Interaction between RAAS inhibitors and ACE2 in the context of COVID-19

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In the Comment article by Zheng and colleagues (COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-0360-5 (2020))[1], the crucial role of angiotensin-converting enzyme 2 (ACE2) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease 2019 (COVID-19), was highlighted. ACE2 is a membrane-bound aminopeptidase that cleaves angiotensin I and angiotensin II into the angiotensin-(1–9) and angiotensin-(1–7) peptides. Several studies support the existence of a cardiovascular-protective ACE2–angiotensin-(1–7)–Mas receptor axis[2]. ACE2 is overexpressed in heart failure, arterial hypertension and diabetes mellitus[3]. Moreover, ACE2 has been identified as a functional receptor for the entry of coronaviruses generally, and SARS-CoV-2 specifically, into host cells[4].

Given that most of the severe forms of COVID-19 have occurred in elderly patients with cardiovascular comorbidities, Zheng and colleagues speculate about the influence of chronic treatment with blockers of the renin–angiotensin–aldosterone system (RAAS) on the severity of the infection, stating that "ACE2 levels can be increased by the use of renin–angiotensin–aldosterone system inhibitors"[1]. Consequently, the authors suggest that "the safety and potential effects of antihypertension therapy with ACE inhibitors or angiotensin-receptor blockers in patients with COVID-19 should be carefully considered".

We wish to clarify that different RAAS inhibitors have different effects on ACE2 levels. By acting at different levels of the system, RAAS inhibitors result in heterogeneous effects on the peptides and enzymes involved. Whereas angiotensin-receptor blockers and mineralocorticoid-receptor blockers have been shown to increase the levels of ACE2 expression and activity in various experimental and clinical models[5,6], administration of ACE inhibitors increased cardiac *Ace2* mRNA levels but had no effect on ACE2 activity in experimental models[7,8]. In addition, in an animal model of diabetic nephropathy, the chronic administration of aliskiren (a direct inhibitor of renin) was associated with a reduction in ACE2 expression[9]. For these reasons, we believe that chronic treatment with ACE inhibitors has no reason to influence the course of SARS-CoV-2 infection. By contrast, the use of angiotensin-receptor blockers or mineralocorticoid-receptor blockers might warrant caution and further analysis in the context of SARS-CoV-2 infection. The reduced expression of ACE2 with aliskiren treatment could be an interesting option in the context of SARS-CoV-2 infection that requires further investigation.

There is a reply to this letter by Zheng, Y. Y. et al. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-0369-9 (2020).

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Competing interests
J.-J.M. has received fees for consultancy from Mylan, Pfizer and Servier. B.I.L. has received grants and personal fees from Bayer, Roche and Servier.

Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19'

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We thank Mourad and Levy for their constructive Correspondence (Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-0368-x (2020))[1] on our Comment article (COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-0360-5 (2020))[2]. We agree with their comments and acknowledge that different renin–angiotensin–aldosterone system (RAAS) inhibitors have different effects on angiotensin-converting enzyme 2 (ACE2) levels. Ferrario and colleagues[3] reported that administration of either ACE inhibitors or angiotensin-receptor blockers (ARBs) increased the levels of *Ace2* mRNA in Lewis rats compared with rats receiving placebo. In particular, cardiac levels of *Ace2* mRNA increased by 4.7-fold or 2.8-fold in rats given either lisinopril (an ACE inhibitor) or losartan (an ARB), respectively. Furthermore, the researchers found that losartan treatment, but not lisinopril treatment, increased ACE2 activity compared with placebo. However, the researchers did not shed light on the mechanisms that might account for these differences. Nevertheless, Li and colleagues[4] found that treatment with captopril (an ACE inhibitor) can significantly increase ACE2 protein expression in rats with acute lung injury. Furthermore, Wösten-van Asperen and colleagues[5] reported that, in a rat model of acute respiratory distress syndrome, ACE activity and angiotensin II expression are increased, whereas ACE2 activity and angiotensin-(1–7) levels are reduced.

The protective effects of the ACE2–angiotensin-(1–7)–Mas receptor axis are primarily mediated by reductions in angiotensin II level[6]. Both ACE inhibitors and ARBs can reduce angiotensin II levels[7]. The former inhibit the substrate of angiotensin II generation, and the latter directly inhibit the conversion of angiotensin I to angiotensin II. Therefore, RAAS inhibitors, including ACE

inhibitors and ARBs, can activate the ACE2–angiotensin-(1–7)–Mas receptor axis. However, as mentioned in our Comment article[2], whether patients with coronavirus disease 2019 (COVID-19) and hypertension who are taking an ACE inhibitor or ARB should switch to another antihypertensive drug remains controversial. In one study, the use of ACE inhibitors or ARBs did not increase mortality in 112 patients with COVID-19 and cardiovascular disease[8]. Further evidence is required to clarify the effects of ACE inhibitors and ARBs in patients with COVID-19. On 12 March 2020, the European Society of Hypertension published a statement on the topic of hypertension, RAAS blockers and COVID-19, concluding that the available data do not support the differential use of RAAS blockers (ACE inhibitors or ARBs) in patients with COVID-19 (REF.[9]). However, the authors cautioned that the statement reflected the current evidence at the time of release and might need updating according to new evidence.

Indeed, ACE2 might be equivalent to a natural ARB or ACE inhibitor[10]. Decreasing the levels of ACE2 will shift the balance of the RAAS to promote the ACE–angiotensin II–angiotensin II receptor type 1 axis, leading to lung injury and the progression of inflammatory storms. Increasing the levels of ACE2 will transfer the balance towards the angiotensin-(1–7)–Mas receptor axis, which has anti-inflammatory and antioxidant effects that are cardiopulmonary protective.

In their Correspondence article, Mourad and Levy also suggest that aliskiren treatment could be an interesting option in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, given that aliskiren can reduce the expression of ACE2. Although ACE2 has been identified as the functional receptor for SARS-CoV-2, the role of ACE2 in the progression of COVID-19 after SARS-CoV-2 infection is still controversial, so the benefits of aliskiren use in patients with COVID-19 needs further investigation.

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Competing interests
The authors declare no competing interests.