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Weekly Journal Scan

A randomized trial supports the recommendation to continue treatment with ACEi or ARBs during hospitalization for COVID-19

Comment on “Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19” published in *JAMA* (doi:10.1001/jama.2020.25864)

Key points

- The BRACE CORONA (Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients With COVID19) trial is a multicentre, registry-based, open-label, randomized clinical trial (RCT) with blinded end-point assessment of patients hospitalized with coronavirus 2019 disease (COVID-19) who were on treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) prior to hospital admission.¹ Patients taking >3 antihypertensive agents, those taking sacubitril/valsartan for heart failure (HF), and those hospitalized for HF within the last 12 months were not eligible. The aim was to determine whether discontinuation of ACEi/ARBs compared with continuation affected the number of days alive and out of the hospital through 30 days. Secondary outcomes included death, cardiovascular death, and COVID-19 progression.
- The study included 659 patients (334 in the discontinuation group and 325 in the continuation group) with a median age of 55 years (15% >70 years), a median time from symptom onset to hospital admission of 6 days, and an oxygen saturation <94% of room air at baseline in 27% of patients. Clinical severity at hospital admission was considered mild in 57% and moderate in 43% of cases. All the enrolled subjects completed the 30-day follow-up.
- The discontinuation of ACEi or ARBs did not affect the number of days alive and out of the hospital [22 days in the discontinuation group vs. 23 days in the continuation group; mean ratio 0.95, 95% confidence interval (CI) 0.90–1.01]. There was no difference in death rate [2.7% vs. 2.8% in the discontinuation and continuation groups, respectively; odds ratio (OR) 0.97, 95% CI 0.38–2.52], cardiovascular death (0.6% vs. 0.3%; OR 1.95, 95% CI 0.19–42.12), or COVID-19 progression (38.3% vs. 32.3%; OR 1.30, 95% CI 0.95–1.80). Moreover, the incidence of respiratory failure requiring invasive mechanical ventilation (9.6% in the discontinuation group vs. 7.7% in the continuation group), shock requiring vasopressors (8.4% vs. 7.1%), acute myocardial infarction (7.5% vs. 4.6%; RR 1.62, 95% CI 0.88–3.09), new or worsening HF (4.2% vs. 4.9%), and acute kidney failure requiring haemodialysis (3.3% vs. 2.8%) was not significantly different between the discontinuation and continuation groups.

Comment

A predictable aftermath of the discovery that ACE2 represents the cell receptor through which SARS-CoV-2 enters human cells was the concern that ACEi and ARBs, through up-regulation of the expression of ACE2, may contribute to disease worsening and adverse outcomes related to COVID-19.² On the other hand, the binding of SARS-CoV-2 to ACE2 leads to ACE2 down-regulation, as part of the host defence mechanism to limit continued viral proliferation.³ As a consequence, an unopposed production of angiotensin II by ACE occurs, contributing to increased inflammation, fibrosis, thrombosis, vasoconstriction, vascular permeability, and lung damage. According to these findings, ACEi and ARBs may theoretically turn out to be protective against COVID-19 injury and adverse outcomes. Moreover, angiotensin (1–7), the product of ACE2, exerts several beneficial effects by triggering nitric oxide synthase, promoting vasorelaxation, and inhibiting oxidative stress.³

Large epidemiological studies as well as a meta-analysis of 16 studies⁴ confirmed the lack of association between ACEi/ARBs and a higher risk of infection or more severe or fatal course of COVID-19.^{5,6}

BRACE CORONA was the first RCT specifically designed to determine whether ACEi or ARBs are beneficial, harmful, or neutral with respect to clinical outcomes in COVID-19.¹ Its results showed that withdrawing ACEi/ARBs did not affect the number of days alive and out of the hospital, in the whole study population and across major predefined subgroups.¹ Although the study was not powered to assess the effects of ACEi/ARBs withdrawal on the secondary endpoints, it is interesting to note that most cardiovascular and renal events trended in favour of continuing renin-angiotensin-aldosterone-system (RAAS)-inhibitory therapy,¹ suggesting that withdrawal of effective cardioprotective drugs during COVID-19 may actually be detrimental.

The authors recognize some limitations of the study, including the restriction to the in-hospital clinical setting, the lack of information about the effects of RAAS inhibitors on infection susceptibility, and the limited number of HF patients.¹ It should also be highlighted that most patients received ARBs (83%) and had a relatively low-risk profile, in terms of disease severity and in-hospital mortality.¹ Moreover, a short-term temporary withdrawal of ACEi/ARBs at randomization cannot be considered equivalent to the absence of previous drug exposure, in view of their long-lasting structural and functional cardiovascular and renal effects.

The REPLACE COVID (Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019) trial of 152 hypertensive patients (mean age 62 years; 45% women) randomized to continue or discontinue ACEi/ARBs also demonstrated that there were no significant differences between groups in the incidence of the primary outcome, consisting in a global rank score of time to death, duration of mechanical ventilation or extracorporeal membrane oxygenation, time on renal replacement, or inotropic or vasopressor therapy and multiorgan dysfunction during hospitalization.⁷ Another ongoing trial—RAMIC (Ramipril for the Treatment of COVID-19)—is investigating the potential benefits of ramipril 2.5 mg compared to placebo in improving survival, reducing intensive care unit admissions, or use of mechanical ventilator support in 560 patients admitted to hospital for severe COVID-19 disease.⁸

The BRACE CORONA trial supports the current recommendation to continue treatment with ACEi or ARBs during hospitalization for COVID-19 since these drugs are not associated with a worse course of the disease and the opposite may be true.

Supplementary material

supplementary material is available at European Heart Journal online.

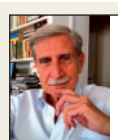
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