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Angiotensin Converting Enzyme Inhibition and Mortality in Pulmonary Hypertension Associated With Chronic Obstructive Pulmonary Disease (PH-COPD)

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ABSTRACT

In 567 PH-COPD patients from the PVRI GoDeep Meta-Registry, ACE inhibitor use was associated with improved survival only in severe PH (PVR > 5 WU), supporting prospective trials targeting this high-risk subgroup.

1 | Introduction

Pulmonary hypertension (PH) is characterized by increased right ventricular afterload and encompasses a heterogeneous group of associated diseases [1]. Chronic lung diseases are among the most prevalent causes of PH worldwide [1]. Whereas inhaled Treprostinil has recently been FDA-approved for PH associated with interstitial lung disease, no PH-targeting therapies are available for PH associated with chronic obstructive lung disease (PH-COPD) [2, 3].

Recently, Ozaltin et al. reported that angiotensin-converting enzyme inhibitor (ACEi) therapy was associated with reduced mortality in idiopathic pulmonary fibrosis (IPF), but not in COPD patients [4]. Beyond the direct role of ACE in chronic lung disease pathobiology, both experimental and clinical studies indicate that ACE contributes to pulmonary vascular remodeling and right ventricular dysfunction [5]. Notably, a key difference between the IPF and COPD cohorts analyzed by Ozaltin et al. is the prevalence of PH: whereas approximately 5% of IPF patients (7% in the treated group) had documented PH, only 22 of 3579 COPD patients (0.6%) were diagnosed with PH in that study [4].

Given the well-established involvement of the renin–angiotensin–aldosterone system in pulmonary vascular remodeling and endothelial dysfunction, it is plausible that the survival benefit observed in IPF was partly mediated via effects on the pulmonary

For a complete list of the PVRI GoDeep Consortium, see the Acknowledgments section.

vasculature and right heart function [5]. This raises the possibility that any analogous benefit in COPD may have been obscured by the very low prevalence of PH in the analyzed cohort.

Thus, we analyzed the association between ACEi therapy and survival in patients with invasively diagnosed PH-COPD in the PVRI GoDeep meta-registry.

2 | Methods

2.1 | Patient Selection

Patients invasively diagnosed with PH-COPD from the PVRI GoDeep meta-registry, originating from the PH centers in Giessen, Nashville, Heidelberg, Rochester, and Stanford, were retrospectively analyzed [6]. Diagnosis of PH-COPD was established at the participating PH expert centers according to the international guideline recommendations applicable at the time of diagnosis based on the comprehensive clinical assessment performed at each center. Further inclusion criteria were: (i) age ≥ 18 years and (ii) the availability of hemodynamic parameters, including mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), and systolic pulmonary arterial pressure (sPAP) assessed at the time of diagnosis. For survival analyses, survival time was defined as the time from diagnosis of PH for patients who were not treated with ACE inhibitors, and as the time from initiation of ACE inhibitor treatment for those who started treatment after PH diagnosis, to reduce immortal time bias. The PVRI GoDeep registry was approved by the University of Giessen Ethics Committee and the relevant local ethics committees (NCT05329714).

2.2 | Statistical Analysis

Data were analyzed in R version 4.5.2 using the packages survival (version 3.8-3), rms (version 8.1-0), and splines (version 4.5.2). Continuous variables were summarized as medians [Q1, Q3]. For individual variables (BMI, $FEV1_{\%predicted}$, FVC $_{\%predicted}$), missing data were imputed using the mice package version 3.16.0, utilizing information from center, diagnosis decade, sex, age at diagnosis, mPAP, and PVR. The plausibility of the imputed data distribution was verified using diagnostic plots. The Cox proportional hazard models were adjusted for age (modeled using a natural spline with two degrees of freedom), BMI, $FEV1\%_{predicted}$, FVC $\%_{predicted}$, PVR, pulmonary artery wedge pressure (PAWP), PH-targeting therapy (none, mono, dual, and triple or more), as well as strata for center, diagnosis decade, and sex. Center was additionally included as a clustering variable. In an additional analysis, the Cox proportional hazards models were further adjusted for the cardiovascular risk factors cardiac diseases, arterial hypertension, diabetes, and obesity. Sample size was determined by simulation-based power analysis of the prespecified 5-year Cox model using 1000 stratified resamples per candidate sample size with 80% power derived from a spline-smoothed power curve. Sensitivity analyses for unmeasured confounders were carried out using *E*-values, which quantify the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome in order to explain the observed effect estimate.

3 | Results

We identified a subgroup of 567 patients diagnosed with PH-COPD in the PVRI GoDeep meta-registry and evaluated the association between ACEi and all-cause mortality. Median age was 66 [59, 72] years, 244 (43%) were female, and 97 (17%) received ACEi. As expected, FEV1/FVC ratio (47 [34, 60] %), $FEV1_{predicted}$ (45 [29, 62]%), mPAP (32 [26, 40] mmHg), cardiac output (4.7 [4.0, 5.8] L/min), PAWP (10 [7, 12] mmHg), PVR (4.7 [3.3, 6.7] WU), and WHO functional class (258 [66%] and 77 [20%] in WHO FC III and IV, respectively) corresponded to a COPD population with relevant PH.

While in non-severe PH-COPD patients (i.e., PVR ≤ 5 WU) no significant association between ACEi and survival was observed, a beneficial association of ACEi and survival was noted in PH-COPD with PVR > 5 WU (1-, 3-, 5-year survival: 97%, 82%, and 75% vs. 83%, 54%, and 34%, log-rank $p = 0.002$, Figure 1). Patients receiving ACE inhibitor therapy were more frequently PH-targeted therapy naïve compared with those not receiving ACE inhibitors (51% vs. 64%, χ^2 $p = 0.112$). The findings remained robust in Cox-regression analyses adjusting for $FEV1_{\%predicted}$, $FVC_{\%predicted}$, and PH-targeting treatment, as well as after further adjustment for cardiovascular comorbidities (HR 0.453 [0.429, 0.479], $p < 0.001$, Figure 1).

E-value analysis yielded an *E*-value of 2.88, suggesting that substantial unmeasured confounding would be required to fully account for the observed association between ACE inhibitor therapy and outcome.

Based on these findings, a prospective study designed to assess the effect of ACEi on mortality in COPD patients with severe PH (PVR > 5 WU) over 5 years would require approximately 312 patients with 80% power at a two-sided α of 0.05 based on the Wald *z*-test *p* value.

4 | Discussion

In this study, the association of ACEi therapy with survival in PH-COPD patients enrolled in the international PVRI GoDeep meta-registry was investigated. We observed that ACEi use was not significantly associated with improved survival in patients with non-severe PH, whereas a significant survival benefit was seen in those with severe PH (i.e., PVR > 5 WU). This association remained robust after adjustment for lung function, PH-targeted therapy, and cardiovascular comorbidities.

These findings suggest that the impact of ACE inhibition in COPD might be confined to patients with severe pulmonary vascular disease, highlighting PH severity as a key modifier of treatment effect. Stratifying patients by PH severity is therefore crucial when evaluating ACEi therapy in COPD populations and may partly explain observed differences in the impact of

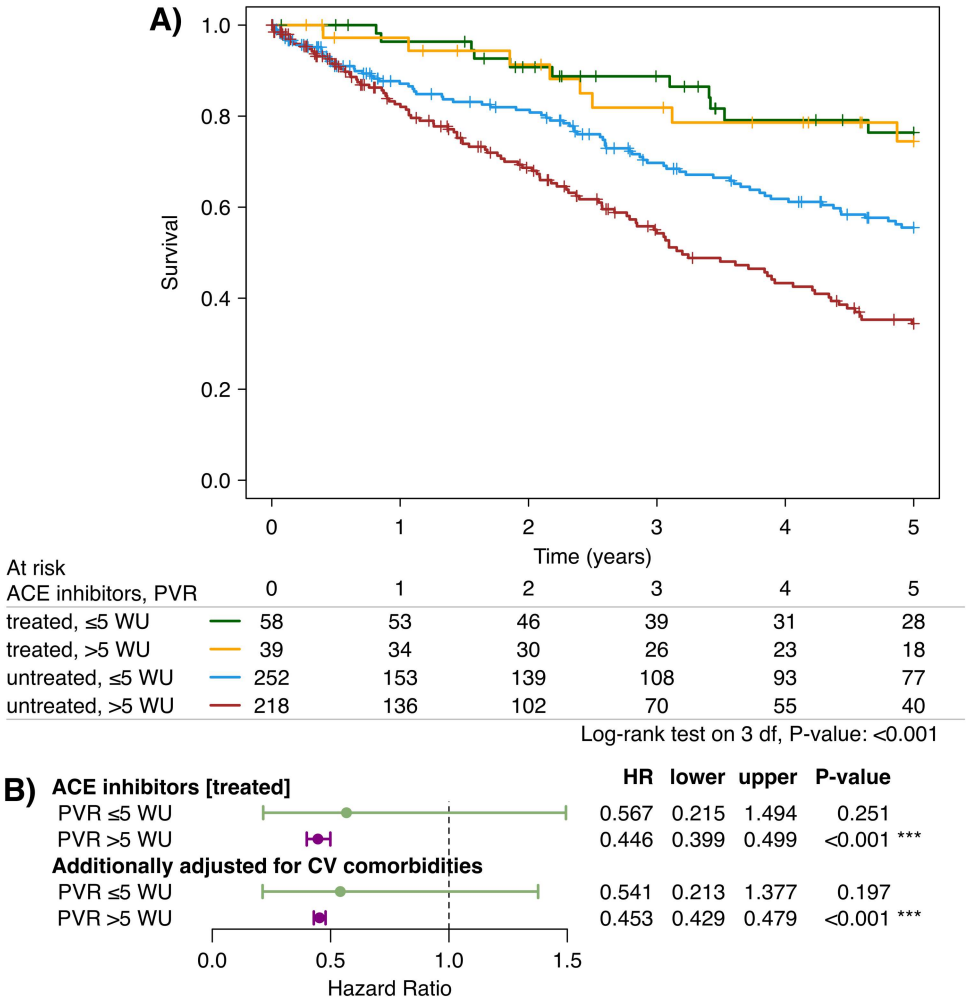

FIGURE 1 | Survival and hazard ratios by ACEi and PVR. (A) Kaplan–Meier survival curves. (B) Hazard ratios comparing patients treated with ACEi versus those not treated with ACEi, for the interaction analysis between PVR (≤ 5 vs. > 5 WU) and ACEi. The Cox proportional hazard models were adjusted for BMI, $FEV1_{\%predicted}$, $FVC_{\%predicted}$, PVR, PAWP, PH-targeting therapy (none, mono, dual, and triple or more), as well as strata for center, diagnosis decade, and sex. Center was additionally included as a clustering variable. Additionally, in a second analysis, the Cox proportional hazards models were further adjusted for cardiovascular risk factors/diseases (cardiac diseases, arterial hypertension, diabetes, and obesity). BMI = body mass index, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HR = hazard ratio, lower/upper = lower and upper limits of the 95% confidence interval of the HR, PAWP = pulmonary artery wedge pressure, PVR = pulmonary vascular resistance, WU = wood units.

ACEi therapy between IPF and COPD patients by Ozaltin et al [4]. Given that PH-targeted therapy has previously been associated with improved survival in PH-COPD, the lower prevalence of such treatment in the ACE inhibitor group would be expected to bias results toward the null, thereby supporting the robustness of the observed association between ACE inhibitor therapy and improved outcomes [7]. Moreover, although residual confounding cannot be fully excluded, sensitivity analyses including adjustment for comorbidities as well as *E*-value analysis suggested that a relatively strong unmeasured confounder would be required to fully explain the observed association.

Based on our data, a prospective study designed to assess ACEi effects on mortality in severe PH-COPD would require approximately 312 patients for 5-year follow-up, assuming 80% power at a two-sided α of 0.05. These estimates can inform future trial design, emphasizing the need to focus on the high-risk severe PH-COPD subgroup.

Mechanistically, our results align with experimental and clinical evidence that the renin–angiotensin–aldosterone system contributes to pulmonary vascular remodeling, endothelial dysfunction, and right ventricular maladaptation [8, 9]. Taken together, our findings provide a strong rationale for prospective trials evaluating ACE inhibition as a targeted intervention in severe PH-COPD patients.

Author Contributions

A.Y., M.F., K.W., J.S.A., E.B., C.A.E., E.G., H.R.C., R.F., A.J.S., R.T.Z., F.G, J.W., H.-A.G., K.T., and W.S. collected the epidemiological and clinical data and contributed to the interpretation. A.Y., M.F., K.W., and J.W. processed the statistical data. A.Y. and W.S. drafted the manuscript. All authors revised the final manuscript.

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Ethics Statement

The University of Giessen/University Hospital Ethics Committee and the responsible local ethics committees have approved the PVRI-GoDeep central data repository, listed under ClinTrial.gov (NCT05329714).

Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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