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CORRESPONDENCE

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Long-term effects of discontinuing renin–angiotensin system inhibitors in COVID-19

To the Editors:

Several randomized trials investigated the effects of discontinuing chronic treatment with renin–angiotensin system inhibitors (RASi) in COVID-19 with overall neutral results in the short term (within 30 days). However, temporary discontinuation of RASi might have effects that occur beyond 30 days and were missed by the short follow-up of previous trials.[1–3] Importantly, half of the survivors of COVID-19 develop post-acute sequelae of SARS-CoV-2 infection (PASC),[4] which could potentially be affected by RASi discontinuation.

To address this, we conducted a long-term follow-up of patients enrolled in ACEI-COVID trial (NCT04353596), which was previously published.[1] ACEI-COVID was a prospective, randomized, multicentre trial that evaluated the

TABLE 1 Follow-up characteristics

	Discontinuation group ($n = 53$)	Continuation group ($n = 46$)	p value
Prevalence of PASC			
After 30 days	32 (60%)	24 (52%)	0.411
After 3 months	27 (51%)	19 (41%)	0.338
After 12 months	21 (40%)	14 (30%)	0.340
Components of PASC after 30 days			
Fatigue	23 (43%)	16 (35%)	0.382
Dyspnoea	24 (45%)	13 (28%)	0.081
Vertigo	9 (17%)	2 (4%)	0.046
Depression	3 (6%)	6 (13%)	0.202
Myalgia	4 (8%)	3 (7%)	0.843
Cough	5 (9%)	2 (4%)	0.325
Chest pain	3 (6%)	4 (9%)	0.557
Headache	4 (8%)	2 (4%)	0.506
Taste/smell disorder	4 (8%)	2 (4%)	0.506
Memory deficits	4 (8%)	2 (4%)	0.506
Sleep disorder	2 (4%)	2 (4%)	0.885
Flu-like symptoms	2 (4%)	1 (2%)	0.643
Diarrhoea	3 (6%)	0 (0%)	0.101
Palpitations	3 (6%)	0 (0%)	0.101
Loss of appetite	1 (2%)	1 (2%)	0.919
Paraesthesia	0 (0%)	2 (4%)	0.125
Antihypertensive treatment			
RASi treatment	42 (79%)	43 (94%)	0.043
Alternative antihypertensive treatment	6 (11%)	1 (2%)	0.077
Blood pressure control			
Normal (<140/90 mm Hg)	48 (91%)	41 (89%)	0.572
EQ-5D-5L questionnaire			
EQ VAS	80 (10.0)	78 (13.0)	0.138
EQ level sum score	6 (4.0)	7 (4.0)	0.126

Note: Data are median (interquartile range) or *n* (%). Two-sided Wilcoxon Mann–Whitney rank sum test or chi-square tests were used as appropriate.
Abbreviations: PASC, post-acute sequelae of SARS-CoV-2 infection; RASi, renin–angiotensin system inhibitors; VAS, visual analogue scale.

effects of a 30-day discontinuation of chronic treatment with RASi on the maximum severity of disease in 204 patients. Due to regulatory reasons, this post hoc analysis was restricted to the 115 Austrian patients, who, however, did not differ with respect to their baseline characteristics from the original study population. Fifty-eight (50%) patients had been assigned to the discontinuation and 57 (50%) patients to the continuation group. Per protocol, patients had been instructed to resume their medications after 30 days or to consult their treating physician.

Patients were contacted for a detailed telephone interview after a median of 367 days (interquartile range 356–389) after randomization. If a patient could not be reached, vital status was obtained from their relatives or treating physicians. One patient of the discontinuation group was lost to follow-up. With the exception of chronic obstructive pulmonary disease, which was more common in the continuation group (10% vs. 26%; $p = 0.027$), baseline characteristics were balanced between the two treatment groups.

Within the follow-up period, five patients (9%) died in the discontinuation group and 11 patients (19%) died in the continuation group (log-rank $p = 0.101$). Of these, one death in the discontinuation group and two deaths in the continuation group occurred after 30 days. PASC were frequent but not significantly different between the 53 patients of the discontinuation group and the 46 patients of the continuation group after 30 days, 3 months and 12 months (Table 1). The most commonly reported symptoms were fatigue (39%) and dyspnoea (37%). There was also no difference in quality of life at 12 months as assessed by the EQ-5D-5L-questionnaire (Table 1). Four patients (8%) in the discontinuation group and five patients (11%) in the continuation group were re-hospitalized due to COVID-19-related symptoms but still alive during follow-up ($p = 0.543$). At 12 months, RASi treatment was less frequent in the discontinuation group than in the continuation group (79% vs. 94%; $p = 0.043$), but self-reported blood pressure control did not significantly differ between both groups (Table 1).

Our findings do not suggest that temporary discontinuation of chronic RASi treatment affects the development of PASC or has negative impact on long-term outcomes.

AUTHOR CONTRIBUTION

Fabian Theurl: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Nikolay Sappler:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Konstantinos D. Rizas:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Steffen Massberg:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Axel Bauer:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Michael Schreinlechner:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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KEYWORDS

antihypertensive drugs, COVID-19, hypertension, renin–angiotensin-system inhibitors (RASi), SARS-CoV-2

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

De-identified data collected during the conduct of the study can be made available for collaborative analyses on request after appropriate data sharing agreements have been concluded. Data will be made available after review and approval of research proposals by the principal investigators, to the extent permitted by existing local regulations and data sharing agreements. Proposals should be addressed to the corresponding authors.

HUMAN ETHICS APPROVAL DECLARATION

The trial design was approved by the local ethics committee in Innsbruck (Approval number ECS 1083/2020) as well as by the legal authorities in Austria (Austrian Agency for Health and Food Safety). All patients have given informed consent. Clinical Trial registration: NCT04353596 at https://clinicaltrials.gov

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