ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) may disproportionately affect people with cardiovascular disease. Concern has been aroused regarding a potential harmful effect of angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in this clinical context.

METHODS

Using an observational database from 169 hospitals in Asia, Europe, and North America, we evaluated the relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 who were admitted between December 20, 2019, and March 15, 2020, and were recorded in the Surgical Outcomes Collaborative registry as having either died in the hospital or survived to discharge as of March 28, 2020.

RESULTS

Of the 8910 patients with Covid-19 for whom discharge status was available at the time of the analysis, a total of 515 died in the hospital (5.8%) and 8395 survived to discharge. The factors we found to be independently associated with an increased risk of in-hospital death were an age greater than 65 years (mortality of 10.0%, vs. 4.9% among those ≤65 years of age; odds ratio, 1.93; 95% confidence interval [CI], 1.60 to 2.41), coronary artery disease (10.2%, vs. 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, vs. 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, vs. 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, vs. 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40), and current smoking (9.4%, vs. 5.6% among former smokers or nonsmokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47). No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; odds ratio, 1.23; 95% CI, 0.87 to 1.74).

CONCLUSIONS

Our study confirmed previous observations suggesting that underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with Covid-19. Our results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital death in this clinical context. (Funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.)

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AS THE CORONAVIRUS DISEASE 2019 (Covid-19) pandemic has spread around the globe, there has been growing recognition that persons with underlying increased cardiovascular risk may be disproportionately affected.[1-3] Several studies of case series have noted cardiac arrhythmias, cardiomyopathy, and cardiac arrest as terminal events in patients with Covid-19.[1-4] Higher incidences of cardiac arrhythmias, acute coronary syndromes, and heart failure–related events have also been reported during seasonal influenza outbreaks, which suggests that acute respiratory infections may result in activation of coagulation pathways, proinflammatory effects, and endothelial cell dysfunction.[5] In addition, however, concern has been expressed that medical therapy for cardiovascular disease might specifically contribute to the severity of illness in patients with Covid-19.[6,7]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Covid-19, has been shown to establish itself in the host through the use of angiotensin-converting enzyme 2 (ACE2) as its cellular receptor.[8] ACE2 is a membrane-bound monocarboxypeptidase found ubiquitously in humans and expressed predominantly in heart, intestine, kidney, and pulmonary alveolar (type II) cells.[7,9] Entry of SARS-CoV-2 into human cells is facilitated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE2 receptor.[10]

ACE2 is counterregulatory to the activity of angiotensin II generated through ACE1 and is protective against detrimental activation of the renin–angiotensin–aldosterone system. Angiotensin II is catalyzed by ACE2 to angiotensin-(1–7), which exerts vasodilatory, antiinflammatory, antifibrotic, and antigrowth effects.[11] It has been suggested that ACE inhibitors and angiotensin-receptor blockers (ARBs) may increase the expression of ACE2, which has been shown in the heart in rats,[12] and thereby may confer a predisposition to more severe infection and adverse outcomes during Covid-19.[6,7] Others have suggested that ACE inhibitors may counter the antiinflammatory effects of ACE2. However, in vitro studies have not shown direct inhibitory activity of ACE inhibitors against ACE2 function.[9,13]

Despite these uncertainties, some have recommended cessation of treatment with ACE inhibitors and ARBs in patients with Covid-19.[6] However, several scientific societies, including the American Heart Association, the American College of Cardiology, the Heart Failure Society of America, and the Council on Hypertension of the European Society of Cardiology, have urged that these important medications should not be discontinued in the absence of clear clinical evidence of harm.[14,15] We therefore undertook a study to investigate the relationship between underlying cardiovascular disease and Covid-19 outcomes and to evaluate the association between cardiovascular drug therapy and mortality in this illness.

METHODS

DATA SOURCE

We analyzed deidentified data from the Surgical Outcomes Collaborative (Surgisphere), an international registry. Our analysis included data from 169 hospitals located in 11 countries in Asia, Europe, and North America. The collaborative uses automated extraction of data from inpatient and outpatient electronic health records, supply-chain databases, and financial records, combined with point-of-care data entry for procedures. A manual data-entry process is used for quality assurance and validation. Data are collected through automated data transfers that capture information from each health care entity at regular intervals on a prospective, ongoing basis. Verifiable source documentation for the data elements includes electronic inpatient and outpatient medical records.

Data acquisition is facilitated through the use of a standardized Health Level Seven–compliant data dictionary. After this data dictionary is harmonized with data from electronic health records, the majority of the data acquisition is completed with automated interfaces. The collected data sample from each health care entity is validated against financial records and external databases. All protected health information is stripped from each record before storage in a cloud-based data warehouse. The collaborative is compliant with the Agency for Healthcare Research and Quality guidelines for registries and the Food and Drug Administration guidance on real-world evidence. The collection and analysis of data in the registry have been deemed exempt from ethics review.

DATA COLLECTION

The collaborative registry was used as a resource to analyze data from all patients with polymerase-

chain-reaction (PCR)–proven Covid-19 who were admitted to the hospital between December 20, 2019, and March 15, 2020, and who were recorded in the registry as having either died in the hospital or survived to hospital discharge as of March 28, 2020. Data from the registry can be analyzed only after a patient's hospitalization is complete, and therefore our sample did not include patients who were admitted to the hospital during this time window but were still hospitalized at the end of it. Our sample also may have excluded some patients who had died or were discharged by March 28 but whose discharge status had not yet been recorded by the hospital.

The presence in the record of a positive laboratory finding confirming SARS-CoV-2 infection was used for classifying a patient as positive for Covid-19. A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–PCR (RT-PCR) assay of nasal or pharyngeal swab specimens. At each site, Covid-19 was diagnosed on the basis of the World Health Organization guidance.[16] Patients who did not undergo testing, had no record of testing in the collaborative database, or had a negative test were not included in the present study. For this study, only one positive test was necessary for the patient to be included in the analysis.

Data on patients' demographic characteristics, coexisting conditions (based on codes from the *International Classification of Diseases, 10th Revision, Clinical Modification*), and cardiovascular drug therapy were included in this analysis. Clinical information included age, sex, continent of origin, and underlying coexisting conditions as noted in either the inpatient or the outpatient electronic health record. Coexisting conditions included chronic obstructive pulmonary disease (COPD), an immunosuppressed condition (glucocorticoid use, a preexisting immunologic condition, or ongoing chemotherapy in patients with cancer), current or remote history of smoking, and a history of hypertension, diabetes mellitus, hyperlipidemia, or underlying cardiovascular disease (including coronary artery disease, heart failure, and cardiac arrhythmia). Cardiovascular drug therapy recorded at the time of hospital admission was also included, including any antiplatelet therapy, use of insulin or other hypoglycemic agents, beta-blockers, statins, ARBs, and ACE inhibitors.

All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data provided.

STATISTICAL ANALYSIS

The primary analysis was an evaluation of the relationship of preexisting cardiovascular disease and drug therapy with the end point of in-hospital death while controlling for confounders, including demographic characteristics and coexisting conditions. Categorical variables are shown as frequencies and percentages, and continuous variables as means and standard deviations. Independent sample t-tests were completed, and point differences with 95% confidence intervals are reported for all comparisons between variables. Multiple imputation for missing values was not possible because for disease and drug variables there were no codes to indicate that data were missing; if the patient's electronic health record did not include information on a clinical characteristic, such as hyperlipidemia or the use of beta-blockers, it was assumed that that characteristic was not present.

A multivariable logistic-regression analysis was performed to ascertain the effects of age, race, coexisting conditions (coronary artery disease, congestive heart failure, cardiac arrhythmia, diabetes mellitus, COPD, current smoking, former smoking, hypertension, immunocompromised state, and hyperlipidemia), hospital location (according to country), and medications (ACE inhibitors, ARBs, beta-blockers, antiplatelet agents, statins, insulin, and oral hypoglycemic agents) on the likelihood of in-hospital death. Linearity of the continuous variables with respect to the logit of the dependent variable was confirmed. Odds ratios and corresponding 95% confidence intervals were calculated. Separate age- and sex-adjusted analyses were also performed. The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

On the basis of the results of the initial analyses, additional analyses were performed to examine the robustness of the estimates initially obtained. Analyses according to continent of origin as well as country classification (as either high income or low–middle income) were performed. A tipping-point analysis (an analysis that shows the effect size and prevalence of an unmeasured confounder that could shift the upper boundary

of the confidence interval toward null) was performed. In addition, we sought to determine whether the effect of ACE inhibitors and statins noted in the overall study was also seen when the analysis was confined to a subgroup of patients who might have an indication for these agents. Thus, the association of ACE inhibitor use with in-hospital death was examined in the subgroup of patients with hypertension, and the association of statin use with in-hospital death was examined in the subgroup of patients with hyperlipidemia, with the use of age- and sex-adjusted logistic-regression analysis. All statistical analyses were performed with R software, version 3.6.3 (R Foundation for Statistical Computing), and SPSS Statistics software, version 26 (IBM).

RESULTS

PATIENTS

Our study population included 8910 hospitalized patients from 169 hospitals who had Covid-19, who were admitted between December 20, 2019, and March 15, 2020, and who completed their hospital course (discharged alive or died) by March 28, 2020. Patients who were hospitalized during this time without a completed course could not be included in the analysis. Our sample was made up of 1536 patients (17.2%) from North America, 5755 (64.6%) from Europe, and 1619 (18.2%) from Asia (details of the study population according to continent, country, and number of hospitals are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The mean (±SD) age was 49±16 years (16.5% of the patients were >65 years of age), 40.0% of the patients were women, 63.5% were white, 7.9% were black, 6.3% were Hispanic, and 19.3% were Asian.

With respect to cardiovascular risk factors, 30.5% of the patients had hyperlipidemia, 26.3% had hypertension, 14.3% had diabetes mellitus, 16.8% were former smokers, and 5.5% were current smokers. Preexisting cardiovascular disease in this sample included coronary artery disease (present in 11.3% of the patients), a history of congestive heart failure (2.1%), and a history of cardiac arrhythmia (3.4%). Other coexisting conditions included COPD (in 2.5% of the patients) and an underlying immunosuppressed condition (2.8%). Medical therapy included ACE inhibitors (8.6%

of the patients), ARBs (6.2%), statins (9.7%), beta-blockers (5.9%), and antiplatelet agents (3.3%). Insulin was used in 3.4% of the patients, and other hypoglycemic agents were used in 9.6%. The mean length of hospital stay was 10.7±2.7 days, with an overall in-hospital mortality of 5.8% (515 of 8910 patients) in this population of patients with completed outcomes. Of the patients who had been admitted to an intensive care unit (ICU) at any time during their hospitalization, 24.7% died, as compared with 4.0% of the patients who had not been admitted to an ICU.

ANALYSIS OF SURVIVORS AS COMPARED WITH NONSURVIVORS

Table 1 shows the distribution of demographic characteristics and coexisting conditions among survivors and nonsurvivors, along with the between-group differences and 95% confidence intervals. Nonsurvivors were older, more likely to be white, and more often men, and they had a greater prevalence of diabetes mellitus, hyperlipidemia, coronary artery disease, heart failure, and cardiac arrhythmias. Patients who died were also more likely to have had COPD and a history of current smoking. Among medications, ACE inhibitors and statins were more commonly used by survivors than by nonsurvivors (Table 2), whereas no association between survival and the use of ARBs was found. The length of hospital stay differed between survivors and nonsurvivors (10.5±2.5 days vs. 7.5±2.8 days). When the data were analyzed according to age decile, continent, or income category of the country in which the hospital was located (high income or low–middle income), the results were similar (Fig. S1 and Tables S2 and S3).

MULTIVARIABLE LOGISTIC-REGRESSION ANALYSIS

A multivariable logistic-regression model was developed. Independent predictors of in-hospital death and their corresponding odds ratios and 95% confidence intervals are shown in Figure 1. An age greater than 65 years, coronary artery disease, congestive heart failure, cardiac arrhythmia, COPD, and current smoking were associated with a higher risk of in-hospital death. Female sex, the use of ACE inhibitors, and the use of statins were associated with a better chance of survival to hospital discharge, with no association found for the use of ARBs. For female sex,

Table 1. Demographic Characteristics and Coexisting Conditions among Survivors and Nonsurvivors of Covid-19.*

Characteristic or Condition	Survivors (N=8395)	Nonsurvivors (N=515)	Difference (95% CI)†
Age — yr	48.7±16.6	55.8±15.1	−7.1 (−8.4 to −5.7)
Age >65 yr — no. (%)	1327 (15.8)	147 (28.5)	−12.7 (−16.0 to −9.4)
Female sex — no. (%)	3392 (40.4)	179 (34.8)	5.6 (1.3 to 10.0)
Race or ethnic group — no. (%)‡			
White	5306 (63.2)	351 (68.2)	−5.0 (−9.1 to −0.8)
Black	672 (8.0)	34 (6.6)	1.4 (−0.8 to 3.6)
Hispanic	529 (6.3)	32 (6.2)	0.1 (−2.0 to 2.3)
Asian	1637 (19.5)	84 (16.3)	3.2 (−0.2 to 6.5)
Native American	34 (0.4)	1 (0.2)	0.2 (−0.3 to 0.8)
Other	219 (2.6)	13 (2.5)	0.1 (−1.4 to 1.4)
Coexisting conditions — no. (%)			
Coronary artery disease	907 (10.8)	103 (20.0)	−9.2 (−12.8 to −5.7)
Congestive heart failure	160 (1.9)	29 (5.6)	−3.7 (−5.8 to −1.8)
Cardiac arrhythmia	269 (3.2)	35 (6.8)	−3.6 (−5.8 to −1.4)
Diabetes mellitus	1175 (14.0)	97 (18.8)	−4.8 (−8.3 to −1.3)
Hypertension	2216 (26.4)	130 (25.2)	1.2 (−2.8 to 5.1)
Hyperlipidemia	2535 (30.2)	180 (35.0)	−4.8 (−9.0 to −0.5)
COPD	193 (2.3)	32 (6.2)	−3.9 (−6.1 to −1.8)
Current smoker	445 (5.3)	46 (8.9)	−3.6 (−6.2 to −1.1)
Former smoker	1410 (16.8)	83 (16.1)	0.7 (−2.6 to 4.0)
Immunosuppressed condition	227 (2.7)	22 (4.3)	−1.6 (−3.4 to 0.2)

* Plus–minus values are means ±SD. The 95% confidence intervals (CIs) have not been adjusted for multiple testing and should not be used to infer definitive effects. COPD denotes chronic obstructive pulmonary disease, and Covid-19 coronavirus disease 2019.
† For mean age, the difference is given in years; for all other characteristics, the difference is given in percentage points.
‡ Race and ethnic group were reported by the patient.

the odds ratio for dying in the hospital was 0.79 (95% confidence interval [CI], 0.65 to 0.95); for ACE inhibitor use, the odds ratio was 0.33 (95% CI, 0.20 to 0.54); and for statin use, the odds ratio was 0.35 (95% CI, 0.24 to 0.52). For ARB use, the odds ratio was 1.23 (95% CI, 0.87 to 1.74). The presence or absence of an immunosuppressed condition, the race or ethnic group, and the presence or absence of hyperlipidemia or diabetes mellitus were not independent predictors of death in the hospital. The analyses according to continent and according to the income category of the country (high or low–middle) were consistent with the overall results (Tables S4 and S5). Data from the age- and sex-adjusted multivariable logistic-regression analyses are shown in Table S6.

Table 2. Cardiovascular Drug Therapy at Hospitalization among Survivors and Nonsurvivors of Covid-19.*

Drug Class	Survivors (N=8395)	Nonsurvivors (N=515)	Difference (95% CI)
	number (percent)		percentage points
ACE inhibitor	754 (9.0)	16 (3.1)	5.9 (4.3 to 7.5)
ARB	518 (6.2)	38 (7.4)	−1.2 (−3.5 to 1.1)
Beta-blocker	497 (5.9)	28 (5.4)	0.5 (−1.6 to 2.6)
Antiplatelet	282 (3.4)	13 (2.5)	0.8 (−0.6 to 2.2)
Statin	824 (9.8)	36 (7.0)	2.8 (0.5 to 5.1)
Insulin	279 (3.3)	23 (4.5)	−1.2 (−3.0 to 0.7)
Other hypoglycemic agent	792 (9.4)	59 (11.5)	−2.1 (−4.9 to 0.8)

* The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

ADDITIONAL ANALYSES

In the tipping-point analysis to assess the potential effect of an unmeasured confounder, it was estimated that a hypothetical unobserved binary confounder with a prevalence of 10% in the study population would need to have an odds ratio of at least 10 in order for the observed associations for either ACE inhibitors or statins to have 95% confidence intervals crossing the odds ratio boundary of 1.0 (Table S7). We also separately examined the interaction of ACE inhibitor use with mortality in the subgroup with hypertension and the interaction of statin use with mortality in the subgroup with hyperlipidemia. These analyses, shown in Table S8, are consistent with the results of the primary analysis.

DISCUSSION

Our investigation confirms previous reports of the independent relationship of older age, underlying cardiovascular disease (coronary artery disease, heart failure, and cardiac arrhythmias), current smoking, and COPD with death in Covid-19. Our results also suggest that women are proportionately more likely than men to survive the infection. Neither harmful nor beneficial associations were noted for antiplatelet therapy, beta-blockers, or hypoglycemic therapy. It is important to note that we were not able to confirm previous concerns regarding a potential harmful association of either ACE inhibitors or ARBs with in-hospital mortality in this clinical context.

In viral infections such as influenza, older age is associated with an increased risk of cardiovascular events and death.[5] In the 2003 epidemic of severe acute respiratory syndrome (SARS, caused by SARS-CoV-1 infection), sex differences in the risk of death similar to those we observed were noted.[17] Women have stronger innate and adaptive immunity and greater resistance to viral infections than men.[18] In animal models of SARS-CoV-1 infection, higher susceptibility of male mice to SARS-CoV-1 and greater accumulation of macrophages and neutrophils in the lungs have been described.[19] Ovariectomy or the use of estrogen-receptor antagonists increased mortality from SARS-CoV-1 infection in female animals. Furthermore, the difference in risk between the sexes increased with advancing age.[19] These findings may support the observation in our investigation that suggested an association between survival and female sex, independent of older age.

Infection with SARS-CoV-2 is a mild disease in most people, but in some the disease progresses to a severe respiratory illness characterized by a hyperinflammatory syndrome, multiorgan dysfunction, and death.[20] In the lung, the viral spike glycoprotein of SARS-CoV-2 interacts with cell-surface ACE2, and the virus is internalized by endocytosis. The endocytic event upregulates the activity of ADAM metallopeptidase domain 17 (ADAM17), which cleaves ACE2 from the cell membrane, resulting in a loss of ACE2-mediated protection against the effects of activa-
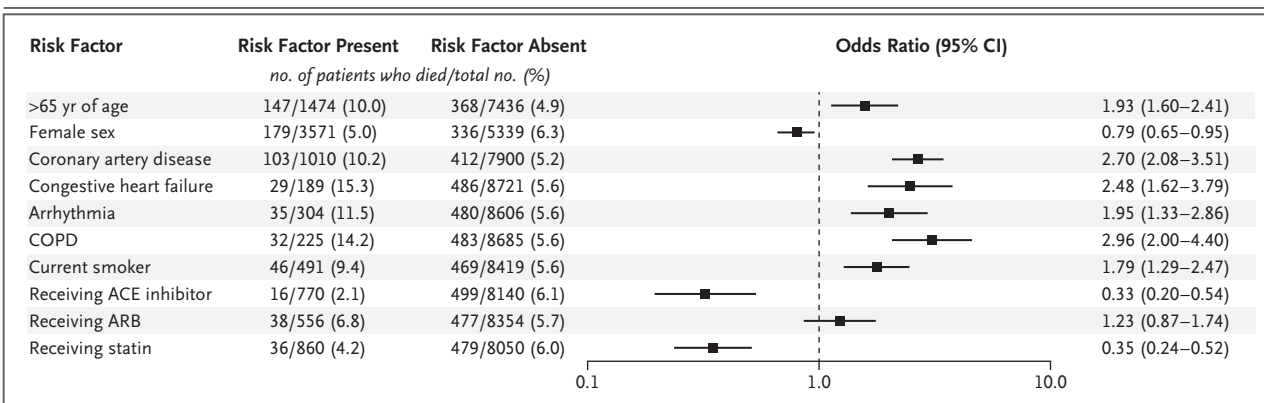
Risk Factor	Risk Factor Present	Risk Factor Absent	Odds Ratio (95% CI)
	no. of patients who died/total no. (%)		
>65 yr of age	147/1474 (10.0)	368/7436 (4.9)	1.93 (1.60–2.41)
Female sex	179/3571 (5.0)	336/5339 (6.3)	0.79 (0.65–0.95)
Coronary artery disease	103/1010 (10.2)	412/7900 (5.2)	2.70 (2.08–3.51)
Congestive heart failure	29/189 (15.3)	486/8721 (5.6)	2.48 (1.62–3.79)
Arrhythmia	35/304 (11.5)	480/8606 (5.6)	1.95 (1.33–2.86)
COPD	32/225 (14.2)	483/8685 (5.6)	2.96 (2.00–4.40)
Current smoker	46/491 (9.4)	469/8419 (5.6)	1.79 (1.29–2.47)
Receiving ACE inhibitor	16/770 (2.1)	499/8140 (6.1)	0.33 (0.20–0.54)
Receiving ARB	38/556 (6.8)	477/8354 (5.7)	1.23 (0.87–1.74)
Receiving statin	36/860 (4.2)	479/8050 (6.0)	0.35 (0.24–0.52)

Figure 1. Independent Predictors of In-Hospital Death from Multivariable Logistic-Regression Analysis.

Numbers and percentages of patients with each risk factor who died (risk factor present) and of patients without each risk factor who died (risk factor absent) are shown. The 95% confidence intervals (CIs) of the odds ratios have not been adjusted for multiple testing and should not be used to infer definitive effects. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and COPD chronic obstructive pulmonary disease.

tion of the tissue renin–angiotensin–aldosterone system while mediating the release of proinflammatory cytokines into the circulation.[21] The stress of critical illness and inflammation may unite in destabilizing preexisting cardiovascular illness. Vascular endothelial cell dysfunction, inflammation-associated myocardial depression, stress cardiomyopathy, direct viral infection of the heart and its vessels, or the host response may cause or worsen heart failure, demand-related ischemia, and arrhythmias.[22] These factors may underlie the observed associations between cardiovascular disease and death in Covid-19.

In our analyses, use of either ACE inhibitors or statins was associated with better survival among patients with Covid-19. However, these associations should be considered with extreme caution. Because our study was not a randomized, controlled trial, we cannot exclude the possibility of confounding. In addition, we examined relationships between many variables and in-hospital death, and no primary hypothesis was prespecified; these factors increased the probability of chance associations being found. Therefore, a cause-and-effect relationship between drug ther-

apy and survival should not be inferred. These data also offer no information concerning the potential effect of initiation of ACE inhibitor or statin therapy in patients with Covid-19 who do not have an appropriate indication for these medications. Randomized clinical trials evaluating the role of ACE inhibitors and statins will be necessary before any conclusion can be reached regarding a potential benefit of these agents in patients with Covid-19.

In this multinational observational study involving patients hospitalized with Covid-19, we confirmed previous observations suggesting that underlying cardiovascular disease is independently associated with an increased risk of in-hospital death. We were not able to confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital mortality in this clinical context.

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