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

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Chronic obstructive pulmonary disease (COPD) is highly prevalent, and predictive of worse outcomes, in 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 LVEF.[4] We investigated the influence of milder obstructive lung disease - defined by the absence of use of steroids or supplemental O_2 - on cardiovascular outcomes among patients with HFpEF enrolled in the Treatment of Preserved Cardiac Function Heart Failure with and 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 cardiovascular morbidity and mortality in 3,445 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 1,767 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 report by the site investigator of any diagnosis of COPD or asthma at enrolment. Of 1,765 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, BMI, and heart rate. We further adjusted for NYHA class in separate models. Interaction between pulmonary disease and randomized treatment assignment (spironolactone versus 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 (Supplemental Table S1). At 2.4 years median follow-up, 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 1,059 (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). After adjustment for demographics and co-morbidities, associations persisted with the primary composite endpoint, HF hospitalization and all-cause hospitalization (Table).

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 with compare to those without pulmonary disease (Table). 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 MI and higher prevalence of beta-blocker use (Supplemental Table S2). Results remained unchanged in models adjusting for randomization strata, and further adjusting for prior MI and beta-blocker use (Supplemental Table S3).

Among 653 patients in the Echocardiographic Study, 159 (24%) had pulmonary disease (Supplemental Table S4). Pulmonary disease was associated with greater LV wall thickness and LV hypertrophy prevalence, higher LVEF and TDI s', and smaller LA volume index in unadjusted analysis. Only associations with LVEF, TDI s', and LA volume index persisted after accounting for age, sex, and race (Supplemental 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 LA volume index, without differences in RV 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 heighted 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 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 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 HFrEF, 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.

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Conflict of interest

Dr. Shah has received research support from Novartis and consulting fees from Philips Ultrasound and Bellerophon. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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

Outcomes		**Risk associated with pulmonary disease**			**Effect of randomized treatment allocation**			
		Events, n(%)	**HR (95%CI)**	**Adj. HR (95%CI)**[†]	**Spironolactone Events, n(%)**	**Placebo Events, n(%)**	**HR (95%CI)** (Reference: Placebo)	**p-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*	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 Hospitaliz-ation	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)	
Heart	Without PD	285 (21%)	Ref.	Ref.	128 (19%)	157 (23%)	0.81 (0.64-1.02)	0.96

Failure Hospitaliz-ation	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)

PD- pulmonary disease; Aborted cardiac arrest was not individually considered because of 6 events only. *Unequivocal and documented non-cardiovascular primary cause of death; unknown causes were not considered. †Adjusted for age, female gender, white race, treatment group, previous HF hospitalization strata, current smoking, percutaneous coronary intervention, use of betablockers, body mass index and ECG heart rate. When NYHA class was added to this model, only the association of pulmonary disease with HF hospitalization (HR1.28[1.03-1.60]; p=0.03) and all-cause hospitalization (HR 1.28[1.11-1.47]; p<0.01) persisted. Randomization among patients without pulmonary disease (668 spironolactone; 681 placebo) and with pulmonary disease (218 spironolactone; 198 placebo)

Supplementary Information

Additional tables supplementary to this article can be found online, in the Supporting Information section

Table S1: Baseline clinical characteristics in the study sample overall and stratified by the presence of pulmonary disease. Categorical data expressed as n(%) and continuous data expressed as mean±SD or median [25-75th percentile].

Table S2: Baseline clinical characteristics, stratified by the presence of pulmonary disease and randomization treatment assignment. Categorical data expressed as n(%) and continuous data expressed as mean±SD or median [25-75th percentile].

Table S3: Impact of randomized treatment allocation (spironolactone versus 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. Categorical data expressed as n(%) and continuous data expressed as mean±SD or median [25-75th percentile].

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