Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

is unlikely that hydroxychloroquine has any effect on disease progression, but its use might bias estimates towards the null compared with treatment with azithromycin alone.

The results of COALITION II corroborate those of COALITION I,[10] which was done by the same study group and evaluated hydroxychloroquine with or without azithromycin in patients admitted to hospital with mild or moderate COVID-19. In COALITION I, there was no significant difference in outcomes in patients receiving hydroxychloroquine with or without azithromycin, and no evidence of an increase in adverse events. The results of these trials suggest that azithromycin might not provide benefit to patients once the disease has progressed and patients require hospitalisation. Because azithromycin is currently the most commonly prescribed outpatient therapy for COVID-19, establishing whether azithromycin is helpful earlier in the disease course is an important research priority. If azithromycin does not have a role in the treatment of COVID-19, avoiding its use would reduce unnecessary antibiotic consumption.

The results of COALITION II are an important contribution to the randomised trials evaluating therapeutics for COVID-19. For patients with COVID-19, the addition of azithromycin to existing standard of care regimens does not appear to improve outcomes. Additional placebo-controlled trials in hospitalised patients, and earlier in the disease course, would strengthen the evidence and provide a comprehensive understanding of the role of azithromycin in COVID-19.

We declare no competing interests.

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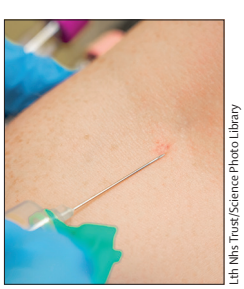
Circulating ACE2: a novel biomarker of cardiovascular risk

Dysregulation of the renin–angiotensin system plays a major role in the progression of cardiovascular disease in humans. The enzymatic reactions within the renin–angiotensin system generate angiotensin II, which promotes vasoconstriction and inflammation and deleterious cardiovascular effects.[1] Angiotensin-converting enzyme 2 (ACE2) acts to counterbalance the renin–angiotensin system by degrading angiotensin II.[2,3] In 2005, ACE2 was identified as the cellular receptor for severe acute respiratory syndrome coronavirus (SARS-CoV),[4] and we now know that ACE2 also facilitates viral entry of SARS-CoV-2, leading to widespread systemic illness in COVID-19.[5] Notably, ACE2 is present on endothelial cells and can undergo so-called shedding into the circulation. In patients with cardiovascular disease, increased circulating ACE2 activity predicts adverse cardiovascular outcomes in patients with heart failure, coronary artery disease, and aortic stenosis.[6–8] However, in the general population, the role of circulating ACE2 as a biomarker of risk is not well established.

In *The Lancet*, Sukrit Narula and colleagues[9] present one of the largest epidemiological datasets on plasma ACE2 concentration in the general population. They did a case-cohort study involving 10 753 participants from the multinational Prospective Urban Rural Epidemiology study, including 5084 patients randomly selected as the subcohort and 5669 with an incident event of interest. In the subcohort, 2935 (57·7%) were men and 2149 (42·3%) were women; the mean age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was 50·79 years (SD 9·58). They report that ACE2 concentration was the highest-ranked independent predictor of deaths compared with standard cardiovascular risk markers (smoking, diabetes, systolic blood pressure, non-HDL cholesterol, and body-mass index).[9] Increased concentration of plasma ACE2 was associated with increased risk of all-cause mortality (hazard ratio [HR] 1·35 per 1 SD increase [95% CI 1·29–1·43]), incident heart failure (HR 1·27 per 1 SD increase [1·10–1·46]), stroke (HR 1·21 per 1 SD increase [1·10–1·32]), myocardial infarction (HR 1·23 per 1 SD increase [1·13–1·33]), and incident diabetes (HR 1·44 per 1 SD increase [1·36–1·52]).

We commend the authors for the enormity of the data that was compiled. Study strengths include the large sample size, the well phenotyped patient population, and long duration of follow-up (median 9·42 years [IQR 8·74–10·48]). A notable feature of the study is the use of mendelian randomisation analyses to understand how antecedents of cardiovascular disease and drugs might causally affect circulating ACE2 levels. These analyses in combination with phenotypic data suggest a possible causal relationship between increased body-mass index and history of diabetes with increased circulating ACE2. The main study limitation is the absence of external replication and ultimately, validation of the findings by Narula and colleagues in independent cohorts is needed before the use of circulating ACE2 as a biomarker of risk can be recommended. Validation in independent cohorts is essential because the performance of biomarkers is rarely as good in the validation cohort as in the cohort in which they were initially assessed.[10] Furthermore, only a solitary ACE2 measurement was obtained in each individual, and it is unknown whether circulating ACE2 levels change with disease progression, or if they can be used to guide response to therapy. If circulating ACE2 is to be used as a marker of risk in the clinical setting, then standardised methods with gender-specific reference ranges that take into account the effect of different disease states on ACE2 levels will need clarification.

Other questions remain. There is a long history of using blood biomarkers to predict disease and adverse outcomes in cardiovascular medicine. These markers, the original personalised medicine, permit patient-specific prediction of risk. However, is there a need for yet another biomarker? Screening for biomarkers such as circulating ACE2 will probably compete for scarce health-care funding, and only those with excellent performance characteristics will be used in primary-care settings.[10] Only cost-effective biomarkers with therapeutic implications to prevent the adverse sequelae of cardiovascular disease will survive such competition. A dedicated cost–utility analysis is needed to compare the cost-effectiveness of plasma ACE2 measurements over standard clinical care—eg, based on the outcome of incremental cost per additional quality-adjusted life-year (QALY).[11] This type of analysis is particularly important because cost-effectiveness of biomarkers in terms of QALYs is likely to be smaller than those associated with direct interventions.[11]

Perhaps one of the most important pieces of information from the study by Narula and colleagues in the setting of the ongoing COVID-19 pandemic is the absence of any association between ACE2 levels and the use of ACE inhibitors, angiotensin-receptor blockers (ARBs), β blockers, calcium channel blockers, and diuretics.[9] These results, validated by simultaneously performed mendelian randomisation studies, add support to the evidence that renin–angiotensin system inhibitors should not be withheld in patients with COVID-19 for the sole purpose of modifying ACE2.[12] They are also in line with our previous findings that neither ACE inhibitors nor ARBs alter plasma ACE2 activity in patients with cardiovascular disease.[8,13] Although observational data show that ACE inhibitors and ARBs have no adverse effects in patients with COVID-19, we must await the results of ongoing randomised controlled clinical trials in this area that are assessing the effects of moving patients off or onto renin–angiotensin system blockers. The CLARITY trial, a controlled evaluation of ARBs for COVID-19 respiratory disease, will randomly assign renin–angiotensin system inhibitor naive patients with COVID-19 to an ARB or placebo, with sites in India and Australia (NCT04394117).

Narula and colleagues state that plasma ACE2 might be a marker of renin–angiotensin system dysregulation.[9] Indeed, this characteristic could guide both preventive and therapeutic approaches in the future, with specific targeting of individuals with increased circulating ACE2 levels for more intensive lifestyle or pharmacological interventions to improve outcomes—a hypothesis that needs testing in the clinical setting.

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Reframing the NCD agenda: a matter of justice and equity

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The international development community has never taken non-communicable diseases (NCDs) seriously. Seen largely as a challenge for high-income nations, NCDs and their community of advocates have met with, at best, warm words and, more commonly, indifference. There have been moments for optimism. The landmark 2005 WHO report, *Preventing Chronic Diseases: a Vital Investment*;[1] the 2011 Political Declaration on NCDs;[2] and the inclusion of NCDs in the Sustainable Development Goals (SDG) in 2016 (SDG 3.4: by 2030, reduce premature mortality from NCDs by a third and promote mental health and wellbeing). But, despite an increasingly well organised civil society response, NCDs have not broken through into the mainstream of development and global health.

One reason could lie in the framing of NCDs. A biomedical model, for example, emphasises genetic and other biological risk factors and processes. When viewed through the lens of epidemiological transitions, changes in NCD prevalence are associated with industrialisation, growing economic prosperity, and rises in life expectancy. And when NCDs are viewed as lifestyle conditions, attention is paid to individual behaviours rather than to wider social and commercial determinants of health.[3]

The current 5 × 5 approach to NCDs, favoured by WHO, focuses on five diseases (cardiovascular disease, cancer, diabetes, chronic respiratory diseases, and mental ill-health) and five risk factors (tobacco use, unhealthy diets, physical inactivity, harmful use of alcohol, and air pollution).[4] But, as the NCD Countdown 2030 showed, "Although premature mortality from NCDs is declining in most countries, for most the pace of change is too slow to achieve SDG target 3.4".[5] The global NCD community needs to consider a different approach to the framing of chronic diseases.

The central argument of *The Lancet* NCDs and Injuries (NCDI)[6] Poverty Commission is that although the

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