Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19

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Angiotensin-converting enzyme 2 (ACE2) has emerged as the negative regulator of the renin–angiotensin system (RAS) and was more recently identified as the SARS-CoV-2 receptor responsible for the current COVID-19 pandemic. The high burden of illness and high case fatality rate in patients with COVID-19 is driven in part by the high affinity of SARS-CoV-2 for ACE2, leading to viral entry and multisystem illness with pulmonary, gut, renal, central nervous system, and cardiovascular manifestations. The novel dual role of ACE2 in human ACE2 in pre-clinical models and patients with pulmonary arterial hypertension and acute lung injury led to a prompt increase in the Ang 1-7/Ang II ratio, reflecting ACE2 action. During this unprecedented time of a rapidly expanding global epidemic, both the lay and medical communities are struggling to find relevant information concerning medical therapies to mitigate the impact of COVID-19. With the current paucity of data, associations which generally would be insufficient to guide medical therapy are given more weight than would be anticipated under more usual circumstances. The coronavirus SARS-CoV-2 and COVID-19 interface with the RAS and ACE2 to a great deal of speculation regarding the role of pharmacological inhibitors of the RAS and COVID-19 infection. Pharmacological antagonists of the RAS, such as ACE inhibitors and ARBs, protect the cardiovascular system partly by increasing ACE2 levels with a concomitant increase in myocardial inflammation and fibrosis.

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underlying cardiovascular disease. Indeed there are already many opinion-based reports and society recommendations regarding maintaining or discontinuing these cardiovascular therapies in patients faced with COVID-19.

In this issue of the European Heart Journal, Sama et al. utilized existing cooperative Biobank samples to measure ACE2 concentrations in 1485 men and 537 women with heart failure (index cohort) and repeated this analysis in a validation cohort consisting of 1123 men and 575 women.9 Using a high-throughput multiplex immunoassay, relative ACE2 levels were determined and correlated with demographic and clinical variables and the use of RAS inhibitors. In the index cohort, patients with higher concentrations of ACE2 were more often men, had atrial fibrillation, higher heart rate, and lower systolic blood pressure, which was largely confirmed in the validation cohort. These results are consistent with previous studies showing elevated ACE2 levels and activity in various cohorts of patients with cardiovascular disease including patients with heart failure.10–13 In heart failure, elevated plasma ACE2 activity is associated with worsened prognosis and is higher in the acute setting compared with ambulatory heart failure patients.10,11 In the current study, male sex was the strongest predictor of elevated plasma ACE2 concentrations in both cohorts,9 which complements previous studies showing that men displayed higher ACE2 levels, and is consistent with a worse prognosis in men with heart failure.12,13 Since Ace2 is an X-linked gene, this highlights an avenue of interest requiring further exploration with regards to sex-specific differences in the control of Ace2 expression and ACE2 processing and shedding into plasma.

In previous studies, the differing rates of ACE inhibitor/ARB use between groups and its impact on plasma ACE2 levels and activity were not addressed. Importantly, the authors examined the impact of RAS inhibitors and the impact on plasma ACE2 levels.9 In the validation cohort, ACE inhibitor and ARB use were independent

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/41/19/1818/5834646)
up-regulates ADAM-17 activity by interacting with AT1 receptors, additional ACE2 results in excessive Ang II action. Ang II further feedback pathway during SARS-CoV-2 infection since loss of function SARS-CoV-2 increases ADAM-17 activity, leading to further proteolytic cleavage of membrane-bound ACE2, and represents a positive feedback pathway during SARS-CoV-2 infection since loss of functional ACE2 results in excessive Ang II action. Ang II further up-regulates ADAM-17 activity by interacting with AT1 receptors, leading to more shedding of ACE2 and thereby accelerating RAS-mediated injury including severe lung damage (Figure 1). When faced with the rapidly expanding COVID-19 pandemic and in the absence of definitive data, the results of Sama et al. obtained in heart failure patients in the pre-COVID-19 period offer supporting evidence to continue ACE inhibitors or ARBs in patients at risk for SARS-CoV-2 infection. However, this field is moving so rapidly that we now have two observational studies of ARB/ACE inhibitor use in hospitalized COVID-19 patients showing no augmented risk to heart failure patients in the pre-COVID-19 period offer supporting evidence to continue ACE inhibitors or ARBs in patients at risk for SARS-CoV-2 infection. However, this field is moving so rapidly that we now have two observational studies of ARB/ACE inhibitor use in hospitalized COVID-19 patients showing no augmented risk to COVID-19 patients and even suggesting a possible benefit. Moving ahead, measuring plasma angiotensin peptides and plasma ACE2 levels and activity in COVID-19 patients can provide a direct evaluation of the state of the RAS and guide therapeutic interventions as we await the results of ongoing randomized clinical trials (NCT04312009, NCT04311177, and NCT04335786). The speed at which these levels of evidence are forthcoming shows the commitment of the scientific and clinical communities to use the best available evidence to guide their therapeutic decisions while striving to obtain more definitive data.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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