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Inhibitors of the renin–angiotensin–aldosterone system and COVID-19 in critically ill elderly patients

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus that causes COVID-19, uses the membrane-bound form of the aminopeptidase angiotensin-converting enzyme 2 (ACE2) to enter cells. Since ACE2 is centrally involved in the regulation of the renin–angiotensin–aldosterone system (RAAS), it has been speculated that RAAS inhibitors influence clinical courses. Mehta *et al.*[1] found no association between use of RAAS inhibitors and likelihood of COVID-19 testing positivity in 18 472 patients. Reynolds *et al.* performed a study based on data from electronic health records (5894 COVID-19 cases), where a Bayesian analysis showed no positive association of RAAS inhibitors with either a positive test result or severe illness.[2] Mancia *et al.*[3] also found no evidence in a population-based case-control study (6272 case-patients) for RAAS inhibitors to affect the risk of contracting COVID-19.

However, although these retrospective studies report essential data, they are of limited use to inform on elderly, comorbid and severely ill patients, who represent the most vulnerable group of patients affected by COVID-19 and are also most likely treated with RAAS inhibitors within the general population. To investigate special clinical features in COVID-19, the COVIP study (Very old intensive care patients, VIP network; NCT04321265) is ongoing. COVIP prospectively includes patients equal to or above 70 years of age with proven COVID-19 who are admitted to an intensive care unit (ICU). A total of 244 ICUs in 38 countries are registered to participate in COVIP. The primary endpoint is death after 30 days. Inclusion criteria are (i) age ≥70 years, (ii) ICU admission, and (iii) infection with SARS-CoV-2. Furthermore, a follow-up will be performed after 3 months to assess death and quality of life. The prospective design aims to create high-quality data about risk factors, comorbidities, pre-existing frailty, ICU-treatment including treatment limitations, and the use of experimental drugs in this critically ill patient collective of elderly patients. An interim analysis was performed on 7th of May with respect to RAAS inhibitor use.

In total, 324 patients were evaluated (*Table 1*): 157 (48%) were on RAAS inhibitors, 62 (19%) on angiotensin-converting enzyme inhibitors (ACE-I), and 95 (29%) on angiotensin II receptor blockers (ARB) before disease onset. Overall ICU mortality was 45% and was similar between patients with and without previous ARB (45% vs. 45%; $P = 0.98$), but lower in patients with previous ACE-I (31% vs. 49%; $P = 0.01$). A propensity for being on ACE-I was calculated using logistic regression, the covariates were age, body mass index, sex, sequential organ failure assessment (SOFA) score, as well as existing comorbidities of chronic heart failure, ischaemic heart disease, renal insufficiency, chronic pulmonary disease, arterial hypertension, and diabetes mellitus (*Table 1*). The primary endpoint was ICU mortality. Both univariable (Model 1) and multivariable (Model 2, propensity score correction) logistic regression models were built to evaluate associations with the primary endpoint. Odds ratios (OR, Model 1, *Table 1*) and adjusted ORs (aOR, Model 2) with respective 95% confidence intervals (CIs) were calculated. The univariate association of previous ACE-I with lower mortality (OR 0.46, 95% CI 0.26–0.84; $P = 0.01$; *Table 1*) remained statistically significant after propensity score adjustment (aOR 0.32, 95% CI 0.15–0.67; $P = 0.002$).

In conclusion, in a prospective study of elderly, critically ill and comorbid patients, we do find a beneficial association of previous ACE-I use with ICU survival. The current data confirms the notion that there is either a positive or no effect of RAAS inhibitor use. In addition, our data support the current view that continuation of RAAS inhibitor use should be

Table 1 Patient characteristics in all patients and in survivors and non-survivors, respectively

	All patients ($n = 324$)	Survivors ($n = 177$)	Non-survivors ($n = 147$)	*P*-values	OR (95% CI)
Age	75 (70–93)	74 (70–93)	77 (70–88)	<0.0001*	—
BMI	26.8 (18.3–51.4)	26.9 (18.3–41.5)	26.5 (18.3–51.4)	0.65	—
Male/female sex	224/100 (69/31)	116/61 (52/61)	108/39 (48/39)	0.12	1.46 (0.90–2.35)
SOFA score	6 (1–17)	5 (2–13)	7 (1–17)	<0.0001*	—
Chronic heart failure	45 (14.1)	20 (11.5)	25 (17.2)	0.14	1.60 (0.85–3.03)
Ischaemic heart disease	63 (19.7)	31 (17.8)	32 (22.1)	0.40	1.31 (0.75–2.27)
Renal insufficiency	49 (15.2)	18 (10.2)	31 (21.1)	0.007*	2.35 (1.25–4.40)*
Pulmonary disease	82 (25.5)	41 (23.3)	41 (28.3)	0.31	1.30 (0.79–2.15)
Arterial hypertension	211 (65.1)	115 (65.0)	96 (65.3)	0.95	1.02 (0.64–1.61)
Diabetes mellitus	95 (29.4)	48 (27.1)	47 (32.2)	0.32	1.28 (0.79–2.06)
ACE-I	62 (19.1)	43 (24.3)	19 (12.9)	0.01*	0.46 (0.26–0.84)*
ARB	95 (29.3)	52 (29.4)	43 (29.3)	0.98	0.99 (0.62–1.61)

All continuous variables were non-normally distributed, are presented as median (range) and were compared using Mann–Whitney *U* tests; categorical variables are presented as *n* (%) and were compared using χ^2 tests; *P*-values and Cochran–Mantel–Haenszel estimates are reported, presented as odds ratios (ORs) with 95% confidence intervals (CIs); statistical significance was assumed at $P < 0.05$ and is indicated by asterisk (*).

recommended.[4] In summary, this is the first prospective multinational study that demonstrates beneficial associations of ACE-I in high-risk COVID-19 patients and thus impact on daily practice. However, further research evaluating potential causality is warranted.

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Christian Jung[1]*, Raphael Romano Bruno[1], Bernhard Wernly[2], Michael Joannidis[3], Sandra Oeyen[4], Tilemachos Zafeiridis[5], Brian Marsh[6], Finn H. Andersen[7,8], Rui Moreno[9], Ana Margarida Fernandes[9], Antonio Artigas[10], Bernardo Bollen Pinto[11], Joerg Schefold[12], Georg Wolff[1], Malte Kelm[1], Dylan W. De Lange[13], Bertrand Guidet[14], Hans Flaatten[15,16], and Jesper Fjølner[17]; on behalf of the COVIP study group

[1]Department of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, Heinrich-Heine-University Duesseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany; [2]Department of Cardiology, Paracelsus Medical University, Müllner Hauptstraße 48, A-5020 Salzburg, Austria; [3]Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria; [4]Department of Intensive Care 1K12IC, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Gent, Belgium; [5]Intensive Care Unit, General Hospital of Larissa, Tsakalof 1, Larisa 412 21, Greece; [6]Mater Misericordiae University Hospital, Eccles St, Northside, Dublin 7, D07 R2WY, Ireland; [7]Department of Anaesthesia and Intensive Care, Ålesund Hospital, Åsehaugen 5, 6017 Ålesund, Norway; [8]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway; [9]Unidade de Cuidados Intensivos Neurocríticos e Trauma, Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Faculdade de Ciências Médicas de Lisboa, Nova Médical School, R. José António Serrano, 1150-199 Lisboa, Portugal; [10]Department of Intensive Care Medicine, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Parc Taulí, 1, 08208 Sabadell, Spain; [11]Department of Acute Medicine, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland; [12]Department of Intensive Care Medicine, Inselspital, Universitätsspital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland; [13]Department of Intensive Care Medicine, University Medical Center, University Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; [14]Assistance Publique—Hôpitaux de Paris, Hôpital Saint-Antoine, service de réanimation médicale, 184 Rue du Faubourg Saint-Antoine, Paris F-75012, France; [15]Department of Clinical Medecine, University of Bergen, Jonas Lies vei 65, 5021 Bergen, Norway; [16]Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Jonas Lies vei 65, 5021 Bergen, Norway; and [17]Department of Intensive Care, Aarhus University Hospital, Palle Juul-Jensens Blvd. 161, 8200 Aarhus N, Denmark

*Corresponding author. Tel: +492118118912, Email: christian.jung@med.uni-duesseldorf.de