continued inhalation, and subgroup analysis revealed an evident benefit in patients with any idiopathic interstitial pneumonias and connective tissue disease–associated PH-ILD but not combined pulmonary fibrosis and emphysema nor idiopathic pulmonary fibrosis alone; thus, targeting the optimal candidates is particularly important for delaying disease progression and improving prognosis (3). In addition, the high proportion of adverse reactions is a problem that cannot be ignored in the INCREASE trial, as adverse events frequently occurred among 93.3% of patients receiving inhaled treprostinil, and serious ones accounted for 23.3%, and 16 of 40 (40%) patients discontinued the assigned treprostinil prematurely owing to an adverse event (1). Therefore, it was conceivable that more patients might abandon continued inhalation in case of clinical worsening.

Post hoc analysis is inherently more prone to selection bias, and the current study had only a 16-week observation period, warranting further prospective multicenter randomized controlled studies with longer duration to evaluate the effect of continued treatment with inhaled treprostinil in patients with PH-ILD, especially those with a specific subtype. ■

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Reply to Jin *et al.*

From the Authors:

We thank the authors of the letter for their comments. Pulmonary veno-occlusive disease (PVOD) or PVOD-like areas have not only been reported in scleroderma but also in other forms of fibrotic lung disease, including idiopathic pulmonary fibrosis (1). We did not specifically look for PVOD or try to parse out patients who might have PVOD-like lesions in the context of this study. Indeed, this is a difficult diagnosis to confirm without a lung biopsy, which was not mandated in this study. Therefore, we cannot rule out that those who failed to respond to therapy or had clinical worsening on therapy might have had a component of PVOD. However, the fact that our study was positive, including in the subgroup of patients with connective tissue disease-related interstitial lung disease (ILD), suggests that the existence of any PVOD or PVOD-like lesions are of limited concern when starting patients on inhaled treprostinil (2, 3). We suspect that episodes of worsening seen in the context of the study were related to the severe underlying lung disease rather than necessarily being attributable to any PVOD.

Regarding targeted agents or other interventions that may have been used, the INCREASE clinical trial protocol did not allow patients to initiate antifibrotic medications or U.S. Food and Drug Administration-approved therapies for pulmonary arterial hypertension during the course of the 16-week study (2). Consequently, it is reasonable to conclude that the benefits in disease progression observed in the treatment arm are most likely attributable to inhaled treprostinil.

The authors state that additional studies of longer duration and specific subtypes should be undertaken. The INCREASE study is the largest study to date in group 3 pulmonary hypertension and was unequivocally positive, including the secondary endpoints, with no suggestion of harm in any subgroup. We, therefore, posit that doing longer studies of inhaled treprostinil is idealistic and not pragmatic. Furthermore, patients with a very poor prognosis are difficult to recruit and retain in long-duration clinical trials. Indeed, the enemy of good is better, or in this case, longer. Nonetheless, it is hoped that further supportive information might be gleaned from the open-label extension of the INCREASE study.

The authors highlight that some subgroups might not benefit from therapy, but therein lies the purpose of casting a broad net and including different forms of ILD since each group by itself might be too small to definitively demonstrate benefit. We should certainly not deny these patients with a morbid condition and few treatment options a viable, proven therapy based on theoretical concerns that they might not be of the right phenotype.

The authors accurately cite the incidence of adverse events of 93.3% in the active treatment arm of the INCREASE study

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but neglect to contextualize this against a very sick population with comorbidities and on concomitant medications, as evidenced by adverse events in 91.4% of the placebo patients. Similarly, as the authors point out, serious adverse events were reported in 23.3% of the active treatment arm, but once again, the 25.8% incidence of serious adverse events in the placebo arm is omitted. True, there was no survival benefit over 16 weeks, with 12 deaths in the placebo arm versus 10 in the treatment arm; but notably, all of the deaths in the placebo group occurred after a clinical-worsening event, which underscores the need to persist with therapy even in the face of disease progression. This surely then answers the author's question of "to continue or not to continue." ■

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High Renin Concentrations in Severe COVID-19 Are Indicative for a Hypo–Renin–Angiotensin-System State

To the Editor:

With great interest, we read the paper by Leisman and colleagues on injury marker dynamics in severe coronavirus disease (COVID-19) (1). These authors propose that endothelial injury markers rise later and associate with renin–angiotensin system (RAS) activation and 28-day outcome. The RAS activation consisted of rises in renin, the (pro)renin receptor, and ACE2 (angiotensin-converting enzyme 2). Given that these observations were made by Olink plasma proteomic assays, they indicate the soluble variants of both the (pro)renin receptor [s(P)RR] and ACE2 (sACE2). Leisman and colleagues speculate that the renin rise reflects the response to either a relative hypo-RAS state or prolonged sedation-induced vasodilatation or hypovolemia after diuresis in these patients.

We recently made the same observation with regard to renin and sACE2 in severe COVID-19, and by simultaneously measuring aldosterone, we were able to show that the aldosterone concentrations were actually lower in such patients (2). As a consequence, the aldosterone-to-renin ratio was remarkably decreased, and as such, this biomarker was correlated most strongly with COVID-19 severity. A decreased aldosterone-to-renin ratio is a well-known consequence of RAS blockade (e.g., by ACE inhibitors).

A unifying concept is that severe COVID-19 not only results in endothelial damage but simultaneously lowers the endothelial enzyme ACE (sometimes described as ACE1), responsible for angiotensin II generation. Given its endothelial origin, it seems logical that ACE concentrations might fall in severe COVID-19. Indeed, several recent studies also found low ACE concentrations in the plasma of patients with severe COVID-19 (3–5). In this respect, it may not be surprising that acute respiratory distress syndrome is associated with reduced pulmonary ACE activity (6).

ACE2 is one of many angiotensin II–degrading enzymes. Leisman and colleagues suggested that the upregulated sACE2 might have contributed to the rapid degradation of angiotensin II, thus creating a hypo-RAS state. However, if this mechanism is true, high sACE2 concentrations should correlate positively with high renin concentrations. We were unable to find such a correlation (2). Thus, we hypothesize that the most likely explanation for the rise in renin is a hypo-RAS state due to dropped ACE concentrations related to endothelial damage. This implies that even patients with severe COVID-19 who do not receive treatment with RAS blockers are in a state of relative RAS blockade. Finally, despite its name, the s(P)RR is unrelated to RAS activity, and thus its rise in COVID-19 warrants further research into its role in this disease.

In conclusion, we fully agree with Leisman and colleagues that renin's utility as a marker of severe COVID-19 should be further explored. We suggest exploring the aldosterone-to-renin ratio in future studies as this might be an even stronger marker. ■

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