ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

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ABSTRACT

BACKGROUND

A potential association between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (Covid-19) has not been well studied.

METHODS

We carried out a population-based case–control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from regional databases of health care use. Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression.

RESULTS

Among both case patients and controls, the mean (±SD) age was 68±13 years, and 37% were women. The use of ACE inhibitors and ARBs was more common among case patients than among controls, as was the use of other antihypertensive and non-antihypertensive drugs, and case patients had a worse clinical profile. Use of ARBs or ACE inhibitors did not show any association with Covid-19 among case patients overall (adjusted odds ratio, 0.95 [95% confidence interval {CI}, 0.86 to 1.05] for ARBs and 0.96 [95% CI, 0.87 to 1.07] for ACE inhibitors) or among patients who had a severe or fatal course of the disease (adjusted odds ratio, 0.83 [95% CI, 0.63 to 1.10] for ARBs and 0.91 [95% CI, 0.69 to 1.21] for ACE inhibitors), and no association between these variables was found according to sex.

CONCLUSIONS

In this large, population-based study, the use of ACE inhibitors and ARBs was more frequent among patients with Covid-19 than among controls because of their higher prevalence of cardiovascular disease. However, there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

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Studies in animals have shown that angiotensin-converting enzyme 2 (ACE2), a membrane-bound aminopeptidase that is abundantly expressed in the lungs, the heart, and other tissues,[1] is used by coronaviruses as a functional receptor for their entrance into the cells.[2,3] Angiotensin-receptor blockers (ARBs) and ACE inhibitors are considered first-choice drugs in hypertension, heart failure, post–myocardial infarction states, and chronic kidney disease and also increase the expression of ACE2.[4,5] Given these facts and observations, the hypothesis that their use may modify susceptibility to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in humans has developed. There is, however, no consensus as to whether the risk and severity of SARS-CoV-2 infection might be increased or reduced with the use of such agents.[1,6-10]

Current published clinical data are largely limited to small, uncontrolled studies of the demographic and clinical characteristics of patients with coronavirus disease 2019 (Covid-19), with little or no information regarding the type of antihypertensive treatment that they were taking at or close to the time of infection.[11-15] This lack of information has been problematic, given the possibility that blockers of the renin–angiotensin–aldosterone system (RAAS) may affect the susceptibility to and the severity of Covid-19, an issue that has received much press and may influence patient behavior with respect to taking or discontinuing these agents, despite the advice of a number of professional scientific societies not to discontinue them.[16-19] To date, reports indicate that withdrawal of RAAS blockers in patients with conditions for which these medications are commonly used leads to a marked increase in the risk of complications and death.[20-22]

The recent Covid-19 epidemic spread to and increased exponentially in Italy earlier than in any other Western country. By far the most severely hit part of Italy is Lombardy, a northern region in which SARS-CoV-2 has infected thousands of patients and has been associated with a high incidence of hospitalization for intensive care and a high mortality.[23] The Regional Health Authority promptly established a population-based registry of patients with a confirmed diagnosis of infection with SARS-CoV-2. Taking advantage of the regional availability of databases of health care use that cover the dispensed essential drugs and services provided to beneficiaries of the Regional Health Service (i.e., virtually all residents), we carried out a case–control investigation to evaluate the association between the use of RAAS blockers and the risk of Covid-19. The analysis was extended to other antihypertensive agents as well as to a large number of other medications. Data were also analyzed according to sex, age, and the severity of Covid-19 (i.e., patients receiving intensive hospital care or who died vs. other patients with the disease).

Methods

Target Population and Data Sources

Residents in Lombardy, 40 years of age or older, who were beneficiaries of the Regional Health Service formed the target population (just over 6 million people, approximately 17% of the entire Italian population in that age group). Italian citizens have equal access to essential health care services provided by the National Health Service. In Lombardy, that association has been paired with an automated system of databases that collect a variety of information, including codes in the *International Classification of Diseases, 9th Revision, Clinical Modification*, for inpatient diagnoses and services supplied from public or private hospitals as well as Anatomical Therapeutic Chemical codes of outpatient dispensation of drugs reimbursed to the pharmacies after filing doctors' prescriptions. These various types of data can be interconnected, since a single individual identification code is used by all databases for each citizen enrolled. To preserve privacy, each identification code was automatically deidentified, the inverse process being allowed only to the Regional Health Authority on request from judicial authorities.

All the authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol (available with the full text of this article at NEJM.org). Deidentified data were extracted and processed from the regional repository, using statistical programs developed by the authors, according to a protocol previously discussed with and approved by the Regional Health Authority. Further details of the databases of health care use in Lombardy have been reported in previous studies.[24-26]

Case Patients and Controls

Since February 21, 2020, patients with a diagnosis of Covid-19 have been revealed to the Regional

Health Authority from several sources: public and private hospitals (persons seen in the first aid service for an acute respiratory infection and infected inpatients, including those who received assisted ventilation); general practitioners (symptomatic outpatients receiving only home care); municipal registries (deaths due to Covid-19); and laboratories accredited by the Regional Health Authority. Diagnosis was based on the protocol released by the World Health Organization[27] — that is, positive nasopharyngeal swab specimens tested with at least two real-time reverse-transcriptase–polymerase-chain-reaction assays targeting different genes (E, RdRp, and M) of SARS-Cov-2. Up to February 25, diagnostic tests were carried out in all patients with suspected cases, whereas only symptomatic patients were tested from February 26 onward.

The date of Covid-19 diagnosis was considered as the index date, and patient data were extracted from the registry until March 11, 2020. We excluded patients who were not beneficiaries of the Regional Health Service (361 patients); who became beneficiaries of the Regional Health Service after January 1, 2019 (8 patients); or who were younger than 40 years of age at the index date (619 patients). The remaining 6292 patients were included in the study as case patients. Among them, the 617 patients who received assisted ventilation or died were classified as having a critical or fatal infection; the remaining patients were regarded as having relatively mild-to-moderate clinical manifestations of the infection. Approximately half the patients with mild-to-moderate cases received home care, and the remaining patients were hospitalized but did not received intensive care.

For each case patient, up to five controls were randomly selected from the target population to be matched for sex, age at index date, and municipality of residence. Before matching, persons who became beneficiaries of the Regional Health Service after January 1, 2019, were excluded from the target population. Patients who had received a diagnosis of Covid-19 had been eligible as potential controls until they became case patients, and all matches had to be at risk for Covid-19.

CLINICAL FEATURES AND DRUG EXPOSURE

Previous hospitalizations for cardiovascular disease, cancer, respiratory disease, and kidney disease in case patients and controls were traced in the regional databases for a 5-year period before the index date. In addition, case patients and controls were categorized according to the Chronic Related Score (CReSc), a new index of patients' clinical profiles derived from inpatient and outpatient services provided by the Regional Health Service and validated for outcome prediction.[28] A detailed description of the CReSc, which scores the presence or absence of 31 diseases or conditions in each patient, is provided in the Supplementary Appendix, available at NEJM.org. CReSc values range from 0 to 4, with higher values indicating a worse clinical status.

Major classes of antihypertensive agents (ACE inhibitors, ARBs, calcium-channel blockers, diuretics [including subtypes], and beta-blockers) that were dispensed to case patients and controls during 2019 were traced from the databases of health care use. In addition to ACE inhibitors and ARBs, other drugs that were dispensed and are known to act through the RAAS were noted — renin inhibitors and sacubitril–valsartan, the latter used only in heart failure. We also noted antihypertensive drugs dispensed as monotherapy and as combination therapies (typically an RAAS blocker with another agent). Other drugs that were dispensed during 2019 included lipid-lowering agents (mainly statins), oral hypoglycemic agents (noted together and as the more commonly dispensed individual classes), insulin, antiplatelet agents, antiarrhythmic agents, anticoagulant agents, digitalis, nitrates, inhaled glucocorticoids, nonsteroidal antiinflammatory drugs, immunosuppressive agents (i.e., glucocorticoids, calcineurin inhibitors, antiproliferative agents, and monoclonal antibodies), short-acting β-agonists, long-acting β-agonists, and other agents used for chronic respiratory diseases. Diagnostic, therapeutic, and procedural codes that were used for the current study are shown in Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The between-group relative difference in clinical features and drug exposures was used for comparing case patients and controls. Conditional logistic-regression models were fitted for estimating the odds ratio and corresponding 95% confidence interval for the risk of Covid-19 associated with exposures of interest. Models separately included clinical features and drug exposures listed above (unadjusted models), as well

Table 1. Demographic and Clinical Characteristics of Patients with Covid-19 (Case Patients) and Matched Controls.*

Characteristic	Case Patients (N = 6272)	Controls (N = 30,759)	Relative Difference
			%
Age — yr	68±13	68±13	MV
Female sex — no. (%)	2303 (36.7)	11,357 (36.9)	MV
Drugs — no. (%)†			
Antihypertensive drugs overall	3632 (57.9)	15,319 (49.8)	14.0
ACE inhibitors	1502 (23.9)	6,569 (21.4)	10.5
ARBs	1394 (22.2)	5,910 (19.2)	13.3
Calcium-channel blockers	1446 (23.1)	5,926 (19.3)	13.1
Beta-blockers	1826 (29.1)	7,123 (23.2)	20.5
Diuretics	1902 (30.3)	7,420 (24.1)	20.5
Thiazide or thiazide-like diuretics	1104 (17.6)	5,074 (16.5)	6.4
Loop diuretics	871 (13.9)	2,411 (7.8)	43.6
Mineralocorticoid-receptor antagonists	239 (3.8)	738 (2.4)	37.1
Monotherapy	1067 (17.0)	4,903 (15.9)	6.4
Combination therapy	2565 (40.9)	10,416 (33.9)	17.3
Oral antidiabetic drugs overall	861 (13.7)	3,158 (10.3)	25.0
Metformin	628 (10.0)	2,331 (7.6)	24.4
Sulfonylureas	214 (3.4)	781 (2.5)	25.6
DPP-4 inhibitors	89 (1.4)	313 (1.0)	28.4
GLP-1–receptor agonists	65 (1.0)	195 (0.6)	38.9
SGLT2 inhibitors	47 (0.7)	109 (0.4)	52.8
Thiazolidinediones	35 (0.6)	95 (0.3)	44.7
Other oral antidiabetic agents	219 (3.5)	825 (2.7)	23.3
Insulin	338 (5.4)	863 (2.8)	47.8
Lipid-lowering drugs	1928 (30.7)	7,833 (25.5)	16.9
Antiplatelet drugs	1363 (21.7)	4,868 (15.8)	26.9
Oral anticoagulant agents	643 (10.3)	2,173 (7.1)	30.9
Digitalis	66 (1.1)	170 (0.6)	47.3
Nitrates	201 (3.2)	624 (2.0)	36.5
Drugs for respiratory disease overall	943 (15.0)	3,170 (10.3)	31.3
Long-acting β-agonists	508 (8.1)	1,527 (5.0)	38.5
Short-acting β-agonists	268 (4.3)	880 (2.9)	32.8
Inhaled glucocorticoids	499 (8.0)	1,658 (5.4)	32.0
Other drugs for respiratory disease	258 (4.1)	614 (2.0)	51.3
Immunosuppressive agents	802 (12.8)	2,711 (8.8)	30.9
Nonsteroidal antiinflammatory drugs	1036 (16.5)	4,579 (14.9)	10.0
Nonselective COX inhibitors	864 (13.8)	3,914 (12.7)	7.7
Selective COX2 inhibitors	252 (4.0)	1,039 (3.4)	16.0

Table 1. (Continued)

Characteristic	Case Patients (N = 6272)	Controls (N = 30,759)	Relative Difference
			%
Coexisting conditions and associated procedures — no. (%)			
Cardiovascular disease	1891 (30.1)	6,679 (21.7)	28.0
Coronary artery disease	473 (7.5)	1,519 (4.9)	34.6
Percutaneous coronary intervention	244 (3.9)	823 (2.7)	31.3
Heart failure	323 (5.1)	759 (2.5)	52.1
Respiratory disease	651 (10.4)	1,716 (5.6)	46.3
Chronic obstructive pulmonary disease	188 (3.0)	433 (1.4)	53.1
Asthma	18 (0.3)	35 (0.1)	60.4
Kidney disease	311 (5.0)	818 (2.7)	26.8
Chronic kidney disease	181 (2.9)	393 (1.3)	55.8
Dialysis	49 (0.8)	54 (0.2)	77.6
Cancer	1091 (17.4)	4,639 (15.1)	13.3
Chronic Related Score — no. (%)‡			
0	2116 (33.7)	13,051 (42.4)	–25.8
1	1450 (23.1)	7,625 (24.8)	–7.2
2	1117 (17.8)	4,856 (15.8)	11.4
3	676 (10.8)	2,458 (8.0)	25.9
4	913 (14.6)	2,769 (9.0)	38.2

* Plus–minus values are means ±SD. Cases of coronavirus disease 2019 (Covid-19) were diagnosed between February 21 and March 11, 2020. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, COX cyclooxygenase, COX-2 cyclooxygenase 2, DPP-4 dipeptidyl peptidase 4, GLP-1 glucagon-like peptide 1, MV matching variable, and SGLT2 sodium–glucose cotransporter 2.

† Data are for patients who received at least one prescription during 2019. Only 10 patients (1 case patient and 9 controls) received renin inhibitors, and 87 patients (28 case patients and 59 controls) received sacubitril–valsartan.

‡ The Chronic Related Score is a new index of patients' clinical profile that is derived from inpatient and outpatient services provided by the Regional Health Service and is validated for outcome prediction.[28] Five categories of progressively worsening clinical profile are considered.

as all aforementioned baseline covariates together (adjusted model). Crude and adjusted estimates were obtained for the effect of antihypertensive therapy dispensed always as monotherapy or as a combination of two or more agents, both compared with the absence of any antihypertensive drug therapy dispensed during 2019. To test the hypothesis that exposure may affect the severity of clinical manifestations of Covid-19, analyses were restricted to the stratum of patients who had a critical or fatal infection. Stratifications for sex and age categories (<60 years vs. ≥60 years) were performed as secondary analyses.

To verify the robustness of our findings, we performed two further analyses. First, because records of exposure to antihypertensive drugs were not available after December 2019, data were analyzed according to three criteria — any prescriptions during 2019, at least three consecutive prescriptions during 2019, and at least one prescription in the last quarter of 2019, under the assumption that the two latter criteria might identify more reliably treatment that did not change. Second, because the strategy that was used for testing for coronavirus changed during the data collection, analyses were stratified according to the date of Covid-19 diagnosis (up to February 25, 2020, vs. February 26, 2020, and after).

Table 2. Odds Ratios for Covid-19 Associated with Use of RAAS Blockers, Other Blood-Pressure–Lowering Drugs, Drugs for Other Disease, and Other Features.*

Variable	Odds Ratio for Covid-19 (95% CI)†	
	Unadjusted	Adjusted
Drugs‡		
Antihypertensive drugs overall	1.53 (1.43–1.63)	
ACE inhibitors	1.16 (1.08–1.24)	0.96 (0.87–1.07)
ARBs	1.20 (1.12–1.29)	0.95 (0.86–1.05)
Calcium-channel blockers	1.28 (1.18–1.38)	1.03 (0.95–1.12)
Beta-blockers	1.42 (1.33–1.51)	0.99 (0.91–1.08)
Diuretics as a whole	1.69 (1.57–1.83)	
Thiazide or thiazide-like diuretics	1.09 (1.01–1.17)	1.03 (0.86–1.23)
Loop diuretics	2.01 (1.83–2.20)	1.46 (1.23–1.73)
Mineralocorticoid-receptor antagonists	1.59 (1.37–1.85)	0.90 (0.75–1.07)
Oral antidiabetic drugs overall	1.40 (1.28–1.52)	1.07 (0.97–1.17)
Insulin	1.98 (1.74–2.25)	1.37 (1.19–1.58)
Lipid-lowering drugs	1.33 (1.24–1.41)	1.02 (0.94–1.10)
Antiplatelet drugs	1.52 (1.41–1.63)	1.19 (1.09–1.30)
Oral anticoagulant agents	1.51 (1.37–1.66)	1.16 (1.04–1.30)
Digitalis	1.94 (1.45–2.59)	1.24 (0.91–1.69)
Nitrates	1.55 (1.31–1.83)	1.04 (0.87–1.24)
Drugs for respiratory disease overall	1.54 (1.43–1.67)	1.25 (1.15–1.36)
Immunosuppressant agents	1.50 (1.38–1.63)	1.30 (1.20–1.42)
Nonsteroidal antiinflammatory drugs	1.13 (1.05–1.22)	1.06 (0.98–1.15)
Coexisting conditions		
Cardiovascular disease	1.66 (1.55–1.78)	1.01 (0.91–1.10)
Respiratory diseases	1.19 (1.10–1.28)	1.37 (1.23–1.54)
Kidney disease	1.97 (1.79–2.17)	1.13 (0.94–1.36)
Cancer	1.93 (1.68–2.21)	1.04 (0.94–1.16)
Chronic Related Score		
0	1.00 (reference)	1.00 (reference)
1	1.33 (1.23–1.43)	1.19 (1.09–1.31)
2	1.70 (1.56–1.86)	1.38 (1.23–1.54)
3	2.12 (1.91–2.36)	1.55 (1.34–1.78)
4	2.63 (2.37–2.91)	1.57 (1.34–1.84)

* CI denotes confidence interval, and RAAS renin–angiotensin–aldosterone system.
† Shown are odds ratios for Covid-19 associated with exposure to treatments and coexisting conditions. Absence of exposure was considered as the reference, unless otherwise indicated. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown. Fully adjusted estimates were obtained from a unique multivariate analysis.
‡ Data are for patients who received at least one prescription during 2019.

RESULTS

CASE PATIENTS AND CONTROLS

Among the 6292 case patients, a control of the same sex, age, and municipality of residence could not be found for 20 persons. The remaining 6272 case patients (99.7%) who were included in the analysis were matched to 30,759 controls; the 1:5 matching was fully successful for 6015 included case patients, whereas fewer than 5 controls were

available for the remaining 257 case patients (4.1%). At the index date, the mean (±SD) age of case patients and controls was 68±13 years, and nearly 37% were women (matching variables).

Table 1 shows that ARBs and ACE inhibitors were both more frequently prescribed in case patients than in controls. The percentage of patients who received ARBs was 22.2% among case patients and 19.2% among controls (relative difference, 13.3%); the percentage of patients who received ACE inhibitors was 23.9% and 21.4%, respectively (relative difference, 10.5%). Other antihypertensive drugs were also used more in case patients than in controls, the difference usually being larger than for ACE inhibitors and ARBs, particularly for loop diuretics (13.9% vs. 7.8%; relative difference, 43.6%) and mineralocorticoid-receptor antagonists (3.8% vs. 2.4%; relative difference, 37.1%). Use of renin inhibitors (1 case patient) and sacubitril–valsartan (28 case patients) was uncommon, and no further analysis of these treatments was carried out. Case patients also used a combination of antihypertensive drugs more frequently than controls, had a more frequent history of hospitalization for cardiovascular and noncardiovascular diseases, and, according to the CReSc index, had an overall substantially worse clinical profile.

ARBs, ACE Inhibitors, and Covid-19

Table 2 shows unadjusted estimates of the risk of Covid-19 according to the drugs shown in Table 1, which suggested a possible effect. However, after multivariable adjustment, neither ARBs nor ACE inhibitors had a significant association with the risk of Covid-19. This was also the case for calcium-channel blockers, beta-blockers, and diuretics. An association with Covid-19 after multivariable adjustment was maintained by loop diuretics and some other non-antihypertensive drugs (insulin, antiplatelet agents, anticoagulants, immunosuppressant drugs, and drugs used for respiratory disease). As compared with patients who did not use antihypertensive drugs during 2019, those to whom antihypertensive agents were dispensed as monotherapy or as a combination of two or more agents appeared to have a greater risk of Covid-19 in the unadjusted (crude) analysis, but after multivariable adjustment, neither monotherapy nor combination therapy showed a significant association with the risk of Covid-19 (Table 3). The multivariable adjusted risk of Covid-19 was increased in patients with previous hospitalizations for cardiovascular or noncardiovascular diseases. It also became progressively greater as the CReSc increased (Table 2).

Table 3. Odds Ratios for Covid-19 Associated with Use of Antihypertensive Drugs Dispensed as Monotherapy or Combination Therapy.

Variable	Odds Ratio for Covid-19 (95% CI)*	
	Unadjusted	Adjusted
No use during 2019	1.00 (reference)	1.00 (reference)
Use only as monotherapy	1.39 (1.28–1.51)	1.03 (0.90–1.18)
Use as combination therapy	1.60 (1.50–1.72)	0.99 (0.90–1.09)

* Shown are odds ratios for Covid-19 associated with drug use. Nonuse was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown.

Subgroup and Sensitivity Analyses

Data on the risk of Covid-19 infection associated with the use of RAAS blockers and other drugs were similar in men and in women (Table 4 and Tables S2 and S3). There was no statistical evidence that the findings obtained for the entire cohort were modified by age or the severity of the clinical manifestations and course of Covid-19 (Table 4 and Tables S3 through S5). As shown in Figure S1, the data on Covid-19 and antihypertensive drugs were consistent regardless of whether drug use was assessed through loose or more strict criteria. Furthermore, the findings did not change substantially when case patients were stratified according to the date of Covid-19 diagnosis (Table S6).

DISCUSSION

In the present study, the use of ARBs and ACE inhibitors was more frequent among patients who were infected with SARS-CoV-2 than among the large number of controls who were matched for age, sex, and place of residence. However, all other major antihypertensive drugs, such as calcium-channel blockers, beta-blockers, and diuretics, were also used more frequently in patients with Covid-19, with differences from controls that were larger than those shown by ARBs and ACE inhibitors. Furthermore, in a multivariable analysis in which data were adjusted for a number of treatment-related covariates and markers of patient clinical status, the use of ARBs or ACE in-

Table 4. Adjusted Odds Ratios for Covid-19 Associated with Use of RAAS Blockers and Other Antihypertensive Drugs.

Variable	Odds Ratio for Covid-19 (95% CI)*				
	ACE Inhibitors	ARBs	Calcium-Channel Blockers	Diuretics	Beta-Blockers
Severity of clinical manifestations†					
Mild to moderate	0.97 (0.88–1.07)	0.96 (0.87–1.07)	1.01 (0.92–1.10)	1.07 (0.97–1.19)	0.98 (0.89–1.07)
Critical or fatal	0.91 (0.69–1.21)	0.83 (0.63–1.10)	1.15 (0.91–1.44)	0.96 (0.74–1.26)	1.07 (0.84–1.37)
Sex‡					
Female	0.95 (0.81–1.12)	0.89 (0.76–1.05)	1.06 (0.92–1.23)	1.12 (0.94–1.34)	1.04 (0.91–1.20)
Male	0.98 (0.87–1.11)	0.98 (0.86–1.11)	1.00 (0.90–1.11)	1.02 (0.91–1.15)	0.97 (0.87–1.08)
Age at diagnosis§					
<60 Yr	0.94 (0.71–1.25)	0.89 (0.67–1.18)	1.13 (0.88–1.46)	0.99 (0.75–1.31)	1.00 (0.78–1.29)
≥60 Yr	0.97 (0.87–1.08)	0.95 (0.85–1.06)	1.01 (0.93–1.11)	1.07 (0.97–1.19)	0.99 (0.90–1.08)

* Shown are odds ratios for Covid-19 associated with exposure to antihypertensive drugs (at least one prescription during 2019). Absence of exposure was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Estimates were fully adjusted for drugs and coexisting conditions.

† Data are for 5655 case patients with mild-to-moderate disease and 27,790 matched controls and for 617 case patients with critical or fatal disease and 2969 matched controls.

‡ Data are for 13,660 women (2303 case patients and 11,357 controls) and 23,371 men (3969 case patients and 19,402 controls).

§ Data are for 11,547 patients (1932 case patients and 9615 controls) younger than 60 years of age and 25,484 patients (4340 case patients and 21,144 controls) 60 years of age or older.

hibitors was not significantly associated with the risk of Covid-19. Finally, there was no statistical evidence of an independent association between the use of a combination of antihypertensive drugs (in which an ACE inhibitor or an ARB is by far the most common component) and the risk of Covid-19. Thus, our results do not provide evidence of an independent relationship between RAAS blockers and the susceptibility to Covid-19 in humans.

We found that patients with Covid-19 had a higher baseline prevalence of cardiovascular conditions and diseases (hypertension, coronary heart disease, heart failure, and chronic kidney disease) for which treatment with the medications studied here is often used. Such observations confirm previous observations by Chinese investigators that patients with Covid-19 generally have poorer health than the general population,[11-15] a conclusion that in the present study is strongly supported by the evidence that patients with Covid-19 were more frequently treated with drugs for many noncardiovascular diseases, had a higher incidence of previous hospitalizations for a variety of causes, and had higher scores for chronic coexisting conditions than controls.[6,29,30]

The present study provides several additional findings. First, the conclusion that RAAS blockers do not modify susceptibility to Covid-19 applies to both sexes as well as to younger and older persons. Second, our data provide no evidence that, rather than modifying the susceptibility to Covid-19, RAAS blockers alter the evolution of the disease, thereby mainly affecting its severity. In our study, neither ACE inhibitors nor ARBs showed an independent association with Covid-19 in patients with mild-to-moderate disease or in those with severe disease. Third, patients with Covid-19 had much more frequent use of loop diuretics and mineralocorticoid-receptor antagonists than controls, and treatment with loop diuretics was associated with an increased risk of Covid-19 in the multivariable analysis. Rather than suggesting an association (for which there is no mechanistic support), this finding is likely to mean that use of loop diuretics reflects the existence of clinical conditions such as heart failure or advanced renal damage, the severity of which was not appropriately quantified by the available clinical data and scores. These observations from our study may account for the independent relationship that was found between Covid-19 and some noncardiovascular drugs, although more direct investigations with appro-

priate experimental designs would be required to clarify this issue.

One strength of the study is the large number of case patients as well as the inclusion of a large and well-matched control group, without which interpretation of the collected data would have been difficult. It is also a strength that the Lombardy database included previous hospitalizations and allowed the drugs prescribed to outpatients to be accurately observed, because pharmacists must file outpatient prescriptions to claim reimbursement, and incorrect reports carry legal consequences.

Limitations of the study include the fact that information on drug use is limited to prescriptions, and actual drug consumption by the case patients and controls could not be assessed. Drugs that were purchased by the patients (because doctors prescribed them privately, and no records were in the National Health Service system) as well as those dispensed after December 31, 2019, were not captured by our analysis. However, the availability of free antihypertensive agents makes out-of-pocket purchase of these drugs rare, and an exploratory analysis involving patients in whom antihypertensive treatment had been taken regularly or closer to the time of infection did not modify the results. Our results reflect the doses of RAAS blockers used in Italian medical practice but did not allow us to investigate other doses, because this information was not included in the database. It is likely that the control group included some persons with Covid-19, since the general population in Italy was not tested. Unmeasured confounders may have been responsible for our findings. For example, given the hypothesis that RAAS blockers increase the risk of severe clinical manifestations of Covid-19, there may have been preferential dispensation of RAAS blockers to patients with better clinical profiles and a lower perceived likelihood of the development of severe Covid-19. However, there was no evidence that patients who received ARBs or ACE inhibitors had a better clinical profile than those who received other antihypertensive medications. Finally, our results apply to a largely white population and cannot be generalized to other races.

The present study does not provide evidence that the use of ACE inhibitors or ARBs is independently associated with the risk of Covid-19.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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