ESC European Society of Cardiology
European Heart Journal (2020) **41**, 2067–2069
doi:10.1093/eurheartj/ehaa487

EDITORIAL

Renin–angiotensin system inhibitors in the COVID-19 pandemic: consequences of antihypertensive drugs

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Online publish-ahead-of-print 4 June 2020

This editorial refers to 'Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study'†, by C. Gao *et al.*, on page 2058.

Arterial hypertension is the leading cause of death in the world and very frequently is accompanied by other comorbidities such as diabetes, obesity, chronic kidney disease (CKD), and established cardiovascular disease of different types. Patients suffering from infection by SARS-CoV2 frequently present arterial hypertension and these accompanying comorbidities. Data recently published have shown that the presence of associated conditions such as cardiovascular disease, diabetes, and hypertension increases the risk of COVID-19 complications in 45.4% of adults in the USA (see: https://medicalxpress.com/news/2020-04-percent-adults-complications-covid-.html). Similar percentages probably exist in Europe and are facilitated by the elevated age of the population that is accompanied by the highest prevalence of hypertension, cardiovascular disease, diabetes, and CKD. Data from China indicate that the situation differs because the percentage of subjects with COVID-19 older than 65 years is only ∼15%.[1] However, the data contained in the article by Gao *et al.* in this issue of the *European Heart Journal* show that the mean age of deceased patients is 70.96 years.[2] The data of Gao *et al.* show that hypertensive patients demonstrate a two-fold relative increase in the risk of COVID-19 mortality, particularly if they do not receive antihypertensive treatment. Therefore, these data confirm that the risk of death in the COVID-19 pandemic is particularly increased in hypertensive patients especially when advanced age is present, facilitated by cardiovascular comorbidities.[2]

Another aspect of interest in hypertensive patients is the presence of CKD that is frequently accompanied by the same comorbidities mentioned above and as a consequence by an increase in morbidity and mortality.[3] Data on renal damage have not been reported frequently albeit acute kidney injury has been described in a small percentage of patients with severe consequences of SARS-CoV2 infection that was accompanied by a very high mortality.[4] Thus, renal protection has to be considered to minimize the fatality rate in severe COVID-19 patients and this includes an adequate control of blood pressure.

It is well established that patients with arterial hypertension, diabetes, established cardiovascular disease, obesity, and CKD need to be treated with renin–angiotensin–aldosterone system (RAAS) blockers in order to attain an adequate blood pressure control and a simultaneous facilitation of prevention of organ damage in the heart, the brain, the vessels, and the kidneys (*Figure 1*). Thus, patients receiving this type of therapy who become infected by SARS-CoV2 theoretically should continue with this treatment to which drugs for COVID-19 should be added. However, some initial publications indicated that the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) could be a potential risk factor for fatal COVID-19.[5,6] This concept was based on the fact that the angiotensin-converting enzyme 2 (ACE2) receptor permitted the entry of SARS-CoV2 into cells.[7] The study by Gao *et al.* reviewing the association of hypertension and antihypertensive treatment with COVID-19 mortality shows that patients with RAAS blockers were not exposed to a higher risk of mortality.[2] In fact, a relevant number of papers have demonstrated similar results, and professional scientific societies, in particular those devoted to arterial hypertension, and experts[8,9] have advised that ACEIs and ARBs should not be discontinued in patients infected by SARS-CoV2. Clinical trials are under way to test the safety and efficacy or RAAS blockers, including ACEIs and ARBs, in COVID-19 patients.[8,9]

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* † doi:10.1093/eurheartj/ehaa433.

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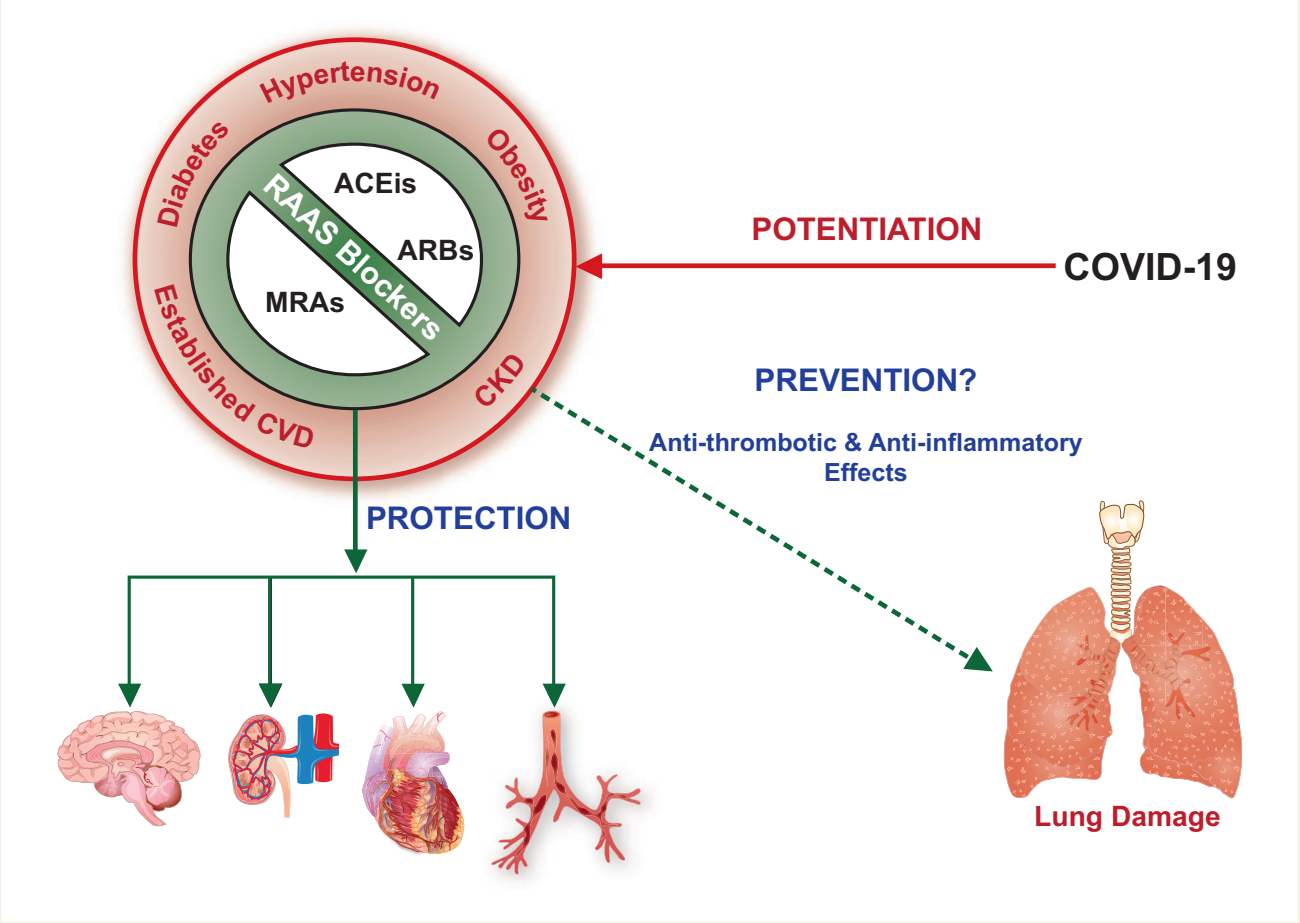

Figure 1 Summary of the findings in the article of *Gao et al.*[2] showing that in COVID-19 patients, RAAS blockers have to be continued to ensure maintained advantages for the brain, kidney, heart, and vessels of this type of therapy for which potential advantages over coagulation and consequences of COVID-19 could be obtained.

However, RAAS blockers, together with calcium channel blockers, beta-blockers, and diuretics, have been shown not to promote COVID-19 infection or its severity.[10] Interestingly, a recent publication[11] has considered that the early administration of the combination of a neprilysin inhibitor and an ARB (sacubitril/valsartan) could be useful in COVID-19 patients due to the anti-inflammatory properties of sacubitril. Another interesting aspect of the study by Gao *et al.* is that after pooling previously published data in a study-level meta-analysis, patients taking RAAS blockers were shown to be potentially associated with a decreased risk in mortality. A positive effect on the damage promoted by COVID-19 could be attributed to an elevated expression of ACE2 according to experimental data in animals.[8] Therefore, studies investigating the potential good effects of RAAS blockers including mineralocorticoid receptor antagonists and sacubitril/valsartan are required, because it is not only the fact that we do not have to abandon RAAS blockers that patients were already receiving but the possibility that these drugs could be considered as a specific treatment for COVID-19 patients could be a reality. Furthermore, the withdrawal of RAAS blockers in these COVID-19 patients would increase the morbidity and mortality risk given the myocardial damage that may occur in COVID-19.[12]

Finally, another positive aspect of RAAS blockers is their antithrombotic properties[13,14] that could ameliorate the frequent thrombotic or thrombo-embolic complications of COVID-19.[15] In fact, hyperinflammation and derangement of the RAAS in COVID-19 could contribute to clinically suspected hypercoagulopathy and microvascular immunothrombosis[14] (*Figure 1*).

In summary, as can be seen in *Figure 1*, the study *Gao et al.*[2] contains data obtained in an adequately controlled retrospective analysis proving the absence of the need to withdraw RAAS blockers and opening the door for a specific indication to improve the prognosis of COVID-19 patients by different mechanisms and independently of the presence of elevated blood pressure.

Conflict of interest: none declared.

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Corrigendum

doi:10.1093/eurheartj/ehz749
Online publish-ahead-of-print 11 October 2019

Corrigendum to: Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial [*Eur Heart J* (2012);33:2821–2830].

In the originally published version of this article figure 3A was duplicated in place of figure 3B. This has now been corrected.