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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Reply to Akin *et al.*

From the Authors:

We thank Akin and colleagues for their comments on our paper (1). We agree fully that attenuated signaling through the classical axis of the renin–angiotensin system (RAS) best explains the RAS abnormalities observed in severe coronavirus disease (COVID-19). We hold this view for reasons we elaborate on in our paper's discussion. Nevertheless, whereas reduced signaling may be the simplest and most reasonable explanation of the pattern of RAS biomarkers observed in COVID-19, it is important to acknowledge the limitations of these observations.

Akin and colleagues state that inappropriately low plasma aldosterone with elevated plasma renin implicates ACE-1 (angiotensin-converting enzyme-1) dysfunction arising from endothelial injury. This interpretation represents one possibility and is supported by the elevations in angiotensin-I/angiotensin-II ratios that are reported in patients with distributive shock (2). In COVID-19 specifically, a small pilot study found that angiotensin-II vasopressor therapy was associated with robust hemodynamic responses and improvement in multiple physiologic indices versus controls (3). However, other abnormalities may be present, for example, angiotensin-II type-1 receptor availability and signaling decrease in sepsis (4). Multiple, even redundant, impairments within a single system represent a common element in critical illness. Such broad dysfunction likely contributes to the limited historical success of novel therapeutics in critical care trials, where the test agents often only target a small subset of pathways. Therefore, we hesitate to attribute RAS abnormalities in COVID-19 acute respiratory distress syndrome (ARDS) to any singular injury or aberrant process.

The abnormalities in renin/aldosterone ratios in COVID-19 discussed by Akin and colleagues are compelling and align with observations in sepsis and vasoplegia after cardiac surgery (5, 6). Although these findings could suggest an attenuated RAS, we note they are not conclusive evidence and must consider that other mechanisms could contribute to them. For example, heparin suppresses aldosterone synthesis and is commonly administered in these patient populations.

We agree with the authors that renin/aldosterone ratio may be useful and "stronger" than renin alone as a biomarker. Potential limitations of this assay, particularly in a point-of-care setting, include weighing the degree of increased performance against the cost, feasibility, and interpretability of a single analyte versus two, particularly given that renin alone has shown strong performance in identifying hypoperfusion, predicting response to angiotensin-II therapy, and prognosing outcome in shock (7, 8).

More importantly, we stress that the key biologic implication of our study remains that in COVID-19 critical illness, disease processes are likely dynamic. As early as 1982, Nikuwa and colleagues showed in the *Journal* that canine experimental inflammatory lung injury induces ACE-1 shedding from the pulmonary endothelium (9). This shedding transiently increased both systemic and alveolar ACE-1 activity before the plasma ACE-1 activity subsequently fell to below baseline concentrations. Notably, in our cohort, we did not see renin elevations until Day 3 (1), and others have reported angiotensin-II decreases over time in COVID-19 ARDS (10). Although at Day 0, we found no correlation between renin and ACE-2 ($R_{adj} = 0.01$; $P = 0.95$), a correlation emerged by Day 3 ($R_{adj} = 0.26$; $P = 0.0045$ at Day 3) and strengthened over time ($R_{adj} = 0.47$; $P < 0.0001$ at Day 7). Therefore, both RAS states may occur, but at different times in the course of the disease, with initial pulmonary RAS excess exacerbating inflammatory injury before progressing to a systemic RAS deficiency impairing cardiorenovascular function. More studies are needed to understand the RAS in COVID-19 and ARDS, its evolution as disease progresses, and how this system can best be leveraged to clinical advantage. ■

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