The recent emergence of the COVID-19 pandemic has required physicians, researchers and health authorities to navigate uncharted territory at lightning speed. This has led to an unprecedented scientific output with a primary focus on antiviral therapy and vaccine development.

Awaiting such advances and to potentially curb some of the immediate pandemic impact, researchers quickly identified advanced age and comorbidities such as hypertension, diabetes mellitus and heart failure as risk factors for hospitalisation with COVID-19 and as prognostic factors for a poor outcome.1 These patients are often treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II type 1 receptor blockers (ARBs).

Concurrently, scientists discovered that the SARS-CoV-2 virus infects human cells via binding to the ACE2 receptor of human cell membranes.2 Because ACE2 plays an important role in the renin–angiotensin system and also acts as a receptor for SARS-CoV-2 cell entry, hypotheses about an association between ACEi/ARBs and COVID-19 outcomes were rapidly generated.3 Since ACEi/ARBs markedly improve outcome in patients with cardiovascular disease, diabetes and hypertension, several scientific societies have advocated that patients should continue prescribed ACEi/ARBs treatment in case of SARS-CoV-2 infection.4 Others have stated that ARBs may even have protective effects against acute respiratory distress syndrome (ARDS) in COVID-19 patients, reflected by the initiation of clinical trials with losartan (ClinicalTrials.gov NCT04311177 and NCT04312009).

Rationale for hypotheses
ACE converts angiotensin I to angiotensin II, which binds to the angiotensin II type 1 (AT1) receptor. ACE and ACE2 are exopeptidases, where ACE2 cleaves angiotensin I to angiotensin (1–9) and angiotensin II to the peptide fragment, angiotensin (1–7). SARS-CoV-2 surface glycoprotein binding to ACE2 is followed by protease (TMPRSS2) cleaving of the virus spike and SARS-CoV-2 entry and infection of human cells.5 Although cell and tissue-dependent, ACE2 is upregulated in heart failure6 and obstructive coronary disease,7 and is traceable in urine of diabetic patients.8 The expression of ACE2 is also markedly upregulated in lung epithelium and in the hearts of rats treated with ACE inhibitors (five-fold) or ARBs (three-fold and significantly less than for ACE inhibitors), and also detectable in the urine of hypertensive patients treated with the ARB, olmesartan.9 Taken together, these findings form the hypothesis of an association between the use of ACEi/ARBs, virus entry and multiorgan dysfunction.

However, complicating the picture, there are two ACE2 forms; a transmembrane structural protein that serves as a receptor for cell entry of SARS-CoV-2, and a soluble circulating ACE2, which SARS-CoV-2 may bind to and thereby prevent SARS-CoV-2 from binding to the transmembrane ACE2 isoform and thus from infecting cells. Shedding of ACE2 from the cells is regulated by the metallopeptidase 17 (ADAM17) and is not affected by treatment with ACEi/ARBs.10 Furthermore, ACE2 knockout in mice seems to aggravate ARDS induced by means other than SARS-CoV infection,11 again suggesting a protective effect of ACE2 for SARS-CoV-2 infection. Finally, ARBs increase angiotensin II levels, which act on AT2 receptors and provide an increased amount of substrate to ACE2 followed by formation of angiotensin (1–7) and activation of Mas receptors (Fig. 1). The activation of AT2 and Mas receptors produces vasodilating and anti-inflammatory effects in the lung.

Therefore, based on available mechanistic evidence, it is unclear whether there is an association between ACEi/
ARB use and SARS-CoV-2 infection and/or COVID-19 outcome or whether the increased risk is solely limited to the presence of the comorbidities, i.e. confounding-by-indication.

Evidence from observational studies
A recent series of observational studies may provide valuable insights into the question of whether ACEi/ARBs medication influences risk of COVID-19 or its prognosis. We manually screened all COVID-19-related publications in each of the journals and subjournals of *New England Journal of Medicine*, *Journal of American Medical Association*, *British Medical Journal*, *The Lancet* and *Annals of Internal Medicine* until 15 May 2020.

Risk studies
Four studies addressed risk of COVID-19 and observed no increased risk among ACEi/ARB users compared with control groups. For patients treated with ACEi, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were 0.89 (95% CI 0.72 to 1.1) and 0.96 (95% CI 0.87 to 1.07) compared with non-ACEi users. Similarly, the adjusted ORs were 1.09 (95% CI 0.87 to 1.37) and 0.95 (95% CI 0.86 to 1.05) for patients treated with ARBs. A third study applied propensity score matching and found median differences in risk of COVID-19 of −2.5 (95% CI −6.7 to 1.6) for ACEi users versus non-ACE users and 2.2 (95% CI −1.9 to 6.3) for similar comparisons of patients treated with ARBs. Finally, a study estimating risk of COVID-19 requiring hospitalisation reported adjusted ORs of 0.80 (95% CI 0.64 to 1.00) for ACEi and 1.10 (95% CI 0.88 to 1.37) for ARBs.

Observational studies on risk of COVID-19 are particularly difficult to conduct and interpret since several confounders and biases are hard to control for. First, testing policies/strategies have evolved rapidly in most countries and often favoured testing certain risk groups. Combined with variations in testing capacity within and between countries during the course of the pandemic, this may result in significant time-dependent selection bias. Second, government appeals of for example, lockdowns, social distancing, hand washing and use of face masks seem to have been key factors for bringing virus reproduction numbers down in many countries. Yet, it remains unclear whether adherence to such measures and similar behavioural patterns differ between ACEi/ARB users and nonusers. For example, ACEi/ARB users may have enforced particularly strict isolation routines upon themselves since the hypotheses of increased risks with these drugs were announced early in a high-impact medical journal and on social media.

Nevertheless, based on these initial observational findings, there seems to be no increased risk of SARS-CoV-2 infection for ACEi/ARB users.

Prognostic studies
Four studies examined the prognosis of COVID-19 patients and uniformly found that risk of severe outcomes was not higher for the collapsed group of ACEi and ARB...
users versus control groups (Table 1). However, one study observed an increased risk of hospitalisation and ICU admission for collapsed ACEi/ARB users, which for ICU admission appeared to be driven by ACEi users. Importantly, this study stressed the explorative nature of these secondary findings and advised that they should be interpreted with caution.

Besides limitations imposed by variations in testing strategies and capacities, confounding-by-identification remains the most obvious and important bias in these studies, that is, outcome is associated with the comorbidity for which the drug is given and not the drug itself. Thus far, prognostic studies have applied multivariable regression, matching and propensity scores, but none has incorporated active comparison to define the control group, for example, by comparing ACEi/ARB users with a control group of calcium channel blocker users. Calcium channel blockers do not interfere with ACE2, so this approach could further decrease the risk of confounding-by-identification. Prognostic studies are also at risk of differential classification of nonfatal outcomes, for example, physician thresholds for ICU admissions may be lower for patients treated with ACEi/ARBs compared with nonusers. This would lead to an increased risk of severe disease in ACEi/ARB users. Nevertheless, clinical indicators of disease severity have been similar between ACEi/ARBs users and nonusers thus far.

The real-time nature of COVID-19 observational studies of ACEi/ARBs is additionally challenged by possible delays in exposure and/or outcome information. For example, prescription information may be delayed if based on registries and deaths may occur late during the course of disease. Another critical aspect of studies of ACEi/ARB is whether patients actually took this medication on the day of infection and/or whether they continued treatment after infection. Contrary to the recommendations of scientific societies’ urging continued use of ACEi/ARBs in patients with cardiovascular disease and diabetes mellitus, others have insisted on conversion to other antihypertensive drugs or stopping treatment in certain patient groups. This raises concern about the exposure, particularly if exposure information is derived from ‘historic’ data in a registry and outcomes are recorded after these publications. Regarding continued ACEi/ARBs use after a positive test, little is reported apart from a recent large study from New York state (n=5700) in which 50% of hospitalised patients treated

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Table 1  Characteristics of included studies investigating prognosis of patients using angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers

<table>
<thead>
<tr>
<th>Study, study design, source population and period</th>
<th>Exposure, outcome and analysis</th>
<th>Demographics and baseline characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.17^</td>
<td>Exposure: ACEi/ARB use Outcomes: In-hospital mortality Severe COVID-19 Analysis: Contingency table tests</td>
<td>Age 55.5 (IQR 38 to 67) Male sex 46.3% Diabetes 203 (17.2%) CHF 21 (1.8%) CKD 44 (3.7%) IHD 103 (8.7%) HT 362 (30%) COPD 54 (4.6%)</td>
<td>In the hypertensive subgroup (n=362) of hospitalised COVID-19 patients, ACEi/ARB use was not associated with disease severity (P=0.65) or mortality (P=0.34)</td>
</tr>
<tr>
<td>Mehta et al.12</td>
<td>Exposure: ACEi/ARB use Outcomes: Use of ventilator ICU admission Hospitalisation Analysis: Overlap propensity weighted analyses</td>
<td>Age 49 (SD 21) Male sex 7384 (40%) Diabetes 3478 (19%) CHF 1879 (10%) CKD, N/A IHD 2179 (12%) HT 7312 (40%) COPD 2186 (12%)</td>
<td>In overlap PS-weighted analyses, ORs for ‘Use of ventilator’ 1.32 (CI 0.80 to 2.18) ‘ICU admission’ 1.64 (CI 1.07 to 2.51) ‘Hospitalisation’ 1.93 (CI 1.38 to 2.71) For ACEi/ARB users</td>
</tr>
<tr>
<td>Reynolds et al.14</td>
<td>Exposure: ACEi/ARB use Outcomes: Severe COVID-19 Analysis: Propensity matched median differences</td>
<td>Age 49 [IQR 34 to 63] Male sex 5229 (41.5%) Diabetes 2271 (18%) CHF 784 (6%) CKD 1214 (10%) IHD 525 (4%) HT 4257 (35%) COPD 1833 (15%)</td>
<td>PS matched median differences between patients treated and untreated for hypertension ACEi –3.3 (CI –8.2 to 1.7) ARB –0.1 (CI –4.8 to 4.9) ACEi/ARB –0.5 (CI –4.3 to 3.2)</td>
</tr>
<tr>
<td>Mancia et al.13</td>
<td>Exposure: ACEi/ARB use Outcomes: Mild/moderate disease severity Critical or fatal illness Analysis: Conditional logistic regression adjusted for baseline covariates</td>
<td>Age 68 (SD 13) Male sex 3969 (63.3%) Diabetes, N/A CHF 323 (5.1%) CKD 181 (2.9%) IHD 473 (7.5%) HT, N/A COPD 188 (3.0%)</td>
<td>Adjusted ORs for Mild-to-moderate illness ACEi 0.97 (CI 0.88 to 1.07) ARBs 0.96 (CI 0.87 to 1.07) Critical or fatal illness ACEi 0.91 (CI 0.69 to 1.21) ARBs 0.83 (CI 0.63 to 1.10)</td>
</tr>
</tbody>
</table>
with ACEi or ARBs discontinued use during hospitalisation. One reason for discontinuation could be development of hypotension, another could be the hypothesised concerns about these drugs. Future studies intended to address continued use of ACEi/ARB and prognosis of COVID-19 should pay particular attention to avoid immortal time bias in outcome analyses.

In conclusion, the currently available evidence from observational studies suggests neither harm nor benefit from taking ACEi or ARBs in terms of risk-of-infection or prognosis of COVID-19. While awaiting the results of ongoing randomised trials, these results are reassuring for both clinicians managing COVID-19 patients and persons treated with ACEi or ARB.

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