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Reply to Althuwaybi *et al.*

From the Authors:

Althuwaybi and colleagues propose an interesting hypothesis to explain the potential mechanism for increased risk of mortality following hospitalization for coronavirus disease (COVID-19) in patients with interstitial lung diseases (ILDs) (1). Unfortunately, in our study these data were not collected, and therefore, we cannot not make comparisons with the control population. Gastroesophageal reflux is strongly linked to hiatus hernia, which is twice as prevalent in patients with idiopathic pulmonary fibrosis (IPF) as the general population (2, 3). It is therefore plausible that proton pump inhibitors (PPIs) may have been prescribed in excess in patients with ILD.

However, the cited evidence for a putative role of PPIs in pathophysiology is inconclusive and likely does not overcome the residual effect of significant comorbidities in our cohort. In an unpowered pilot randomized controlled trial into the effect of omeprazole therapy on cough in IPF, Dutta and colleagues reported safety events including three respiratory tract infections in the placebo group compared with six using omeprazole, which could be explained by chance (4). In a large population-based study of patients with IPF in a real-world clinical practice setting, PPI use was not associated with a difference in survival or the incidence of respiratory-related hospitalization compared with those not using PPIs (5). Althuwaybi and colleagues describe a dose response of PPIs with risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reported in a large North American survey, as well as a retrospective health insurance database study in Korea that observed an association of PPI use with COVID-19 severity (6, 7). In contrast, the same Korean study found no association of PPIs with risk of infection; further study and meta-analyses will be required to build certainty on an effect. Lee and colleagues did observe a significant association between PPI use and severe outcomes in an adjusted model, particularly for a subgroup with $<$30 days of PPI records (7). Although the study included 132,316 individuals, a more limited 267 were currently using PPIs and were positive for SARS-CoV-2. A 79% greater risk of severe intervention was observed from 24/267 people with current PPI use (18/175 with $<$30 d of records), in comparison with 14/267 propensity-matched controls. The propensity-matched group had fewer significant comorbidities, and analyses did not adjust for lung function or body mass index, which we identify as important predictors of hospitalization outcomes. PPI use was not available for the individuals included in the study by Drake and colleagues, although the cited studies suggested little effect in past users or those with $>$30 days of treatment. It is likely that disease status, enhanced respiratory support, and significant comorbidities had a more substantial impact than PPI on outcomes in our cohort.

Furthermore, the role of PPIs in IPF pathogenesis remains uncertain. *Post hoc* analysis from international trials in IPF reported that pulmonary infections were higher in patients with advanced IPF (i.e., FVC $<$70%) who were receiving antacids compared with those not treated with antacids (8). However, PPIs have pleiotropic activity including antiinflammatory and antiproliferative effects (9). It is also worth noting, however, that although hiatus hernia has been independently linked to mortality in patients with IPF (2) and almost 5,000 participants in the AGES-Reykjavic birth cohort (3), in these uncontrolled studies, no association was found between PPI prescription and outcomes. The potential of antacid drugs to contribute to viral infections including COVID-19 has been the subject of some discussion (10). Thus, until further data are available, the potential adverse or favorable effects of PPIs in ILDs during the current pandemic remain to be determined, but understanding the balance of benefits and potential harms from antacids is imperative.

There are also a number of other potential mechanistic explanations why patients with ILD may have had poor outcomes

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following COVID-19, including an increase in SARS-CoV-2 entry genes, such as ACE2 (angiotensin-converting enzyme 2), as well as baseline alterations in IL-6 and type 1 IFN response genes in cells from patients with ILD (11). Furthermore, patients with ILD, but especially IPF, have high levels of the αvβ6 integrin in their alveolar epithelium, which increases mortality in response to a host of viral and bacterial pathogens in animal models (12), is associated with a worse prognosis in patients with IPF (13), and contains a binding site for SARS-CoV-2 virus (14). Finally, SARS-CoV-2 is known to act on the systemic and pulmonary vasculature and patients with IPF are at higher risk of cardiovascular disease and pulmonary thromboembolism (15–17).

Therefore, although at the current time it is not possible to determine whether host or iatrogenic factors are responsible for our observation, this is clearly an area in need of further investigation. We would like to reassure Althuwaybi and colleagues that the audit has been expanded and future waves now record gastroesophageal reflux disease to support such lines of investigation; however, the current evidence for a role of PPIs in the severity of COVID-19 hospitalizations in ILD is insufficient. ■

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Pulmonary Vascular Resistance in Pulmonary Arterial Hypertension: La Pièce de Résistance?

To the Editor:

We read the recent manuscript by Badagliacca and colleagues with great interest (1). In this Italian multicenter retrospective cohort of 181 treatment-naive patients with pulmonary arterial hypertension (PAH), they evaluated the relationship between change in pulmonary vascular resistance (PVR) following initiation of dual oral combination therapy and two widely used approaches for multidimensional risk assessment (2, 3). Failure to achieve treatment goal (i.e., a low-risk profile using the French method or a REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management] 2.0 score <7) was related to smaller reductions or increases in PVR with initial therapy across baseline risk groups. They developed a weighted score using baseline variables to predict an inadequate PVR reduction with initial dual oral combination therapy. This score consisted of male sex, age ≥ 60, and two interaction terms of *1*) mean pulmonary arterial pressure ≥ 48 mm Hg with cardiac index <2.5 L/min/m^2 and *2*) echocardiographic right ventricular area/left ventricular area >1 with a tricuspid annular plane systolic excursion <18 mm.

This study provides new support for the clinical relevance of medication-induced changes in PVR. We recently advocated for the use of risk profiles as clinical trial endpoints (4). The change in PVR and/or a PVR prediction score could very well be integrated into such multidimensional endpoints if their findings are replicated. As they did not analyze survival or whether the weighted PVR prediction score added predictive value to multidimensional risk scores for anticipating clinical outcomes, further validation of their findings in a larger cohort is necessary. However, this study complements our recent work demonstrating that the relative change in PVR from baseline and absolute value of PVR obtained at first follow-up right-heart catheterization were important predictors of long-term survival in large cohorts with idiopathic, heritable, and drug-induced PAH (5) and systemic sclerosis–associated PAH (6). We wished to underscore the importance of considering relative PVR changes together with objective measures of right ventricular function, as some patients may still significantly improve PVR but with deteriorating right ventricular function, which portends a poor prognosis (7).

We have three main comments. First, given the variables in their weighted PVR prediction score, we are curious why the authors chose to add their score to REVAL 2.0, as there are inherent redundancies of variables in their prediction model (age >60 and male sex) within the REVEAL 2.0 score (3). Although they show incremental improvement in the performance of their models, we wondered if there is significant multicollinearity between these variables. If so, it could have resulted in overfitting and make their models less generalizable outside this relatively small cohort.

Second, we wished to commend the authors on demonstrating for the first time the important sex differences in risk scores achieved after initial treatment. Male patients were less likely to improve to low risk and more likely to be in intermediate risk at follow-up, which is possibly explained by the greater improvements in right ventricular function observed in females. Given worse outcomes in males with PAH, dual combination therapy may be inadequate for many men, and a sex-specific strategy may be warranted. However, more between-sex comparisons in Table E4 regarding age, etiology, smoking prevalence, spirometry, and diffusion capacity would be important, as these risk factors for atypical PAH, or the so-called pulmonary vascular phenotype in smoking-related lung disease (8), could have partially explained the inferior responses in men.

Lastly, Badagliacca and colleagues highlight the near certainty of treatment failure with dual oral combination therapy in high-risk patients, as none improved to low risk in their study (1). This reinforces the notion of initial triple combination therapy, including a parenteral prostacyclin for high-risk patients, consistent with previous observational studies (9, 10) and the treatment algorithm proposed in the sixth World Symposium on Pulmonary Hypertension (11). ■

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