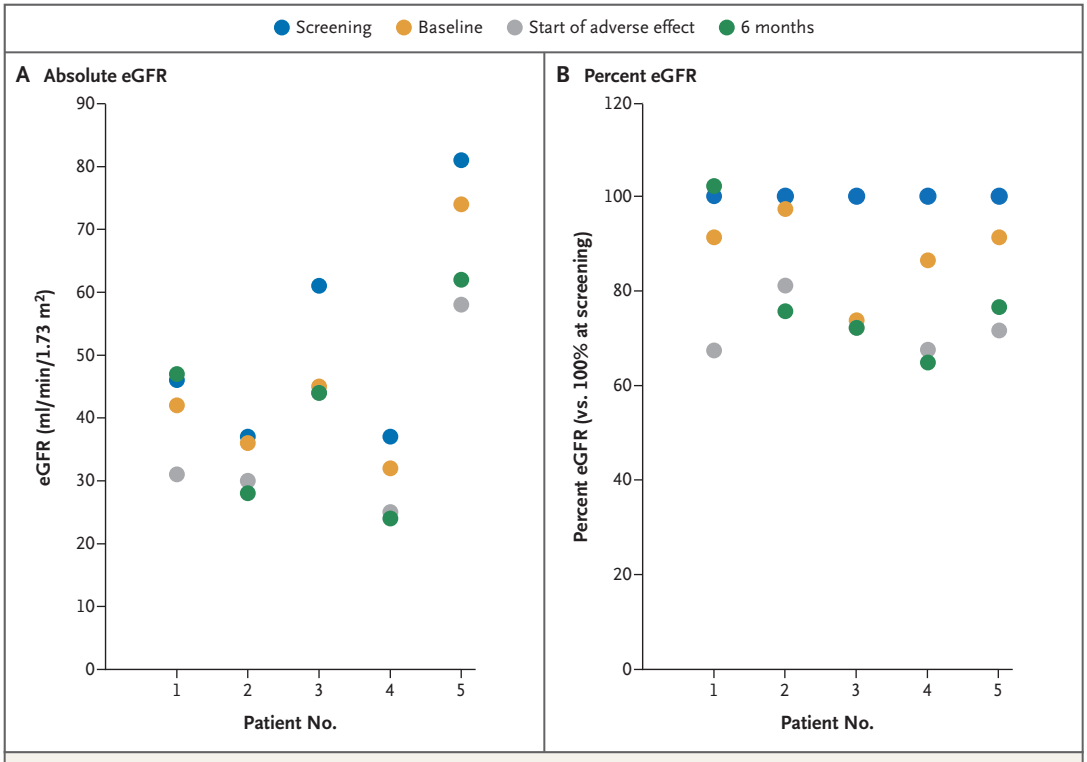

Figure 1. Changes in the Estimated Glomerular Filtration Rate (eGFR) in Five Patients with Adverse Events of Chronic Kidney Disease While Receiving Givosiran.

Panel A shows the absolute eGFR values among the five patients at screening, at baseline (trial initiation), at the beginning of the adverse event, and at 6 months. Panel B shows the eGFR at each time point in the trial as expressed as the percentage of the eGFR at screening, which was considered to be 100%. At some time points, the data points are superimposed. The data in this figure were adapted from Table S7 in the Supplementary Appendix accompanying the article by Balwani et al., available at NEJM.org.

tent with a drug-induced process[3] but rather with the patients' underlying disease. Treatment with givosiran was associated with small increases in creatinine (0.07 mg per deciliter at 3 months) in the overall trial population, changes that were mainly reversible. Some patients with preexisting renal disease had reductions in renal function that stabilized with ongoing administration of givosiran. However, consistent with labeling, monitoring of renal function during givosiran treatment is recommended as clinically indicated.

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Since publication of their article, the authors report no further potential conflict of interest.

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RAAS Inhibitors and Risk of Covid-19

TO THE EDITOR: In a population-based case–control study conducted in Lombardy, Italy, Mancia et al. (June 18 issue)[1] found a significant association between the use of oral anticoagulant agents and coronavirus disease 2019 (Covid-19). The odds ratio for Covid-19 associated with use of

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oral anticoagulant agents was 1.51 (95% confidence interval [CI], 1.37 to 1.66) before adjustment for several potential confounders and 1.16 (95% CI, 1.04 to 1.30) after adjustment.[1]

It would be important to know whether this association reflects the presence of atrial fibrillation, venous thromboembolism, or other cardiovascular disorders that are treated with oral anticoagulants. Furthermore, hospitalized patients with Covid-19 have a high risk of pulmonary embolism.[2]

The prothrombotic state in these patients,[3] indicated by several procoagulant factors, including fibrin degradation products and D-dimers, has been associated with an increased risk of death.[4,5] Thus, it would be of utmost importance to investigate whether patients with Covid-19 with exposure to anticoagulants before hospital admission have a decreased risk of critical or fatal disease.

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TO THE EDITOR: In their editorial related to the articles by Mancia et al. and Reynolds et al.,[1] Jarcho et al.[2] summarize the results of retrospective studies of the use of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) in patients with Covid-19 and conclude that these studies showed no evidence of an increased risk of disease or worsening outcomes. Other studies,[3] most notably that by Zhang et al.,[4] reached similar conclusions or showed beneficial effects.

A critical confounder in retrospective studies was revealed in data on patients with Covid-19 in New York.[5] Approximately 50% of the patients who had been prescribed ACE inhibitors or ARBs discontinued the medication when they were hospitalized. This discrepancy may explain the differences between studies that show a benefit of the use of ACE inhibitors or ARBs and those that show no effect.

A mechanistic model of the pathobiology of Covid-19 strongly implies that ACE inhibitors or ARBs may be beneficial.[6] Accordingly, discontinuation of ACE inhibitors or ARBs may yield worse outcomes than continuation of their use in patients with a diagnosis of Covid-19; this difference may confound retrospective studies that assess the effects of those agents. Studies that separate these two groups of patients may help to clarify the possible benefits or harms associated with continuation or discontinuation of ACE inhibitors or ARBs. Prospective studies — in particular, ongoing randomized, placebo-controlled trials such as the Ramipril for the Treatment of COVID-19 (RAMIC) trial (ClinicalTrials.gov number, NCT04366050) — may provide clearer insight regarding the effect of ACE inhibitors or ARBs in patients with Covid-19.

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Dr. Loomba reports receiving consulting fees from Alnylam–Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Galmed Pharmaceuticals, Intercept Pharmaceuticals, Ionis Pharmaceuticals, Janssen, Merck, Metacrine, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, and Theratechnologies, fees for serving as an advisory board member from 89Bio, CohBar, Galmed Pharmaceuticals, Gilead Sciences, Glympse Bio, Inipharm, Intercept Pharmaceuticals, Sagimet Biosciences, and Viking Therapeutics, being an employee of Liponexus, and receiving grant support, paid to his institution, from Allergan, Boehringer Ingelheim, Bristol Myers Squibb, Cirius, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, General Electric, Genfit, Gilead Sciences, Grail, Intercept Pharmaceuticals, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, NuSirt Sciences, Pfizer, pH Pharma, Prometheus Laboratory, and Siemens; and Dr. Insel, receiving consulting fees from Merck and CuraSen Therapeutics and grant support from Pfizer and Bristol Myers Squibb. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE 2 (ACE2) receptor to enter human cells.[1] ACE2 expression may be up-regulated by ACE inhibitors and ARBs. These observations have led to speculation regarding potential harmful effects of ACE inhibitors and ARBs.

Recent observational studies have shown no association between mortality from Covid-19 and ACE inhibitors and ARBs, after adjustment for a range of potential confounders. However, they have not shown an association between the duration of the underlying diseases or the duration of the ACE inhibitor or ARB treatment and mortality from Covid-19. This lack of an association is particularly important for several reasons. First, ACE2 activity is correlated with the duration of diabetes.[2] Second, in a recent study,[3] the adjusted effects of angiotensin blockade on the incidence of influenza varied nonlinearly, with a higher risk of influenza among patients who received treatment for 0.5 years to less than 1.5 years with ACE inhibitors (adjusted hazard ratio, 1.07; 95% CI, 0.97 to 1.17) and ARBs (adjusted hazard ratio, 1.15; 95% CI, 0.98 to 1.35) than among those who had not received these agents. Third, the spike protein of SARS-CoV-2 is primed by the transmembrane protease, serine 2 (TMPRSS2),[1] the expression of which has also been reported to be associated with disease duration.[4] Therefore, can the authors report the effects according to the duration of underlying conditions, according to the duration of treatment with ACE inhibitors, ARBs, and other inhibitors of the renin–angiotensin–aldosterone system (RAAS), or according to both durations?

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TO THE EDITOR: In the article by Reynolds et al., the data suggest that in patients with Covid-19 and hypertension, previous treatment with an ACE inhibitor was more likely to be associated with a reduced risk of severe disease than previous treatment with an ARB (propensity-score–matched median difference, −3.3 percentage points [95% credible interval, −8.2 to 1.7] and −0.1 percentage points [95% credible interval, −4.8 to 4.9], respectively). This difference might have been more apparent if mortality alone had been considered, rather than the combined end point of severe disease in 634 patients, which included admission to the intensive care unit (in 422 patients) and mechanical ventilation (in 165) as well as death (in 343).

Placebo-controlled trials before Covid-19 showed that the use of ACE inhibitors reduced mortality by 9 to 11% ($P<0.05$) among high-risk patients, whereas ARBs resulted in a nonsignificant excess of deaths.[1] Similar differences in mortality were noted in a meta-analysis of hypertension trials.[2] In these trials, the results of which were published after 2000, the mortality benefits of ACE inhibitors included effects that were independent of blood-pressure lowering.[3] Forthcoming clinical trials are unlikely to evaluate mortality among patients who were randomly assigned to receive ACE inhibitors or ARBs during previous infection with SARS-CoV-2, and since neither medication increases the risk of Covid-19,[4] the use of an ACE inhibitor is preferred. The mortal-

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ity data reported by Reynolds et al., however, are relevant to this question and should be shared.

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DR. MANCIA AND COLLEAGUES REPLY: Angeli et al. focus on the positive association observed in our study between the use of oral anticoagulants and the risk of Covid-19. A superficial reading could suggest that the use of oral anticoagulants per se increases the risk, when in fact, exposure to these drugs is a surrogate for many diseases and conditions (e.g., atrial fibrillation) that in themselves make the patient more susceptible to SARS-CoV-2 infection. An observational study such as ours has a limited ability to discriminate between these possibilities and can at most elucidate signals that could direct us toward understanding a complex phenomenon. We thank Angeli et al. for helping us to clarify that not all associations in our study have direct implications for clinical practice.

Sriram et al. mention a widely debated question — that is, whether outcomes in patients admitted to the hospital for Covid-19 may be affected by the continuation or discontinuation of RAAS blockers. Our study focused on the relationship between pretreatment with RAAS blockers and Covid-19, so it cannot provide an answer to this question. This issue has been addressed by a few observational studies that have shown that the initiation or continuation of RAAS blockers in hospitalized patients with Covid-19 may have a protective effect.[1,2] This was not the conclusion of a recent randomized, open-label trial (BRACE-CORONA, the results of which were presented at the 2020 meeting of the European Society of Cardiology) that showed that in 659 hospitalized patients with Covid-19, there was no difference between continuation and discontinuation of ACE inhibitors or ARBs with respect to the number of days the patients were alive and out of the hospital.

Finally, we agree with Islam et al. that the duration of treatment with ACE inhibitors or ARBs and the duration of underlying diseases warrant much more attention. Some evidence on this issue is currently available. For example, de Abajo et al. did not find any difference between patients with short-term use of RAAS blockers and those with long-term use (i.e., ≤1 year or >1 year) with respect to the risk of Covid-19.[3] A retrospective historical series that is extensive enough to investigate the function between time to exposure and the risk of Covid-19 is lacking. Moreover, in a retrospective study such as ours, an analysis based on the duration of use of RAAS inhibitors would have an implicit selection bias.

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DR. REYNOLDS AND COLLEAGUES REPLY: Sriram and colleagues raise the concern that prehospital use of antihypertensive therapy is not relevant to the outcome in patients with Covid-19 because physicians may have discontinued specific anti-

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Table 1. Likelihood of Death after Positive Test for Covid-19, According to Treatment with Various Antihypertensive Agents, among Propensity-Score–Matched Patients, with Hypertension and Overall.*

Medication	Matched Patients with Hypertension			All Matched Patients		
	Death among Patients Treated with Medication	Death among Patients Not Treated with Medication	Median Difference (95% CI)	Death among Patients Treated with Medication	Death among Patients Not Treated with Medication	Median Difference (95% CI)
	no./total no. (%)		*percentage points*	*no./total no. (%)*		*percentage points*
ACE inhibitor	77/584 (13.2)	86/583 (14.8)	−1.6 (−5.5 to 2.5)	77/627 (12.3)	95/653 (14.5)	−2.3 (−6.0 to 1.5)
ARB	81/629 (12.9)	91/612 (14.9)	−1.9 (−5.8 to 1.9)	79/664 (11.9)	101/639 (15.8)	−3.9 (−7.7 to −0.2)
ACE inhibitor or ARB	127/1019 (12.6)	141/986 (14.3)	−1.8 (−4.8 to 1.2)	134/1110 (12.1)	162/1101 (14.7)	−2.6 (−5.5 to 0.2)
Beta-blocker	119/792 (15.0)	133/829 (16.0)	−1.0 (−4.4 to 2.5)	122/912 (13.4)	149/976 (15.3)	−1.9 (−5.1 to 1.3)
Calcium-channel blocker	128/950 (13.5)	127/930 (13.7)	−0.2 (−3.3 to 2.9)	129/992 (13.0)	140/976 (14.3)	−1.3 (−4.4 to 1.7)
Thiazide diuretic	53/515 (10.3)	63/520 (12.1)	−1.8 (−5.7 to 2.1)	53/549 (9.7)	74/590 (12.5)	−2.8 (−6.6 to 0.8)

* Patients were propensity-score matched for age; sex; race; ethnic group; body-mass index; smoking history; history of hypertension, myocardial infarction, heart failure, diabetes, chronic kidney disease, and obstructive lung disease (e.g., asthma and obstructive pulmonary diseases); and other classes of medication. CI denotes credible interval.

hypertensive therapies in patients after hospital admission, particularly during the period of our study when there were concerns among the medical community about the safety of ACE inhibitors and ARBs. We agree this is a potential confounder. However, ACE inhibitors and ARBs do not act on ACE2, the protein that acts as a SARS-CoV-2 receptor, and treatment with ACE inhibitors or ARBs does not appear to result in increased ACE2 expression.[1-3] In a recently completed trial involving 659 hospitalized patients with Covid-19 who had received ACE inhibitors or ARBs on a long-term basis, the patients were randomly assigned to either suspend use of these medication classes during the following 30 days or to continue use. There was no significant effect on the number of days the patients were alive and out of the hospital over the 30-day follow-up period (mean [±SD], 21.9±8.0 days in the continuing ACE inhibitor–ARB group and 22.9±7.1 days in the suspended ACE inhibitor–ARB group).[4]

Islam and colleagues request additional data on the durations of disease and treatment in our study. We regret that we are not able to provide these data because we cannot be certain that the duration of hypertension or other conditions and the duration of treatment with specific agents would be accurately reflected in our electronic health records. We capture the date when patients start and stop medications while they are patients at New York University (NYU) Langone Health. We do not reliably capture how long they may have taken a medication before establishing care with NYU Langone Health.

The mortality data requested by Strauss and colleagues are provided in Table 1. We report the likelihood of death by April 15, 2020, among patients who tested positive for Covid-19 at our center between March 1 and April 15, 2020, within the cohorts matched according to propensity score for the use of each class of antihypertensive medication, as we reported in our article. In both sets (i.e., matched patients with hypertension and all matched patients), the risk of death was no more than 4 percentage points higher among treated patients than among untreated patients for each medication class tested.

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