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EDITORIAL

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

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This editorial refers to 'Circulating plasma concentrations of ACE2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors'†, by I.E. Sama *et al.*, on page 1810.

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.[1,2] 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 stystem, and cardiovascular manifestations.[3,4] The novel dual role of ACE2 in the RAS and as the SARS-CoV-2 receptor provides a fundamental connection between viral infection, immunity, and cardiovascular disease.[3–5] Direct clinical evidence came from SARS and the current COVID-19 pandemic, where there is down-regulation of tissue ACE2 through endocytosis and proteolytic processing which leads to a corresponding increase in plasma angiotensin II (Ang II) levels as seen in COVID-19 patients (linearly correlated with SARS-CoV-2 viral load), thus providing a direct link between the tissue and systemic RAS.[3–6] The SARS-CoV genome was detected in postmortem autopsy heart samples of patients who succumbed to SARS infection, suggesting prompt viral infiltration of myocardial tissue during infection.[5] These hearts had markedly decreased myocardial ACE2 expression levels with a concomitant increase in myocardial inflammation and fibrosis.

The RAS is an endogenous peptide system with key physiological and pathophysiological roles in cardiovascular disease, as illustrated by the success of its pharmacological blockers [including ACE inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs)] in mitigating cardiovascular disease progression.[7] Ang II (octapeptide) is produced through proteolytic cleavage of Ang I (decapeptide) by ACE which activates angiotensin type 1 receptors (AT_1Rs), thereby mediating downstream pathophysiological effects. The ACE2/Ang 1-7 counter-regulatory axis, by removing a single C-terminus, inactivates Ang II and forms Ang 1-7. This septapeptide acts upon the Mas receptor to initiate vasodilatory and anti-inflammatory effects mediated through beneficial signalling pathways (*Figure 1*).[3,4] ACE2 is widely expressed and, in the cardiovascular system, ACE2 is localized to cardiomyocytes, cardiac fibroblasts, pericytes, vascular endothelium, and vascular smooth cells.[3,4] Various diseases including heart failure, hypertension, and diabetes are characterized by a relative ACE2-deficient state, reducing the homeostatic protective mechanism.[3,4] Importantly, recombinant human ACE2 in pre-clinical models[8] 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.[3,4]

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 with ACE2 led 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 in disease states, thereby dampening the effects of an activated RAS.[3,4] The major conundrum is that these drugs which are used to treat cardiovascular disorders may facilitate COVID-19 infection, while, on the other hand, discontinuing their use will augment

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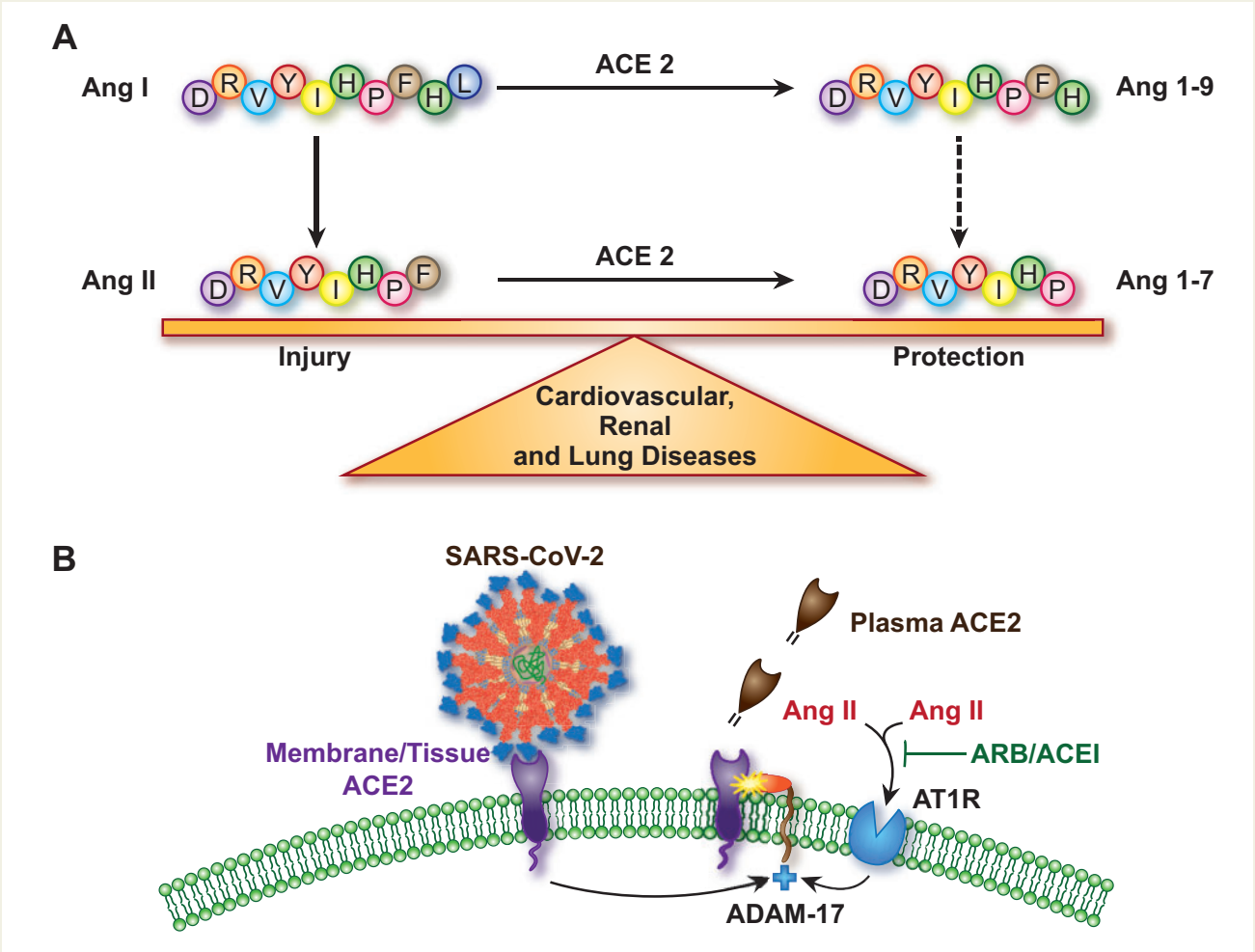

Figure 1 The role of ACE2 in controlling the renin–angiotensin system and the proteolytic shedding of membrane-bound ACE2 by ADAM-17. ACE2 converts Ang I and Ang II into Ang 1-9 and Ang 1-7, respectively, thereby negatively regulating the renin–angiotensin system (*A*). ACE2 serving as the receptor for the SARS-CoV-2 and activation of ADAM-17 by Ang II and SARS-CoV-2 binding leading to a loss of membrane-bound ACE2 attenuates a key homeostatic mechanism limiting Ang II effects in tissues, culminating in cardiovascular, renal, and lung diseases, key components of the heart failure syndrome (*B*). Higher plasma ACE2 levels were associated with male sex, history of atrial fibrillation, and coronary artery bypass graft, higher NYHA class, and heart rate; reduced ACE2 levels were associated with a history of chronic obstructive pulmonary diease, and higher left ventricular ejection fraction and systolic blood pressure (Sama *et al.*[9]). The dotted line indicates a putative role for ACE.

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

predictors of lower plasma ACE2, while use of an MRA was an independent predictor of higher plasma ACE2 concentrations. This differential impact of these RAS inhibitors on plasma ACE2 levels may reflect the differential control of ACE2 levels driven by the suppression of Ang II-mediated activation of ADAM-17 and reduction in ACE2 shedding by ARB/ACE inhibitors, in contrast to MRA acting at the transcriptional level leading to an increase in *Ace2* mRNA levels (and tissue ACE2 levels) and a secondary increase in plasma ACE2 levels.[4]

While Sama *et al.* did not report ACE2 levels in COVID-19 patients, their findings and those of others have important implications for the current COVID-19 pandemic. The underlying factor linking the multiple organ systems affected by the virus is the ubiquitous tissue expression of ACE2, the receptor mediating SARS-CoV-2 binding and entry into cells.[1,2] ACE2-mediated cellular entry of 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 AT_1 receptors, leading to more shedding of ACE2 and thereby accelerating RAS-mediated injury including severe lung damage (*Figure 1*).[4,10,11]

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 COVID-19 patients and even suggesting a possible benefit.[14,15] 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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