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EDITORIAL

Should Patients Receiving ACE Inhibitors or Angiotensin Receptor Blockers be Switched to Other Antihypertensive Drugs to Prevent or Improve Prognosis of Novel Coronavirus Disease 2019 (COVID-19)?

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The epidemic due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been spreading globally, raising increasing concerns. In this scenario, decisions on preventive, symptomatic and potentially life-saving treatments both in the general population and in patients with novel coronavirus disease 2019 (COVID-19) must be based on sound scientific evidence.

Controversial hypotheses about the possible detrimental/protective effects of antihypertensive drugs acting on the renin–angiotensin–aldosterone system (RAAS) in patients with COVID-19 have been postulated in several editorials and letters [1–4].

Through the regulation of vascular peripheral resistance and, potentially, of blood volume, the RAAS plays a crucial role in the etiology of hypertension. Moreover, this system promotes atherogenic processes by increasing oxidative stress, stimulating vascular muscle and monocyte proliferation. Based on their biological target, drugs inhibiting the RAAS may be distinguished as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and direct renin inhibitors (DRIs). ACEIs enact their blood pressure-lowering effects by blocking the peptidyl-dipeptidase that hydrolyzes angiotensin I (A-I) to angiotensin II (A-II). In addition, it inactivates bradykinin, a vasodilating peptide promoting the release of nitrogen monoxide and prostacyclin. ARBs have no effect on bradykinin metabolism and block the effects of A-II more selectively than ACEIs. In detail, ARBs determine their antihypertensive effect by preventing the binding of A-II to the A-II receptor type 1 (AT_1). Finally, DRIs exert blood pressure-lowering effects by decreasing plasma renin activity and inhibiting the conversion of angiotensinogen to A-I [5].

In vitro studies demonstrated that ACEIs and ARBs can significantly increase the expression and activity of angiotensin-conversion enzyme 2 (ACE2), highly expressed in the heart and lungs [6]. Coincidentally, ACE2 is the receptor-binding site for the spike protein of SARS-CoV-2 at the target cell [7]. Hence, Fang et al. [4] recently hypothesized in *The Lancet Respiratory Medicine* that patients with cardiac diseases, hypertension, or diabetes mellitus treated with ACE2-increasing drugs might be at higher risk for severe SARS-CoV-2 infection. Accordingly, the authors suggested that calcium channel blockers (CCBs) may be a more suitable alternative antihypertensive treatment than ARBs/ACEIs because of their lack of increased ACE2 expression or activity.

On the other hand, recently published commentaries outlined the mechanisms by which RAAS inhibitors may be beneficial in patients with COVID-19 and discussed the unclear effects of these drugs on ACE2 levels and activity in humans, recommending against the suspension or withdrawal of RAAS blockers [8, 9]. We present here our contribution to the scientific debate, highlighting the importance of continuing ACEI/ARB treatments and reporting several arguments against switching from ACEIs or ARBs to other antihypertensive drugs and specifically to CCBs.

Italian Society of Pharmacology members are listed in acknowlegements.

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First, to date, there is no sound evidence from clinical studies that replacing ACEIs/ARBs with other antihypertensive drugs, including CCBs, is associated with beneficial effects on either the prevention of COVID-19 or the prognosis for infected patients. The scant available data are mostly derived from in vitro studies. For this reason, in *Nature Cardiology*, Zheng et al. [2] reported, "Whether patients with COVID-19 and hypertension who are taking [an] ACE inhibitor/ARB should switch to another antihypertensive drug remains controversial, and further evidence is required" [2].

Second, other studies carried out in SARS-CoV and probably generalizable to SARS-CoV-2 suggested, paradoxically, a protective effect of ARBs against COVID-19 [1]. The interaction of the coronavirus spike protein with ACE2, its cellular-binding site, leads to ACE2 downregulation. In turn, this results in excessive production of angiotensin by ACE, whereas less ACE2 is capable of converting it to angiotensin (1-7), an heptapeptide with vasodilator activity [1, 10]. It has been suggested that exaggerated stimulation of AT_1 by A-II determines increased pulmonary vascular permeability, thereby mediating increased lung pathology when the expression of ACE2 is decreased [11, 12]. Thus, higher ACE2 expression following chronic treatment with ARBs may protect patients infected with SARS-CoV-2 against acute lung injury rather than increasing the risk of developing COVID-19.

Third, switching among different antihypertensive drugs in older patients with relevant comorbidities may put this very frail population at risk of developing adverse cardiovascular events such as uncontrolled hypertension/symptomatic hypotension or even deterioration of other chronic diseases. Moreover, considering the proven effects of ACEIs and ARBs in reducing mortality in cardiovascular diseases, the discontinuation of these therapies could increase the occurrence of negative outcomes in patients affected by cardiovascular diseases and COVID-19 [13].

Fourth, ACEIs and ARBs are currently approved (with differences across various compounds) for the treatment of hypertension, heart failure and diabetic nephropathy and for secondary prevention after acute myocardial infarction, whereas CCBs and other antihypertensive drugs are not approved for all the same indications.

Finally, none of the drug regulatory agencies worldwide recommend switching from ACEIs/ARBs to other antihypertensive drugs or vice versa during the COVID-19 outbreak. Instead, on 17 March 2020, the Italian Drug Agency issued a warning against any change of antihypertensive therapies in patients with well-controlled hypertension, irrespective of the agents being used, because of the lack of clinical data [14]. Ten days later, the European Medicines Agency advised that, since there is no clinical evidence that these drugs can worsen SARS-CoV-2 infections, it is important that patients do not discontinue their treatment with ACEIs or ARBs and there is no need to switch to other medicines [15]. These recommendations are in line with the position statements of national/international scientific societies (e.g., European Society of Cardiology [16], Italian Society of Pharmacology [17], Heart Failure Society of America, American College of Cardiology and American Heart Association [18], International Society of Hypertension [19], European Society of Hypertension [20]) that recommend continuing RAAS inhibitor therapy for patients who are currently prescribed such agents for indications for which it is known that these agents are safe and effective, such as acute and chronic heart failure [21], acute myocardial infarction [22] and hypertension [23].

Regarding the postulated protective effect, ACEIs/ARBs should never be used in healthy people or patients who are not affected by diseases that are not approved indications as reported in the summary of product characteristics.

No specific information has been described for DRIs. Nevertheless, all the recommendations reported above can be extended to this class of RAAS inhibitors.

In a scenario in which experimental clinical studies cannot rapidly shed light on the association between COVID-19 and ACEI/ARB use, real-world studies based on dedicated COVID-19 patient registries, whenever available, or claims databases from countries with a high incidence of SARS-CoV-2 infection are urgently needed.

In the absence of clinical evidence supporting any change in patients treated with ACEIs/ARBs, clinicians should still follow the old principle "*primum non nocere*."

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