SPECIAL REPORT

Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19

Muthiah Vaduganathan, M.D., M.P.H., Orly Vardeny, Pharm.D., Thomas Michel, M.D., Ph.D., John J.V. McMurray, M.D., Marc A. Pfeffer, M.D., Ph.D., and Scott D. Solomon, M.D.

The renin–angiotensin–aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for the SARS epidemic in 2002 to 2004 and for the more recent coronavirus disease 2019 (Covid-19) pandemic, respectively, interface with the RAAS through angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters RAAS activation but also functions as a receptor for both SARS viruses.^{1,2} The interaction between the SARS viruses and ACE2 has been proposed as a potential factor in their infectivity,3,4 and there are concerns about the use of RAAS inhibitors that may alter ACE2 and whether variation in ACE2 expression may be in part responsible for disease virulence in the ongoing Covid-19 pandemic.5-8 Indeed, some media sources and health systems have recently called for the discontinuation of ACE inhibitors and angiotensin-receptor blockers (ARBs), both prophylactically and in the context of suspected Covid-19.

Given the common use of ACE inhibitors and ARBs worldwide, guidance on the use of these drugs in patients with Covid-19 is urgently needed. Here, we highlight that the data in humans are too limited to support or refute these hypotheses and concerns. Specifically, we discuss the uncertain effects of RAAS blockers on ACE2 levels and activity in humans, and we propose an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. We also explicitly raise the concern that withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected Covid-19.

COVID-19 AND OLDER ADULTS WITH COEXISTING CONDITIONS

Initial reports⁵⁻⁸ have called attention to the potential overrepresentation of hypertension among patients with Covid-19. In the largest of several case series from China that have been released during the Covid-19 pandemic (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), hypertension was the most frequent coexisting condition in 1099 patients, with an estimated prevalence of 15%; however, this estimate appears to be lower than the estimated prevalence of hypertension seen with other viral infections¹⁰ and in the general population in China.^{11,12}

Coexisting conditions, including hypertension, have consistently been reported to be more common among patients with Covid-19 who have had severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died than among patients who have had mild illness. There are concerns that medical management of these coexisting conditions, including the use of RAAS inhibitors, may have contributed to the adverse health outcomes observed. However, these conditions appear to track closely with advancing age,13 which is emerging as the strongest predictor of Covid-19-related death.¹⁴ Unfortunately, reports to date have not rigorously accounted for age or other key factors that contribute to health as potential confounders in risk prediction. With other infective illnesses, coexisting conditions such as hypertension have been key prognostic determinants,10 and this also appears to be the case with Covid-19.15

It is important to note that, despite inferences

about the use of background RAAS inhibitors, specific details have been lacking in studies (Table S1). Population-based studies have estimated that only 30 to 40% of patients in China who have hypertension are treated with any antihypertensive therapy; RAAS inhibitors are used alone or in combination in 25 to 30% of these treated patients. Given such estimates, only a fraction of patients with Covid-19, at least in China, are anticipated to have been previously treated with RAAS inhibitors. Data showing patterns of use of RAAS inhibitors and associated health outcomes that rigorously account for treatment indication and illness severity among patients with Covid-19 are needed.

UNCERTAIN EFFECTS OF RAAS INHIBITORS ON ACE2 IN HUMANS

Tissue-specific and circulating components of the RAAS make up a complex intersecting network of regulatory and counterregulatory peptides (Fig. 1). ACE2 is a key counterregulatory enzyme that degrades angiotensin II to angiotensin-(1-7), thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis. Although angiotensin II is the primary substrate of ACE2, that enzyme also cleaves angiotensin I to angiotensin-(1-9) and participates in the hydrolysis of other peptides.¹⁶ In studies in humans, tissue samples from 15 organs have shown that ACE2 is expressed broadly, including in the heart and kidneys, as well as on the principal target cells for SARS-CoV-2 (and the site of dominant injury), the lung alveolar epithelial cells.¹⁷ Of interest, the circulating levels of soluble ACE2 are low and the functional role of ACE2 in the lungs appears to be relatively minimal under normal conditions¹⁸ but may be up-regulated in certain clinical states.

Because ACE inhibitors and ARBs have different effects on angiotensin II, the primary substrate of ACE2, the effects of these agents on ACE2 levels and activity may be anticipated to differ. Despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct. As a result, ACE inhibitors in clinical use do not directly affect ACE2 activity. Experimental animal models have shown mixed findings with respect to the effects of ACE inhibitors on ACE2 levels

or activity in tissue.²⁰⁻²⁵ Similarly, animal models have had inconsistent findings with respect to the effects of ARBs on ACE2, with some showing that ARBs may increase messenger RNA expression or protein levels of ACE2 in tissue^{21,26-34} and others showing no effect.²³

In contrast to available animal models, there are few studies in humans regarding the effects of RAAS inhibition on ACE2 expression. In one study, the intravenous administration of ACE inhibitors in patients with coronary artery disease did not influence angiotensin-(1-7) production, a finding that calls into question whether ACE inhibitors have any direct effects on ACE2-directed angiotensin II metabolism.35 Similarly, in another study, among patients with hypertension, angiotensin-(1-7) levels appeared to be unaffected after initial treatment with the ACE inhibitor captopril; however, with exposure to captopril monotherapy over a period of 6 months, angiotensin-(1–7) levels increased.³⁶ Furthermore, few studies have examined plasma ACE2 activity or urinary ACE2 levels in patients who have received long-term treatment with RAAS inhibitors. In cross-sectional studies involving patients with heart failure,37 atrial fibrillation,38 aortic stenosis,³⁹ and coronary artery disease,⁴⁰ plasma ACE2 activity was not higher among patients who were taking ACE inhibitors or ARBs than among untreated patients. In a longitudinal cohort study involving Japanese patients with hypertension, urinary ACE2 levels were higher among patients who received long-term treatment with the ARB olmesartan than among untreated control patients, but that association was not observed with the ACE inhibitor enalapril or with other ARBs (losartan, candesartan, valsartan, and telmisartan).41 Previous treatment with ACE inhibitors was associated with increased intestinal messenger RNA levels of ACE2 in one study, but that association was not observed with ARBs25; data are lacking regarding the effects of RAAS inhibitors on lung-specific expression of ACE2.

These seemingly conflicting data indicate the complexity underlying RAAS responses to pathway modulators and reinforce the concept that findings from preclinical models may not readily translate to human physiology. Such data do suggest that effects on ACE2 should not be assumed to be uniform across RAAS inhibitors or even in

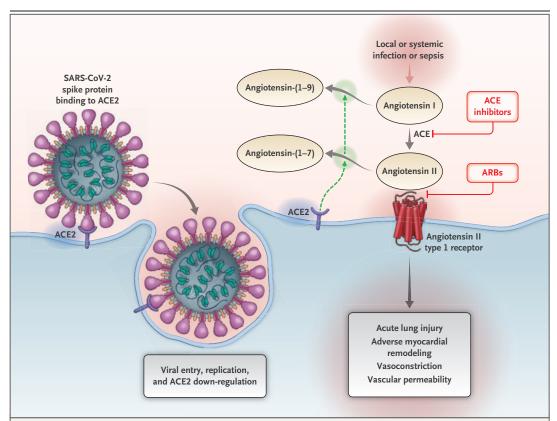


Figure 1. Interaction between SARS-CoV-2 and the Renin-Angiotensin-Aldosterone System.

Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

response to therapies within a given drug class.41 It is important to note that the plasma ACE2 level may not be a reliable indicator of the activity of the full-length membrane-bound form, in part because ACE2 is shed from the membrane, a process that appears to be separately regulated by an endogenous inhibitor.⁴² In addition to the degree of expression, the biologic relevance of ACE2 may vary according to tissue and clinical state. Unfortunately, data showing the effects of ACE inhibitors, ARBs, and other RAAS inhibitors on lung-specific expression of ACE2 in experimental animal models and in humans are lacking. Furthermore, even if RAAS inhibitors modify ACE2 levels or activity (or both) in target tissue beds, clinical data are lacking to indicate whether this would in turn facilitate greater engagement and entry of SARS-CoV-2 spike protein. Further mechanistic studies in humans are needed to better define the unique interplay between SARS-CoV-2 and the RAAS network.

POTENTIAL FOR BENEFIT RATHER THAN HARM OF RAAS BLOCKERS IN COVID-19

SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently downregulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated but unproven that unabated angiotensin II activity may be in part responsible for organ injury in Covid-19.^{43,44} After the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance

on cell surfaces. 45 Continued viral infection and replication contribute to reduced membrane ACE2 expression, at least in vitro in cultured cells.46 Down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin47 and may result in unopposed angiotensin II accumulation and local RAAS activation. Indeed, in experimental mouse models, exposure to SARS-CoV-1 spike protein induced acute lung injury, which is limited by RAAS blockade.45 Other mouse models have suggested that dysregulation of ACE2 may mediate acute lung injury that is secondary to virulent strains of influenza48,49 and respiratory syncytial virus.⁵⁰ In a small study, patients with Covid-19 appeared to have elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and degree of lung injury.44 Restoration of ACE2 through the administration of recombinant ACE2 appeared to reverse this devastating lung-injury process in preclinical models of other viral infections^{49,50} and safely reduced angiotensin II levels in a phase 2 trial evaluating acute respiratory distress syndrome in humans.⁵¹

Dysregulated ACE2 may theoretically also attenuate cardioprotection in the context of myocardial involvement and abnormal pulmonary hemodynamics^{52,53} in Covid-19. Markers of myocardial injury have been shown to be elevated during the disease course of Covid-1954 and to increase rapidly with clinical deterioration and preceding death.¹⁴ Many viruses are cardiotropic, and subclinical viral myocarditis is commonly seen in viremia associated with a wide range of infectious agents. ACE2 has a well-recognized role in myocardial recovery and injury response; in one study, ACE2 knockout in animal models contributed to adverse left ventricular remodeling in response to acute injury driven by angiotensin II.55 In autopsies of patients who died from SARS, 35% of heart samples showed the presence of viral RNA, which in turn was associated with reduced ACE2 protein expression.⁵⁶ Administration of recombinant ACE2 normalizes angiotensin II levels in human explanted hearts with dilated cardiomyopathy.⁵⁷ These hypotheses have prompted trials to test whether the provision of recombinant ACE2 protein may be beneficial in restoring balance to the RAAS network and potentially preventing organ injury (ClinicalTrials

.gov number, NCT04287686). In addition, paired trials of losartan as a treatment for Covid-19 are being conducted among patients who have not previously received treatment with a RAAS inhibitor and are either hospitalized (NCT04312009) or not hospitalized (NCT04311177).

MAINTENANCE OF RAAS INHIBITORS WITH KNOWN OR SUSPECTED COVID-19

Despite these theoretical uncertainties regarding whether pharmacologic regulation of ACE2 may influence the infectivity of SARS-CoV-2, there is clear potential for harm related to the withdrawal of RAAS inhibitors in patients in otherwise stable condition. Covid-19 is particularly severe in patients with underlying cardiovascular diseases,⁹ and in many of these patients, active myocardial injury,^{14,54,58-60} myocardial stress,⁵⁹ and cardiomyopathy⁵⁹ develop during the course of illness. RAAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients.

Although rates of heart failure have been infrequently reported in epidemiologic reports from China to date, the prevalence of heart failure among critically ill patients with Covid-19 in the United States may be high (>40%).59 In the Quinapril Heart Failure Trial, among patients with chronic symptomatic heart failure, withdrawal of quinapril resulted in a progressive decline in clinical status.61 In the TRED-HF trial, among asymptomatic patients with heart failure with recovered left ventricular ejection fraction, the phased withdrawal of medical therapy (including RAAS inhibitors) resulted in rapid relapse of dilated cardiomyopathy.62 In addition, RAAS inhibitors are a cornerstone of therapy after myocardial infarction: maintenance of therapy in the days to weeks after the index event has been shown to reduce early mortality.⁶³ Among patients with unstable clinical status, myocardial injury associated with Covid-19 may pose even higher early risks after withdrawal of RAAS inhibitors.

Withdrawal of RAAS inhibitors that are being administered for the management of hypertension may be less risky than withdrawal of RAAS inhibitors that are being administered for conditions in which they are considered guidelinedirected therapy but may be associated with other challenges. Switching from a RAAS inhibitor to another antihypertensive therapy in a stable ambulatory patient may require careful follow-up to avoid rebound increases in blood pressure. In addition, selection of dose-equivalent antihypertensive therapies may be challenging in practice and may be patient-dependent. Even small and short-lived periods of blood pressure instability after a therapeutic change have been associated with excess cardiovascular risk.64-66 This may be an especially important consideration in patients with Covid-19, which appears to result in a state of RAAS activation,44 and in settings (e.g., China) where baseline blood-pressure control is infrequently reached at the population level. 11,12

The effects of withdrawing RAAS inhibitors or switching treatments are uncertain among patients with chronic kidney disease. Although reported rates of chronic kidney disease appear to be low among hospitalized patients with Covid-19 in China (1 to 3%) (Table S1), the prevalence may be higher among patients who are critically ill and among those in other geographic regions.⁵⁹ Many patients have varying degrees of acute kidney injury during illness.^{14,67,68} For these high-risk patients, individualized treatment decisions regarding the maintenance of RAAS inhibitors that

Key Points Related to the Interplay between Covid-19 and the Renin-Angiotensin-Aldosterone System

- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19
- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19
- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes
- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19

are guided by hemodynamic status, renal function, and clinical stability are recommended.

On the basis of the available evidence, we think that, despite the theoretical concerns and uncertainty regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of Covid-19, RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19 (see text box), a position now supported by multiple specialty societies (Table S2). Although additional data may further inform the treatment of high-risk patients with Covid-19, clinicians need to be cognizant of the unintended consequences of prematurely discontinuing proven therapies in response to hypothetical concerns that may be based on incomplete experimental evidence.⁶⁹

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston (M.V., T.M., M.A.P., S.D.S.); the Center for Care Delivery and Outcomes Research, Minneapolis VA Health Care System, and University of Minnesota, Minneapolis (O.V.); and the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.). Address reprint requests to Dr. Solomon at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at ssolomon@bwh.harvard.edu.

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- 1. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.
- **2.** 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 March 4 (Epub ahead of print).
- **3.** Li W, Zhang C, Sui J, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 2005; 24:1634-43.
- **4.** Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3.
- 5. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020 March 11 (Epub ahead of print).
- **6.** Sommerstein R, Gräni C. Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk factor for fatal COVID-19. BMJ 2020;368:m810 (https://www.bmj.com/content/368/bmj.m810/rr-2).
- **7.** Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020 March 11 (Epub ahead of print).
- 8. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med 2020 March 18 (Epub ahead of print).

- **9.** Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. DOI: 10.1056/NEJMoa2002032.
- **10.** Al-Baadani AM, Elzein FE, Alhemyadi SA, Khan OA, Albenmousa AH, Idrees MM. Characteristics and outcome of viral pneumonia caused by influenza and Middle East respiratory syndrome-coronavirus infections: a 4-year experience from a tertiary care center. Ann Thorac Med 2019;14:179-85.
- **11.** Wang Z, Chen Z, Zhang L, et al. Status of hypertension in China: results from the China Hypertension Survey, 2012-2015. Circulation 2018;137:2344-56.
- **12.** Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet 2017;390:2549-58.
- **13.** Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med 2020 (https://www.nature.com/articles/s41591-020-0822-7).
- 14. 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 March 11 (Epub ahead of print).
- **15.** Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020 March 12 (Epub ahead of print).
- **16.** Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem 2002;277:14838-43.
- 17. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.
- **18.** Serfozo P, Wysocki J, Gulua G, et al. Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyloligopeptidase)-dependent and ACE2 (angiotensin-converting enzyme 2)-independent. Hypertension 2020;75:173-82.
- **19.** Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J 2004;383:45-51.
- **20.** Hamming I, van Goor H, Turner AJ, et al. Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats. Exp Physiol 2008;93:631-8.
- **21.** 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.
- **22.** Ocaranza MP, Godoy I, Jalil JE, et al. Enalapril attenuates downregulation of angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. Hypertension 2006;48:572-8.
- **23.** Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK, Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial infarction: implications for future therapeutic directions. Clin Sci (Lond) 2012;123:649-58.
- **24.** Burrell LM, Risvanis J, Kubota E, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J 2005; 26:369-75.
- Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids 2015;47:693-705.
 Soler MJ, Ye M, Wysocki J, William J, Lloveras J, Batlle D. Localization of ACE2 in the renal vasculature: amplification by angiotensin II type 1 receptor blockade using telmisartan. Am J Physiol Renal Physiol 2009;296:F398-F405.

- **27.** Sukumaran V, Veeraveedu PT, Gurusamy N, et al. Olmesartan attenuates the development of heart failure after experimental autoimmune myocarditis in rats through the modulation of ANG 1-7 Mas receptor. Mol Cell Endocrinol 2012;351:208-19.
- **28.** Lakshmanan AP, Thandavarayan RA, Watanabe K, et al. Modulation of AT-1R/MAPK cascade by an olmesartan treatment attenuates diabetic nephropathy in streptozotocin-induced diabetic mice. Mol Cell Endocrinol 2012;348:104-11.
- **29.** Sukumaran V, Veeraveedu PT, Lakshmanan AP, et al. Olmesartan medoxomil treatment potently improves cardiac myosin-induced dilated cardiomyopathy via the modulation of ACE-2 and ANG 1-7 Mas receptor. Free Radic Res 2012;46:850-60.
- **30.** Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension 2004;43:970-6.
- **31.** Igase M, Strawn WB, Gallagher PE, Geary RL, Ferrario CM. Angiotensin II AT1 receptors regulate ACE2 and angiotensin-(1-7) expression in the aorta of spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 2005;289:H1013-H1019.
- **32.** Zhong J-C, Ye J-Y, Jin H-Y, et al. Telmisartan attenuates aortic hypertrophy in hypertensive rats by the modulation of ACE2 and profilin-1 expression. Regul Pept 2011;166:90-7.
- **33.** Sukumaran V, Veeraveedu PT, Gurusamy N, et al. Cardioprotective effects of telmisartan against heart failure in rats induced by experimental autoimmune myocarditis through the modulation of angiotensin-converting enzyme-2/angiotensin 1-7/mas receptor axis. Int J Biol Sci 2011;7:1077-92.
- **34.** Sukumaran V, Tsuchimochi H, Tatsumi E, Shirai M, Pearson JT. Azilsartan ameliorates diabetic cardiomyopathy in young db/db mice through the modulation of ACE-2/ANG 1-7/Mas receptor cascade. Biochem Pharmacol 2017;144:90-9.
- **35.** Campbell DJ, Zeitz CJ, Esler MD, Horowitz JD. Evidence against a major role for angiotensin converting enzyme-related carboxypeptidase (ACE2) in angiotensin peptide metabolism in the human coronary circulation. J Hypertens 2004;22:1971-6.
- **36.** Luque M, Martin P, Martell N, Fernandez C, Brosnihan KB, Ferrario CM. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. J Hypertens 1996;14:799-805.
- **37.** Epelman S, Shrestha K, Troughton RW, et al. Soluble angiotensin-converting enzyme 2 in human heart failure: relation with myocardial function and clinical outcomes. J Card Fail 2009;15:565-71.
- **38.** Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E, Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. Europace 2017;19: 1280-7.
- **39.** Ramchand J, Patel SK, Kearney LG, et al. Plasma ACE2 activity predicts mortality in aortic stenosis and is associated with severe myocardial fibrosis. JACC Cardiovasc Imaging 2020;13:655-64.
- **40.** Ramchand J, Patel SK, Srivastava PM, Farouque O, Burrell LM. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. PLoS One 2018; 13(6):e0198144.
- **41.** Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens 2015;28:15-21.
- **42.** Lambert DW, Yarski M, Warner FJ, et al. Tumor necrosis factor- α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J Biol Chem 2005;280:30113-9.
- 43. Gurwitz D. Angiotensin receptor blockers as tentative SARS-

- CoV-2 therapeutics. Drug Dev Res 2020 March 4 (Epub ahead of print).
- **44.** Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-74.
- **45.** Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-9.
- **46.** Dijkman R, Jebbink MF, Deijs M, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol 2012-93-1924-9
- **47.** Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg⁹ bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol Lung Cell Mol Physiol 2018;314:L17-L31.
- **48.** Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep 2014;4:7027.
- **49.** Zou Z, Yan Y, Shu Y, et al. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014:5:3594.
- **50.** Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep 2016;6:19840.
- **51.** Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017;21:234.
- **52.** Hemnes AR, Rathinasabapathy A, Austin EA, et al. A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension. Eur Respir J 2018;51(6).
- **53.** Tan WSD, Liao W, Zhou S, Mei D, Wong W-SF. Targeting the renin-angiotensin system as novel therapeutic strategy for pulmonary diseases. Curr Opin Pharmacol 2018;40:9-17.
- **54.** Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020 March 25 (Epub ahead of print).
- **55.** Kassiri Z, Zhong J, Guo D, et al. Loss of angiotensin-converting enzyme 2 accelerates maladaptive left ventricular remodeling in response to myocardial infarction. Circ Heart Fail 2009;2: 446-55.
- **56.** Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39:618-25.
- **57.** Basu R, Poglitsch M, Yogasundaram H, Thomas J, Rowe BH, Oudit GY. Roles of angiotensin peptides and recombinant human ACE2 in heart failure. J Am Coll Cardiol 2017;69:805-19.
- 58. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors

- of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020 March 3 (Epub ahead of print).
- **59.** Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020 March 19 (Epub ahead of print).
- **60.** Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 February 7 (Epub ahead of print)
- **61.** Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebocontrolled study of quinapril. J Am Coll Cardiol 1993;22:1557-63
- **62.** 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.
- **63.** ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. Circulation 1998; 97:2202-12.
- **64.** Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-31.
- **65.** Sever P. The VALUE trial: a commentary. J Renin Angiotensin Aldosterone Syst 2004;5:99-101.
- **66.** Di Somma S. Importance of rapid and effective reduction of blood pressure in treating hypertension for the prevention of cardiovascular diseases: a lesson from the VALUE study. High Blood Press Cardiovasc Prev 2005;12:135-40.
- **67.** Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
- **68.** Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020 March 13 (Epub ahead of print).
- **69.** Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J 2016;37:908-16.

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