widely used. When we have little idea about appropriate therapy, we have an obligation to help by performing studies that will help us to learn together with our patients.

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

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1. Sciama Y. Is France's president fueling the hype over an unproven coronavirus treatment? Science. April 9, 2020 (https://www.sciencemag.org/news/2020/04/france-s-president-fueling--hype-over-unproven-coronavirus-treatment).
2. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;382:2411-8.
3. Lewis S. Arrowsmith. New York: P.F. Collier, 1925.

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Inhibitors of the Renin–Angiotensin–Aldosterone System and Covid-19

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SARS-CoV-2, the coronavirus that causes Covid-19, enters human cells by binding of its viral spike protein to the membrane-bound form of the monocarboxypeptidase angiotensin-converting enzyme 2 (ACE2).[1] From the viewpoint of human physiology, ACE2 plays an important regulatory role in the renin–angiotensin–aldosterone system (RAAS), metabolizing angiotensin II (a potent vasoconstrictor) to generate angiotensin-(1–7) (a vasodilator).[2] Studies in animals have suggested that angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) may up-regulate ACE2 expression,[3] thus increasing the availability of target molecules for SARS-CoV-2.

These considerations have led to speculation that ACE inhibitors and ARBs might be harmful in patients with Covid-19.[4,5] Although this is only a hypothesis, the argument has aroused potential concerns. Case series have indicated that hypertension, diabetes, and coronary artery disease — conditions for which clinicians often prescribe RAAS inhibitors — are more common in patients with severe Covid-19 than in those with milder illness.[6] Coverage of the hypothesis by the press and some websites has emphasized the theoretical risk with statements such as, "People with high blood pressure and diabetes could be at higher risk of severe or fatal coronavirus symptoms because of how their medicines work, scientists say,"[7] and, "[Reports suggest that] you are four times as likely to die from Covid-19 if you are taking one of these drugs, prior to contracting the virus."[8]

In this rapidly evolving setting, clinicians are weighing the alleged harm of continuing these medications in patients for whom ACE inhibitors and ARBs have known benefit against the harm to their cardiovascular and kidney health associated with discontinuing them. Three articles now published in the *Journal* provide data about whether ACE inhibitors and ARBs are indeed harmful in the context of the Covid-19 epidemic. All are observational studies with the looming possibility of confounding, but each has unique strengths, and their message is consistent — none of the three studies showed evidence of harm with continued use of ACE inhibitors and ARBs.

Mehra et al.[9] conducted a database study involving patients who had been hospitalized in 11 countries on three continents. The study included 8910 patients who had received a diagnosis of Covid-19, who had been admitted to the hospital between December 20, 2019, and March 15, 2020, and who had either died in the hospital or survived to hospital discharge. In multivariate logistic-regression analysis, an age greater than 65 years, coronary artery disease, congestive heart failure, history of cardiac arrhythmia,

chronic obstructive pulmonary disease, and current smoking were associated with an increased risk of in-hospital death. Female sex was associated with a decreased risk. Neither ACE inhibitors nor ARBs were associated with an increased risk of in-hospital death. A secondary analysis that was restricted to patients with hypertension (those for whom an ACE inhibitor or ARB would be indicated) also did not show harm.

Mancia et al.[10] conducted a case–control study involving patients with confirmed Covid-19 in the Lombardy region of Italy, which has been severely affected by the pandemic. In this analysis, 6272 people with confirmed SARS-CoV-2 infection that had been diagnosed between February 21 and March 11, 2020, were compared with 30,759 controls who were matched according to age, sex, and municipality of residence. In a conditional logistic-regression multivariate analysis, neither ACE inhibitors nor ARBs were associated with the likelihood of SARS-CoV-2 infection. An additional analysis comparing patients with severe or fatal infections with matched controls also did not show an association between these drugs and severe Covid-19.

Reynolds et al.[11] conducted a study based on data from the electronic health records of 12,594 patients in the New York University (NYU) Langone Health system who were tested for Covid-19 between March 1 and April 15, 2020. A total of 5894 patients had a positive test, among whom 1002 had severe illness (defined as admission to the intensive care unit, mechanical ventilation, or death). Propensity-score matching was performed among all tested patients and among patients with hypertension (to assess whether the likelihood of a positive test result was associated with each of several antihypertensive drug classes), as well as among Covid-19–positive patients and all such patients with hypertension (to assess whether the likelihood of severe illness among those with a positive test was associated with the same drug classes). The investigators' Bayesian analysis showed no positive association for any of the analyzed drug classes, including ACE inhibitors and ARBs, for either a positive test result or severe illness.

Taken together, these three studies do not provide evidence to support the hypothesis that ACE inhibitor or ARB use is associated with the risk of SARS-CoV-2 infection, the risk of severe Covid-19 among those infected, or the risk of in-hospital death among those with a positive test. Each of these studies has weaknesses inherent in observational data, but we find it reassuring that three studies in different populations and with different designs arrive at the consistent message that the continued use of ACE inhibitors and ARBs is unlikely to be harmful in patients with Covid-19. Several other smaller studies from China and the United Kingdom have come to the same conclusion.[12-15]

We note that Mehra et al. found that use of either ACE inhibitors or statins may be associated with a lower risk of in-hospital death than nonuse, but neither of the other two studies estimated a lower risk of Covid-19 or the likelihood of a positive test among patients treated with these agents. The unexpected result in the study by Mehra et al. may be due to unmeasured confounding and, in the absence of a randomized trial, should not be regarded as evidence to prescribe these drugs in patients with Covid-19.

Professional scientific societies and experts have spoken with one voice in advising that patients should not discontinue ACE inhibitor or ARB therapy out of a concern that they are at increased risk for infection, severe illness, or death during the Covid-19 pandemic.[16-18] The data from these three studies support those recommendations. Ultimately, one or more randomized trials will be needed to answer definitively the question of whether ACE inhibitors or ARBs pose a harm to patients with Covid-19.

Note added in proof: An expression of concern in regard to the study by Mehra et al.[9] was published on June 2, 2020, at NEJM.org.

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1. 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(2):271-280.e8.
2. Varagic J, Ahmad S, Nagata S, Ferrario CM. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Curr Hypertens Rep 2014;16:420.
3. Soler MJ, Barrios C, Oliva R, Batlle D. Pharmacologic modulation of ACE2 expression. Curr Hypertens Rep 2008;10:410-4.

4. 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(4):e21.
5. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020;38:781-2.
6. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
7. Blanchard S. Medicines taken by 6.6 million people with high blood pressure and diabetes could raise the risk of deadly coronavirus symptoms, scientists claim. Daily Mail. March 13, 2020 (https://www.dailymail.co.uk/news/article-8108735/Medicines-high-blood-pressure-diabetes-worsen-coronavirus-symptoms.html).
8. Kendrick M. Perhaps 4X more likely to die of COVID-19 if take ACE inhibitors (reduce blood pressure). VitaminDWiki. March 22, 2020 (https://vitamindwiki.com/Perhaps+4X+more+likely+to+die+of+COVID-19+if+take+ACE+inhibitors+%28reduce+blood+pressure%29+-+March+2020).
9. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.
10. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431-40.
11. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020;382:2441-8.
12. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757-60.
13. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020 April 17 (Epub ahead of print).
14. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 2020 April 23 (Epub ahead of print).
15. Bean DM, Kraljevic Z, Searle T, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute hospital trust. May 12, 2020 (https://www.medrxiv.org/content/10.1101/2020.04.07.20056788v1) preprint.
16. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. March 17, 2020 (https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19).
17. European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. March 13, 2020 (https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang).
18. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-9.

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Expression of Concern: Mehra MR et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.

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On May 1, 2020, we published "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19,"[1] a study of the effect of preexisting treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) on Covid-19. This retrospective study used data drawn from an international database that included electronic health records from 169 hospitals on three continents. Recently, substantive concerns have been raised about the quality of the information in that database. We have asked the authors to provide evidence that the data are reliable. In the interim and for the benefit of our readers, we are publishing this Expression of Concern about the reliability of their conclusions.

Studies of ACE inhibitors and ARBs in Covid-19 can play an important role in patient care. We encourage readers to consult two other studies we published on May 1, 2020, that used independent data to reach their conclusions.[2,3]

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1. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.
2. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431-40.
3. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020;382:2441-8.

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