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.

substantial experience of ICUs with venovenous ECMO (defined by the authors as at least 30 cases annually) was found to increase survival to 60%. Thus, centralisation of venovenous ECMO to dedicated high-volume expert units should be pursued, making mobile ECMO teams essential for realising this objective. Second, ventilatory management in the current study was derived from EOLIA. Although EOLIA is the best available randomised controlled trial on the use of ECMO versus protective conventional ventilation, it did not study the best mode of ventilation on ECMO. A driving pressure of 13 cm H_2O and a respiratory frequency of 20 breaths per min, as observed in the current study, will still place substantial mechanical power on a severely injured lung. Further investigation into different modes of mechanical ventilation during ECMO is needed to analyse whether the often observed pronounced reduction of pulmonary compliance with diffuse alveolar damage and risk of fibrotic change can be lessened. Anticoagulation will need to be individualised and adapted to different stages of COVID-19. In addition, a positive preliminary experience of combined cardiorespiratory support, applied from the start of ECMO in these patients, is interesting and promising.[11]

Finally, we do not know whether experience from the first wave can be transferred to the cases that follow. Almost all patients who now develop refractory respiratory failure have been pretreated with remdesivir and steroids, and have often remained on high-flow nasal oxygen or non-invasive ventilation for extended periods of time. Not uncommonly, severe hypercapnia with stiff lungs has become a leading problem necessitating ECMO.

In conclusion, to be able to combat COVID-19 lung failure successfully in the future, continuing supraregional interdisciplinary cooperation will be needed, as shown convincingly in the Greater Paris area. Still, thorough ongoing investigations are required and all the aforementioned aspects underline the clear need for more in-depth analysis of patient profiles, response to ECMO support, and, particularly, the careful assessment of treatment failures. Is the appalling death rate in this pandemic unavoidably due to overwhelming and unpreventable disease-related complications, or will optimised management and growing experience eventually overcome SARS-CoV-2? These questions remain to be answered.

RL is a consultant for Medtronic, LivaNova, and Eurosets, with all honoraria paid to Maastricht University. TM declares no competing interests.

*Roberto Lorusso, Thomas Mueller
roberto.lorusso@mumc.nl

Cardio-Thoracic Surgery Department, Heart & Vascular Centre, Maastricht University Medical Centre, Cardiovascular Research Institute Maastricht, Maastricht 6202 AZ, Netherlands (RL); Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany (TM)

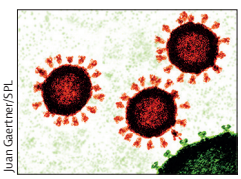
1 Lebreton G, Schmidt M, Ponnaiah M, et al. ECMO network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris: a multicentre cohort study. *Lancet Respir Med* 2021; published online April 19. https://doi.org/10.1016/S2213-2600(21)00096-5.
2 WHO. COVID-19 clinical management: living guidance. Jan 25, 2021. Geneva: World Health Organization, 2021.
3 Lorusso R, Combes A, Coco VL, De Piero ME, Belohlavek J. ECMO for COVID-19 patients in Europe and Israel. *Intensive Care Med* 2021; **47:** 344–48.
4 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020; **396:** 1071–78.
5 Shaefi S, Brenner SK, Gupta S, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Int Care Med* 2021; **47:** 208–21.
6 Sudapy A, Curtis RJ, Abrams D, et al. Allocating scarce intensive care resources during the COVID-19 pandemic: practical challenges to theoretical frameworks. *Lancet Respir Med* 2021; published online Jan 12. https://doi.org/10.1016/S2213-2600(20)30580-4.
7 Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378:** 1965–75.
8 Kowalewski M, Fina D, Słomka A, et al. COVID-19 and ECMO: the interplay between coagulation and inflammation-a narrative review. *Crit Care* 2020; **24:** 205.
9 Bermea RS, Raz Y, Sertic F, et al. Increased intracranial hemorrhage amid elevated inflammatory markers in those COVID-19 supported with extracorporeal membrane oxygenation. *Shock* 2021; published online Jan 20. https://doi.org/10.1097/SHK.0000000000001730.
10 Dweck MR, Bularga Am Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-10. *Eur Heart J Cardiovasc Imaging* 2020; **21:** 948–59.
11 Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *JAMA Surg* 2020; **155:** 990–92.

RAS inhibition and COVID-19: more questions than answers?

Published **Online** June 11, 2021 https://doi.org/10.1016/S2213-2600(21)00233-2

See **Articles** page 863

Since the beginning of the COVID-19 pandemic and the first reports of an increased mortality among patients with COVID-19 treated for hypertension, the potential role of renin–angiotensin system (RAS) blockers on the severity of the disease has been questioned.[1,2] Although RAS blockers have been associated with better outcomes in pneumonia models, they might also upregulate the expression of angiotensin-converting


Juan Gaertner/SPL

enzyme 2 (ACE2) receptor, which acts as a co-receptor for human cell infection by SARS-CoV-2 through the binding with the spike protein.[3-5] Following neutral and reassuring large observational studies and meta-analyses, two randomised trials have been done and published: the BRACE CORONA and the REPLACE COVID trials.[6,7] Both studies concluded an absence of effect of chronic RAS blockade on the course of COVID-19, as previously observed in observational studies.

The Stopping ACE-inhibitors in COVID-19 (ACEI-COVID19) trial by Bauer and colleagues, published in the *Lancet Respiratory Medicine*, is the third randomised study evaluating the risk and benefit of RAS blockers discontinuation on the severity of COVID-19.[8] This trial is specific in its inclusion of an older population who have comorbidities such as overweight, chronic obstructive pulmonary disease, hypertension, and heart failure. This was not intended by the design, but it rather reflects the characteristics of the patients admitted to hospital during the first waves of the disease in Europe. The raw results on the primary endpoint of this well-conducted study confirm the two previous trials: there is no effect of RAS blockers on the severity and evolution of the disease up to 30 days. In this high-risk population, exposed to a high mortality rate (one of ten patients died during the study period), there was no difference in mortality between the two groups. However, it would be overly simplistic to label this trial as negative or neutral on the basis of only the primary endpoint analysis. Bauer and colleagues underline that, after its peak, the mean sequential organ failure assessment scores in the discontinuation group decreased more rapidly and reached lower values than in the continuation group. They, therefore, suggest that discontinuation might lead to a faster and better recovery among these older, high-risk patients with COVID-19.

This conclusion should be interpreted with great caution, considering that it derives from secondary analyses in a study that did not meet its primary endpoint. Are these findings falsely positive? This is not the first time that a negative study has revealed positive findings in secondary outcomes or analyses.[9] The ASCOT-BPLA trial (amlodipine-based regimen *vs* atenolol-based regimen for the treatment of hypertension), is a famous example of such discrepancies. In the ASCOT-BPLA trial, the primary composite outcome (non-fatal myocardial infarction and coronary heart disease related death) did not reach significance, but almost all secondary outcomes, including all cause death, and non-fatal and fatal stroke, were significantly reduced by amlodipine.[10] The results of these secondary endpoints were considered as plausible, consistent within the study and across previous trials, and to be based on a strong rationale.

However, the same considerations cannot fully apply to the results of the ACEI-COVID trial: first, the secondary endpoints did not confirm any previous data from other non-randomised or randomised studies; second there is slender plausibility and no clear explanation for these results; third they derive from a small sample size study with insufficient power and inflation of the risk alpha. Thus, they should be considered for what they are: hypothesis generating, requiring confirmation and, should not be used to guide a clinical decision of RAS blockers discontinuation without more evidence. Although there is no safety signal in the discontinuation group, the risk of RAS blockers discontinuation is well known and the follow-up was probably too short to detect any difference in the adverse events rate between the two groups.[11,12]

Nevertheless, the ACEI-COVID study raises several key questions. Why might older patients have a benefit of discontinuation that younger patients do not have? Is it related to the kidney function or blood pressure control, or to the severity of lung damage, or to the expression ACE2 in this population? Is there a protective effect of calcium channel blockers (which have been used as a replacement therapy) on COVID-19? Why do the patients with COPD have a particular benefit from ACE discontinuation, when the use of RAS blockers in patients with COPD was associated with improved outcomes in observational studies before the COVID-19 era[13]?

The ACEI-COVID study adds more data to the existing evidence showing that RAS blockers should not be systematically discontinued in patients with COVID-19, but it leaves us also with more questions than answers.

MK has received consulting fees from Sanofi, Bayer, and Kiniksa, and research grants from Federation Francaise de Cardiologie and the French Ministry of Health. GM has received grants from Abbott, Amgen, AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Idorsia, Servier, Medtronic, Pfizer, and Quantum Genomics, and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Idorsia, Medtronic, and MSD.

*Mathieu Kerneis, Gilles Montalescot
mathieu.kerneis@aphp.fr

Sorbonne Université, ACTION Study Group, INSERM UMRS_1166, Institut de cardiologie (AP-HP), Paris, France

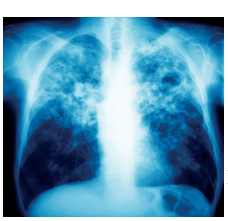
1 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.
2 Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; **8:** e21.
3 Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111:** 2605–10.
4 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181:** 271280.e8.
5 Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; **436:** 112–16.
6 Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. 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: a randomized clinical trial. *JAMA* 2021; **325:** 254–64.
7 Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med* 2021; **9:** 275–84.
8 Bauer A, Schreinlechner M, Sappler N, et al, Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. *Lancet Respir Med* 2021; published online June 11. https://doi.org/10.1016/S2213-2600(21)00214-9.
9 Pocock SJ, Stone GW. The primary outcome fails—what next? *N Engl J Med* 2016; **375:** 861–70.
10 Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.
11 van den Heuvel AF, van Gilst WH, van Veldhuisen DJ, de Vries RJ, Dunselman PH, Kingma JH. Long-term anti-ischemic effects of angiotensin-converting enzyme inhibition in patients after myocardial infarction. *J Am Coll Cardiol* 1997; **30:** 400–05.
12 Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019; **393:** 61–73.
13 Vasileiadis IE, Goudis CA, Giannakopoulou PT, Liu T. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers: a promising medication for chronic obstructive pulmonary disease? *COPD* 2018; **15:** 148–56.

A leap forward in assessing host-directed therapies for tuberculosis

With advances in diagnostic accuracy and therapeutic efficacy, 85% of people with pulmonary tuberculosis are successfully treated.[1] Despite favourable microbiological outcomes, long-term sequelae are common, including lung scarring leading to reduced pulmonary function and chronic respiratory symptoms.[2,3] Certain pulmonary function tests, such as FEV_1, correlate with long-term mortality,[4] yet few tuberculosis treatment trials have included lung function as a primary efficacy outcome.[5] Host-directed therapy, administered concurrently with standard tuberculosis therapy, could mitigate inflammation contributing to lung damage.[6]

We do not yet know which host-directed agents provide benefit for patients with tuberculosis, and there is no clear consensus on appropriate biomarkers, study endpoints, or agent selection criteria for trials investigating these therapies.[7] In a phase 2 trial reported in *The Lancet Respiratory Medicine*, Robert S Wallis and colleagues[8] evaluated the safety and efficacy of four candidate host-directed therapies (CC-11050, everolimus, auranofin, and ergocalciferol) plus rifabutin-substituted standard tuberculosis therapy compared with standard therapy alone.[8] Rifabutin was substituted for rifampicin to avoid drug interactions with everolimus and CC-11050. This trial recruited patients with a high baseline bacillary load and moderately advanced or far advanced radiographic disease. Such individuals have poor outcomes and might have the most to gain from effective host-directed therapies if, in fact, damage is—at least in part—reversible.[9]

Compared with control, CC-11050 and everolimus significantly increased FEV_1 (as a percentage of predicted) at day 180 (6·30%, 95% CI 0·06–12·54; p=0·048; and 6·56%, 0·18–12·95; p=0·044). Although a 6% increase in FEV_1 might seem modest, it is equivalent to an increase of 200 mL and is considerably higher than the difference deemed clinically relevant in trials of chronic obstructive pulmonary disease.[10] Auranofin and ergocalciferol did not show benefit. Furthermore, auranofin was associated with two treatment-attributable serious adverse events, comprising one death (due to intra-abdominal sepsis)


Pr Michel Brauner, ISM/SPL

Published **Online**
March 16, 2021
https://doi.org/10.1016/S2213-2600(20)30528-2

See **Articles** page 897