disease.

Table S5. Cardiac structure and function among TOPCAT Americas patients in the echocardiographic substudy, overall and stratified by the presence of pulmonary disease.

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Body fat phenotypes and treatment response to spironolactone in ambulatory patients with heart failure and preserved ejection fraction: a post-hoc analysis of the Aldo-DHF trial

Obesity and heart failure (HF) with preserved ejection fraction (HFpEF) often co-exist, are increasingly prevalent and with rising incidence.[1] Recent reports have suggested that the development of HFpEF is associated with a systemic proinflammatory state related to commonly coexisting conditions such as obesity, diabetes, hypertension, and the habit of smoking.[2]

In patients enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, those with abdominal obesity had higher event rates, including cardiovascular death.[3] In TOPCAT, spironolactone reduced the primary outcome of HF hospitalization or cardiovascular death in the reliable patient cohort from the 'Americas', who showed unquestioned HF signs and symptoms (and event rates compatible with HFpEF) as well as detectable serum levels of spironolactone metabolites.[4,5] In consequence, spironolactone received a class IIa indication for the treatment of HFpEF in the updated American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines.[6] In TOPCAT, no treatment effect modification (i.e. 'interaction') was found between spironolactone and the obesity parameters, including body mass index (BMI) and waist circumference (WC), with regard to the study outcomes (P for interaction >0,1).[3] In a post-hoc analysis of the EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) trial that enrolled patients with HF and a reduced ejection fraction (HFrEF), eplerenone might have been more effective in patients with abdominal obesity.[7] The 'effect modification' by abdominal obesity could have been specific of HFrEF in comparison to HFpEF patients but needs further validation in different cohorts. To clarify these observations we studied the relationship