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Renin–angiotensin system inhibitors and COVID-19: overwhelming evidence against an association

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Inhibitors of the renin–angiotensin system (RAS) have been reported to increase the expression of angiotensin-converting enzyme 2 (ACE2) in animal models.[1] This possibility, along with the high prevalence of cardiovascular diseases (for which RAS inhibitors are often used) among patients with severe COVID-19[2] prompted some researchers to postulate that these drugs could enhance the access of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, predisposing patients to COVID-19 or progression to more severe forms.[3,4] This hypothesis was widely publicised in mid-March, 2020, coinciding with the surge of the first pandemic wave in Europe, and many physicians faced an awful dilemma: to withdraw or not to withdraw these drugs, with the implicit harms of either decision. Scientific societies and regulatory authorities counteracted by recommending not to discontinue RAS inhibitors until firm evidence was available and urged investigators worldwide to carry out studies to test the hypothesis. In less than 2 months, three large studies, from different countries and using diverse designs, were published, reaching the same conclusion: the absence of an association of RAS inhibitors with COVID-19 diagnosis, hospital admission, and severity,[5–7] which provided a first reassurance on the safety of these drugs. Since then, more than 50 studies have been published,[8] with the same conclusion. However, many of them were small, single centred, and methodologically weak.

In this context, the study by Daniel Morales and colleagues in *The Lancet Digital Health* is a remarkable exception.[9] The authors used three large databases from the USA and Spain (including more than 1·3 million people) to do a cohort study with an active control, and state-of-the-art analytical methods to control for confounding (including p value calibration through negative control outcomes). Furthermore, they showed how to manage multiple databases in a distributed network analysis with a common data model to pool results using meta-analytic techniques. The authors carried out ten pairwise comparisons, including four first-line antihypertensive drugs, ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide or thiazide-like diuretics (THZs), either used in monotherapy, or in monotherapy or combination therapy. They analysed four clinically relevant outcomes: COVID-19 diagnosis, hospital admission with COVID-19, hospital admission with pneumonia, and hospital admission with pneumonia and other complications.

The use of an active control deserves a specific comment. Users of RAS inhibitors present multiple cardiovascular risk factors and, thus, are very different from non-users. However, most studies have compared them relying on statistical methods to adjust for the imbalance, overlooking that in such a comparison there are unknown or unmeasured confounding factors that are elusive to statistical adjustment. Morales and colleagues overcame this problem by including a comparison group consisting of users of drugs that share the main indications of RAS inhibitors, which reduces confounding.

In the main analysis, 363 785 patients with hypertension treated with ACEI or ARB monotherapy were compared with 248 915 users of CCB or THZ monotherapy, and no association was found between ACEI or ARB use and COVID-19 diagnosis (calibrated hazard ratio [HR] 0·98, 95% CI 0·84–1·14). Likewise, 711 799 users of ACEI or ARB in monotherapy or in combination were compared with 473 076 users of CCB or THZ in monotherapy or in combination, which also showed no association between COVID-19 diagnosis and ACEI or ARB use (calibrated HR 1·01, 95% CI 0·90–1·15). In both comparisons, the fully adjusted HRs for COVID-19 diagnosis or hospital admission were almost null, with CIs narrow enough to exclude relevant increased risks. Importantly, the direct comparison of ACEIs with ARBs also did not yield any apparent difference. The effects of duration and dose were not addressed, but other researchers have found no impact.[7,10]

One key question that still needs to be addressed is whether the intra-hospital use of ARBs and ACEIs has an effect on mortality. The issue is important because there are reasons to think that a highly activated RAS, as a consequence of the internalisation of ACE2 induced

by SARS-CoV-2, could play a crucial part in some of the complications observed in patients with severe COVID-19. Some observational studies have suggested a protective effect of RAS inhibitors, but many of them are affected by different types of bias that might have magnified a favourable outcome. On the contrary, the preliminary results of a randomised trial (BRACE CORONA), recently presented at the European Society of Cardiology Congress, does not suggest a beneficial effect, although mortality was so low (2·7–2·8%) that the external validity of such trial is questionable.

The key message of the study by Morales and colleagues, added to the available evidence, is clear: the outpatient use of RAS inhibitors is not associated with an increased risk of a COVID-19 diagnosis, hospital admission, or disease severity. Therefore, physicians should not replace them with other antihypertensive drugs, as many clinicians hastily did in March–April, 2020, passing from hypothesis to action without a proper process of clinical investigation. This lesson is an old one that we must relearn from this crisis: to support clinical decisions with the best available evidence and abstain from converting medical practice into a reckless adventure.

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