Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

pulmonary disease by increasing the number of binding sites available to the virus. Although that conclusion is persuasive at first glance, the data and recommendations presented in the accompanying article by Sanchis-Gomar et al[3] and the recent article by Vaduganathan et al[4] are more compelling. Further analysis of ACE2 mechanisms supports the hypothesis that ACEIs and ARBs are more likely to benefit than harm patients with COVID-19. Coronavirus disease 2019 binds the viral S protein to ACE2, reducing receptor expression, enabling viral and cell membrane fusion and viral replication, with the potential for inflammatory tissue damage, and the severe inflammatory response—a cytokine storm.

At infection onset, an initial inflammatory response is triggered with the production of angiotensin II, via renin-angiotensin-aldosterone system activation (nicely reviewed in the article). This inflammatory response is normally moderated by the activation of ACE2 receptors. Angiotensin-converting enzyme 2 is a key player in minimizing and reversing the inflammatory response by converting angiotensin II to angiotensin 1-7 (Ang 1-7), which, after binding to the Mas receptor, results in a wide array of anti-inflammatory actions.[5] The inflammatory state is a critical organismal response to an invader, but ultimately healing requires inflammation resolution, a process blocked by COVID-19's binding to the cellular membrane ACE2 and downregulating ACE2 expression in host cells, leading to unrelenting inflammation.

The proposal that increased numbers of ACE2 receptors, owing to ACEIs and ARBs, would signal an increase in viral binding and severe disease is unsupported by clinical data. The alternative view that the presence of more functional ACE2 receptors could facilitate inflammation resolution by increasing the production of anti-inflammatory Ang 1-7 is reasonable. More Ang 1-7 would promote and support healthy vascular, pulmonary, myocardial, and renal function and suppress inflammatory cytokine production. If ACEIs and ARBs increase functional ACE2 receptors, the activation of anti-inflammatory pathways may save lives.

Pending more research on this topic and lacking evidence of harm to patients with COVID-19 while taking ACEIs and ARBs, discontinuation of these medications is unjustified and could result in more negative outcomes.

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In reply—Angiotensin-Converting Enzyme 2 and the Resolution of Inflammation: In Support of Continuation of Prescribed Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

We thank Dr Gersh for her interest and comments on our article as well as for taking the time to express her concerns on this subject. We agree with Gersh that discontinuation of antihypertensive drugs angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the management of hypertension (HTN) is unjustified at this moment because of the lack of evidence for negative effects of these drugs in patients with coronavirus disease 2019 (COVID-19). However, in recent weeks, several important articles have been published, shedding new light in reference to the potential interplay of ACEIs and ARBs with COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, penetrates the cells primarily through angiotensin-converting enzyme 2 (ACE2), its natural receptor at the cell surface. Whether ACEI and ARB administration would increase ACE2 levels or expression remains mostly

speculative, as does whether increased ACE2 expression is beneficial or detrimental in COVID-19. As noted by Gersh, Diaz[1] argued that as ACE2 levels increase after the intravenous infusion of ACEIs and ARBs in animal models, taking ACEIs or ARBs may aggravate the infection severity in patients with COVID-19. However, not all studies conducted in animals clearly reported increased ACE2 levels in response to ACEI/ARB administration.[2] Importantly, investigations analyzing changes in plasma or tissue ACE2 levels in humans are limited. In fact, 2 studies[3,4] in patients with atrial fibrillation or coronary heart disease found no differences in plasma ACE2 levels between those taking ACEIs or ARBs and those not taking these medications. Nonetheless, plasma levels may not reflect tissue ACE2 expression, and vice versa, and this topic requires further investigation.

The role of ACE2 expression in COVID-19 morbidity and mortality is still unknown. As HTN is a clear risk factor for COVID-19,[5] Gersh noted that many such patients are likely to be taking ACEIs or ARBs and, as such, these antihypertensive medications may be directly connected with infection severity. However, although a relatively high percentage of patients with COVID-19 hospitalized have HTN, the prevalence of HTN in adults is similar worldwide, increasing with age. In patients with COVID-19, the odds of disease severity with HTN was found, in meta-regression, to be associated with advancing age.[5] As Marin[6] has also stated, an epidemiological association simply based on the prevalence of HTN and ACEIs/ARBs in COVID-19 is inappropriate. Moreover, it has been previously reported that ACE2 expression is reduced in HTN animal models and historically HTN has not affected outcomes of other coronavirus infections.[7] Most concerning is the fact that Marin[6] claimed that many patients from South America, Central America, and Spain have abruptly interrupted their treatments with ACEIs or ARBs over these hypothetical concerns, which may be as dangerous to patients as COVID-19 itself.

Mancia et al[8] conducted a case-control study involving 6272 patients with confirmed COVID-19 from the Lombardy region of Italy. They compared patients with COVID-19 with 30,759 controls matched by age, sex, and municipality of residence. Neither ACEIs nor ARBs were associated with an increased probability of being infected by SARS-CoV-2 in multivariate logistic regression analysis. Moreover, no association was observed between these drugs and SARS-CoV-2 infection severity. Reynolds et al[9] analyzed the data of 5894 patients with COVID-19 (tested positive) from the New York University Langone Health electronic health record, with 1002 with severe disease (intensive care unit admission, mechanical ventilation, or death). Through a Bayesian approach, no association between taking ACEIs or ARBs and positive test result or COVID-19 severity could be found.

In a retrospective single-center case series of 1178 patients with COVID-19 and HTN hospitalized at the Central Hospital of Wuhan, China (from January 15 through March 15, 2020), Li et al[10] studied the association between ACEIs/ARBs and severity of illness and mortality. There were no differences between the percentage of patients with HTN taking ACEIs/ARBs with severe and nonsevere infections (32.9% vs 30.7%; P=.645) or between nonsurvivors and survivors (27.3% vs 33.0%; P=.34).

In a retrospective multicenter study including 1128 adult Chinese patients with COVID-19 and HTN (188 taking ACEIs/ARBs and 940 not taking these agents), Zhang et al[11] reported that the unadjusted mortality rate was lower in the ACEI/ARB group than in the non-ACEI/ARB group (3.7% vs 9.8%; P=.01). After adjusting for age, sex, comorbidities, and in-hospital medications, the risk of all-cause mortality was still lower in the ACEI/ARB group than in the non-ACEI/ARB group (adjusted hazard ratio, 0.42; 95% CI, 0.19 to 0.92; P=.03). Their results also indicated a lower risk of COVID-19 mortality in patients who received ACEIs/ARBs than in those who did not (adjusted hazard ratio, 0.37; 95% CI, 0.15 to 0.89; P=.03) in a propensity score–matched analysis followed by adjusting imbalanced variables in mixed-effect Cox model. Moreover, compared with other antihypertensive drugs, ACEIs/ARBs were associated with lower mortality (adjusted hazard ratio, 0.30; 95% CI, 0.12 to 0.70; P=.01) in COVID-19. Therefore, what can be reasonably concluded from the recently published large single and multicenter studies from multiple countries is that there is no significant risk of disease severity or mortality associated with ACEIs/ARBs, with some even suggesting potential benefits in patients with COIVD-19.

The mechanism behind any potential benefit of ACEIs and ARBs in

COVID-19 is still enigmatic. Differences in inflammatory and immune biomarkers have been reported in patients with COVID-19 taking ACEIs and ARBs. Meng et al[12] found a reduced rate of severe COVID-19 and lower levels of interleukin-6, increased CD3 and CD8 T cells in peripheral blood, and decreased peak viral loads compared with those using other antihypertensive medications. Moreover, Yang et al[13] reported that patients with COVID-19 and HTN taking ACEI and ARBs had substantially lower C reactive protein and procalcitonin levels as well as a decreased rate of critical illness and death.

Angiotensin receptor blockers have also been found to be effective in treating patients with sepsis, pneumonia, and influenza. Moreover, a combination of statins and ARBs appeared to substantially reduce mortality during the recent Ebola outbreak.[14]

It has been suggested that higher doses of ARBs may protect patients with COVID-19 from acute lung injury (ALI) via 2 complementary mechanisms: (1) by blocking excessive angiotensin II binding, promoting vasoconstriction, inflammation, and oxidative damage, and (2) by upregulating ACE2 and increasing angiotensin 1-7 production.[15] This warrants immediate further investigation. We hypothesize that ACEIs may not only attenuate the increase in angiotensin II but, via reduced endothelial dysfunction and decreased expression of tissue plasminogen activator 1 and increase tissue plasminogen activator levels due to decreased bradykinin breakdown, mitigate the reported COVID-19–associated coagulopathy, which may drive ALI and multiple organ dysfunction.[16]

As the COVID-19 pandemic continues, the cardiovascular health of patients must not be neglected at the expense of the outbreak. Angiotensin-converting enzyme inhibitors and ARBs improve outcomes and increase survival in multiple cardiovascular diseases. Although further investigation in prospective studies is warranted, based on the preponderance of current data and evidence, it is highly unlikely that the use of ACEIs/ARBs may be associated with increased severity or mortality risk. In summary, the newly reported data support current guidelines and health professional recommendations for the continuation of ACEIs/ARBs for treating HTN during the COVID-19 pandemic.

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