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Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality

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IMPORTANCE It has been hypothesized that angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) may make patients more susceptible to coronavirus disease 2019 (COVID-19) and to worse outcomes through upregulation of the functional receptor of the virus, angiotensin-converting enzyme 2.

OBJECTIVE To examine whether use of ACEI/ARBs was associated with COVID-19 diagnosis and worse outcomes in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS To examine outcomes among patients with COVID-19, a retrospective cohort study using data from Danish national administrative registries was conducted. Patients with COVID-19 from February 22 to May 4, 2020, were identified using *ICD-10* codes and followed up from day of diagnosis to outcome or end of study period (May 4, 2020). To examine susceptibility to COVID-19, a Cox regression model with a nested case-control framework was used to examine the association between use of ACEI/ARBs vs other antihypertensive drugs and the incidence rate of a COVID-19 diagnosis in a cohort of patients with hypertension from February 1 to May 4, 2020.

EXPOSURES ACEI/ARB use was defined as prescription fillings 6 months prior to the index date.

MAIN OUTCOMES AND MEASURES In the retrospective cohort study, the primary outcome was death, and a secondary outcome was a composite outcome of death or severe COVID-19. In the nested case-control susceptibility analysis, the outcome was COVID-19 diagnosis.

RESULTS In the retrospective cohort study, 4480 patients with COVID-19 were included (median age, 54.7 years [interquartile range, 40.9-72.0]; 47.9% men). There were 895 users (20.0%) of ACEI/ARBs and 3585 nonusers (80.0%). In the ACEI/ARB group, 18.1% died within 30 days vs 7.3% in the nonuser group, but this association was not significant after adjustment for age, sex, and medical history (adjusted hazard ratio [HR], 0.83 [95% CI, 0.67-1.03]). Death or severe COVID-19 occurred in 31.9% of ACEI/ARB users vs 14.2% of nonusers by 30 days (adjusted HR, 1.04 [95% CI, 0.89-1.23]). In the nested case-control analysis of COVID-19 susceptibility, 571 patients with COVID-19 and prior hypertension (median age, 73.9 years; 54.3% men) were compared with 5710 age- and sex-matched controls with prior hypertension but not COVID-19. Among those with COVID-19, 86.5% used ACEI/ARBs vs 85.4% of controls; ACEI/ARB use compared with other antihypertensive drugs was not significantly associated with higher incidence of COVID-19 (adjusted HR, 1.05 [95% CI, 0.80-1.36]).

CONCLUSIONS AND RELEVANCE Prior use of ACEI/ARBs was not significantly associated with COVID-19 diagnosis among patients with hypertension or with mortality or severe disease among patients diagnosed as having COVID-19. These findings do not support discontinuation of ACEI/ARB medications that are clinically indicated in the context of the COVID-19 pandemic.

Editor's Note

Audio and Supplemental content

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Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major threat to global health. Research on modifiable risk factors potentially linked to increased susceptibility to infection or to worse outcomes among those who have the disease has focused on cardiovascular comorbidity, hypertension, and diabetes.[1-5] Interest has been directed to the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) because these drugs may affect the ability of SARS-CoV-2 to infect cells through upregulation of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2 cell entry.[6,7] Based on this suggested mechanism, media reports have raised questions about ACEI/ARB treatment in the setting of COVID-19. In response, opinion leaders[5,8-10] have emphasized that data do not support discontinuation of ACEI/ARBs and have called for outcome studies. Data are emerging from selected cohorts, and results to date have suggested that ACEI/ARB use was not associated with increased risk of COVID-19 or worse outcomes among those with infection.[10-14] To further inform these questions, a nationwide observational study of patients in Denmark through May 4, 2020, examined whether use of ACEI/ARBs was associated with susceptibility to COVID-19 and with risk of death or severe infection among those with COVID-19 when accounting for patients' comorbidities and age.

Key Points

Question Is angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use associated with greater susceptibility to coronavirus disease 2019 (COVID-19) and with worse outcomes after COVID-19 diagnosis?

Findings In a retrospective cohort study of 4480 patients diagnosed as having COVID-19, prior ACEI/ARB use, compared with no use, was not significantly associated with mortality (adjusted hazard ratio, 0.83). In a nested case-control study of a cohort of 494 170 patients with hypertension, use of ACEI/ARB, compared with use of other antihypertensive medications, was not significantly associated with COVID-19 diagnosis (adjusted hazard ratio, 1.05).

Meaning Prior use of ACEI/ARB was not significantly associated with COVID-19 diagnosis or with mortality among patients diagnosed as having COVID-19.

Methods

Retrospective studies do not require ethics approval in Denmark and all data were deidentified and only available through Statistics Denmark. Approval from the Danish Data Protection Agency was secured, and the need for patient informed consent was waived.

Data Sources

Data from Danish national administrative registries were linked on an individual level by the use of a unique personal identifier. By such linkage, data were obtained on civil status, hospitalizations, procedures, and prescription fills. The Danish health care system is administered by the state, and all hospitalizations since 1978 are registered (using *International Classification of Diseases, Eighth Revision* [*ICD-8*] coding of diagnoses from 1978-1994 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] thereafter), all procedures since 1996 are registered, and all prescription fills since 1995 are registered. The Danish registries are validated, previously described in detail, and are of high quality and completeness.[15,16]

Study Patients and Covariates

For the retrospective cohort study, all Danish residents were available for study inclusion, and those who were examined in a hospital and had a diagnosis code for COVID-19 registered after February 1, 2020, were included in this study (explicit *ICD-10* codes B342A, B972, and B972A created for the COVID-19 pandemic by the Danish Ministry of Health in accord with the definition established by the World Health Organization). A local hospital (University Hospital of Copenhagen, Rigshospitalet) approved a quality assessment of COVID-19 *ICD-10* codes for the present study; 98 patient records with an *ICD-10* code for COVID-19 were reviewed and 97 of these had a laboratory-confirmed real-time reverse transcription–polymerase chain reaction test for SARS-CoV-2 (extrapolated positive predictive value, 98%). The index date was day of diagnosis of COVID-19. Socioeconomic status was defined by educational level and the median household income the year prior to the index date by quartiles. Medical histories and use of medications were defined by diagnoses related to prior hospital admissions or outpatient visits and filled prescriptions through Danish pharmacies. Definitions have been used in prior studies and have been validated in the national Danish registries.[15,16] Specifically, hypertension was defined by use of more than 1 antihypertensive drug, as previously defined with good specificity.[17]

For the susceptibility analysis, a nested case-control framework was used. A cohort of all patients with hypertension in Denmark was followed up between February 1, 2020, and until incident COVID-19 diagnosis, death without incident COVID-19 diagnosis, or May 4, 2020, whichever came first. Patients with COVID-19 and prior hypertension were designated as cases in the analysis, and these were matched with 10 controls on age and sex among users of antihypertensive drugs without COVID-19. Patients with other indications for ACEI/ARB therapy (eg, heart failure or chronic kidney failure) were excluded to limit confounding by indication.

Exposure of Interest: Use of ACEI/ARBs

The exposure of interest was patients' use of ACEI/ARBs, and this was captured through prescription fillings (≥1 filling) in a 6-month period prior to the index date. The anatomical therapeutic group code of C09 was used for identifying ACEI/ARBs, C09AA for ACEIs, and C09CA for ARBs. C09BA was used for combinations of ACEIs and diuretics and C09DA for combinations of ARBs and diuretics. Sacubitril/valsartan was categorized as an ARB. To increase the robustness of the exposure definition and results, all analyses were repeated among ACEI/ARB users who filled a prescription within 3 months of

the index date instead of 6 months. In addition, analyses were performed for those who filled more than 1 prescription within 6 months of the index date.

Outcomes, Follow-up, and Comparison

For the retrospective cohort study, there were 3 outcomes of interest compared by ACEI/ARB use or no use. The primary outcome was all-cause death. Secondary outcomes were (1) a composite of death or severe COVID-19 (defined as *ICD-10* diagnosis code B972A designating COVID-19 with SARS or intensive care unit admission designated by procedure code NABE) and (2) severe COVID-19 (*ICD-10* code B972A or intensive care unit admission). Patients were followed up from the index date and until 1 of the following: outcome occurrence, end of study period (May 4, 2020), or emigration from Denmark. For the primary analyses, ACEI/ARB use was the exposure of interest and nonusers were the control group. For the sensitivity analyses, ACEI/ARB users were compared with 2 different active controls: patients using any other antihypertensive drug and patients using calcium channel blockers (CCBs).

For the susceptibility analysis, among patients with hypertension, the association between ACEI/ARB use and COVID-19 diagnosis was analyzed in a nested case-control framework. The primary outcome for this analysis was COVID-19 diagnosis. The incidence rates of COVID-19 among ACEI/ARB users were compared with the incidence rates among (1) patients using other antihypertensive drugs and (2) patients using CCBs.

Statistical Analyses

Patient characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables, and differences were tested with Wilcoxon and χ^2 tests, respectively. Outcomes were analyzed with the Kaplan-Meier method and compared using Cox regression, both unadjusted and adjusted. Adjusted models included the following covariates: age; sex; highest obtained education; income; history of myocardial infarction, heart failure, kidney disease, stroke, peripheral artery disease, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, and malignancy; and use of the following concomitant medications: other antihypertensive drugs, lipid-lowering drugs, anticoagulants, or nonsteroidal anti-inflammatory drugs. Hazard ratios (HRs), 30-day risks of outcomes standardized to the risk factor distribution of all patients in the sample, and differences of standardized 30-day risks are reported.

For the outcome of severe COVID-19, the main Cox regression model was combined with a Cox regression model for the rate of the competing risk of death without severe COVID-19.[18] We tested and found the assumptions of the Cox regression model (proportional hazards, no interactions, linearity of the effect of age) to be valid by comparing the estimate of the model with a random survival forest model, which does not make any of these assumptions.

ACEI/ARB users were compared with nonusers but also with active controls of users of CCBs. This was done in a subgroup of patients using either CCBs or ACEI/ARBs; patients who used both ACEI/ARBs and CCBs were not included. Prior ACEI use vs prior ARB use was also examined separately and compared with nonusers. Subgroup analyses (by sex, patients with known hypertension, hospitalized patients, and age groups) were performed, and differences of HRs between subgroups were tested by Wald tests for statistical interaction. As a sensitivity analysis, all analyses were repeated among ACEI/ARB users who filled a prescription within 3 months of the index date instead of 6 months. In addition, analyses were also performed for those who filled more than 1 prescription within 6 months of the index date.

Susceptibility to COVID-19 associated with ACEI/ARB use was examined with a Cox regression model with baseline hazard rate stratified for age and sex. The model was fitted using a nested case-control design with 10 age- and sex-matched controls for each COVID-19 case as described by Borgan and Samuelsen.[19] The model makes no proportional hazards assumption for the matching variables (age and sex); but the proportional hazards assumption of the other variables was tested visually with marginal residual plots and was found to be met. Cases (patients with COVID-19) were identified for the analysis by following a cohort of patients with hypertension from February 1, 2020 (ensuring that all persons were "event-free"), through May 4, 2020.

Cases were matched with 10 controls on age and sex from the subgroup of the cohort who was still "at-risk," ie, alive and without a COVID-19 diagnosis at the date of the COVID-19 case's diagnosis. The model was further adjusted for history of chronic obstructive pulmonary disease, diabetes, cancer, myocardial infarction, and cerebrovascular disease. Missingness was minimal (only relevant for education and, for that, missingness was <1%), imputation methods were not required, and all analyses represent complete-case analyses. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All statistical analyses were performed using the SAS statistical software (version 9.4; SAS Institute) and R (Version 4.0.1; R Core Team [2019]). The level of statistical significance was set at 5% and all statistical tests were 2-tailed.

Results

For the retrospective cohort study designed to examine outcomes among patients with COVID-19, 4480 patients with COVID-19 were included; 895 (20.0%) used ACEI/ARBs and 3585 (80.0%) did not. Patient selection is shown in the eFigure in the Supplement. The first patient was included on February 22, 2020, and the last on May 4, 2020. Baseline characteristics of the study groups are shown in **Table 1**. Users of ACEI/ARBs were older than nonusers (72.8 years [IQR, 61.0-81.0] vs 50.1 years [IQR, 37.2-64.5]) and were more likely to have comorbid conditions, especially cardiovascular comorbidity (eg, 21.6% vs 5.2% with prior myocardial infarction and 14.6% vs 3.1% with heart failure). ACEI/ARB users were more often men than nonusers (55.1% vs 46.1%). A total of 2222 patients (49.6%) were hospitalized when the diagnosis of COVID-19 was made. The median follow-up time was

Table 1. Baseline Characteristics of Patients With COVID-19 by Use and Nonuse of ACEI/ARBs

Characteristic	ACEI/ARB, No. (%)	
	Users (n = 895 [20.0%])	Nonusers (n = 3585 [80.0%])
Sex		
Male	493 (55.1)	1651 (46.1)
Female	402 (44.9)	1934 (53.9)
Age, median (IQR), y	72.8 (61.0-81.0)	50.1 (37.2-64.5)
Married	537 (60.0)	2139 (59.7)
Living alone	355 (39.7)	1284 (35.8)
Ethnic group		
Native Danish	781 (87.3)	2927 (81.7)
Immigrant	112 (12.5)	546 (15.2)
Descendant from immigrant	<3[a]	112 (3.1)
Medical history		
Hypertension	634 (70.8)	209 (5.8)
Diabetes	217 (24.2)	194 (5.4)
Myocardial infarction	193 (21.6)	186 (5.2)
Cancer	188 (21.0)	367 (10.2)
Cerebrovascular disease	174 (19.4)	228 (6.4)
COPD	171 (19.1)	463 (12.9)
Heart failure	131 (14.6)	112 (3.1)
Atrial fibrillation	128 (14.3)	189 (5.3)
Peripheral artery disease	107 (12.0)	124 (3.5)
Chronic kidney disease	67 (7.5)	105 (2.9)
Concomitant pharmacotherapy		
Lipid-lowering drug	415 (46.4)	382 (10.7)
Calcium channel blocker	291 (32.5)	196 (5.5)
β-Blocker	284 (31.7)	241 (6.7)
Aspirin	192 (21.5)	151 (4.2)
Loop diuretic	187 (20.9)	181 (5.0)
Anticoagulation	146 (16.3)	202 (5.6)
Socioeconomics, income quartile		
Lowest	251 (28.0)	869 (24.2)
Highest	132 (14.7)	988 (27.6)
Highest obtained educational level		
Basic school	313 (35.0)	845 (23.6)
High school/vocational education	369 (41.2)	1300 (36.3)
Short/medium length higher education	150 (16.8)	967 (27.0)
Long higher education	63 (7.0)	473 (13.2)

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a] The exact number of patients is withheld to maintain confidentiality.

34 days (IQR, 25-47) from date of COVID-19 diagnosis. At the end of the study period, 165 patients were still hospitalized.

Mortality and Severe Disease Among Patients Diagnosed as Having COVID-19

In the ACEI/ARB group, 18.1% died within 30 days vs 7.3% in the nonuser group. **Table 2** shows the unadjusted and adjusted HRs from the Cox regression analysis. ACEI/ARB use was significantly associated with greater risk of mortality relative to nonuse in the unadjusted analysis (HR, 2.65 [95% CI, 2.18-3.23]), but the association was not significant after accounting for age and medical history (HR, 0.83 [95% CI, 0.67-1.03]). Standardized 30-day mortality risks are shown in **Table 3** and showed similar results with adjusted standardized mortality of 8.8% (95% CI, 7.6%-10.1%) among ACEI/ARB users and 10.2% (95% CI, 9.1%-11.3%) among nonusers (risk difference, −1.3% [95% CI, −2.9% to 0.2%]; P = .09).

By 30 days, the combined end point of death or severe COVID-19 had occurred in 31.9% of ACEI/ARB users and in 14.2% of nonusers. The adjusted standardized 30-day risk was 17.9% (95% CI, 15.9%-19.7%) in the ACEI/ARB group vs 17.2% (95% CI, 15.9%-18.5%) in the nonuser group (risk difference, 0.6% [95% CI, −1.7% to 2.9%]; P = .62). Table 2 shows the unadjusted and adjusted HRs derived from the Cox regression analysis. Like the primary outcome of death, ACEI/ARB use was significantly associated with a higher rate of the combined end point of death or severe COVID-19 in unadjusted analysis (HR, 2.49 [95% CI, 2.15-2.88]), but this association was not significant after adjusting for age and comorbidities (HR, 1.04 [95% CI, 0.89-1.23]).

Severe COVID-19 was coded in 576 patients (12.9%) within 30 days: 203 (22.6%) among ACEI/ARB users and 373 (10.4%) among nonusers. Adjusted standardized absolute 30-day risk of severe COVID-19 was 14.8% (95% CI, 12.7%-16.9%) in the ACEI/ARB group and 12.9% (95% CI, 11.7%-14.2%) in the nonuser group (risk difference, 1.9% [95% CI, −0.8% to 4.5%]; P = .17). Table 2 shows the unadjusted and adjusted HRs from the Cox regression analysis. ACEI/ARB use was associated with severe COVID-19 in unadjusted analysis (HR, 2.34 [95% CI, 1.97-2.77]), but this association was not significant after adjusting for age and comorbidities (HR, 1.15 [95% CI, 0.95-1.41]).

Analyses of Susceptibility

Table 4 shows the characteristics of the cohort of patients with hypertension at the start of follow-up (February 1, 2020). Users of ACEI/ARBs were of similar age as the overall group of patients with hypertension; the median age was 71 years (IQR, 62-78) for ACEI/ARB users and 71 years (IQR, 62-78) for the entire cohort, whereas CCB users were older (median age, 73 years [IQR, 65-80]). Prevalence of prior diabetes and myocardial infarction were also similar for ACEI/ARB users (12.5% and 12.7%) compared with the entire hypertension cohort (12.1% and 13.5%); more CCB users had prior myocardial infarction (16.9%) but fewer had diabetes (8.0%).

In the nested case-control analysis of COVID-19 susceptibility, cases comprised 571 patients with COVID-19 and prior hypertension (median age, 73.9 years [IQR, 63.1-80.8]; 54.3% men) and these were compared with 5710 age- and sex-matched controls with prior hypertension but not COVID-19. Among cases, 86.5% used ACEI/ARBs vs 85.4% of controls. eTable 1 in the Supplement shows the characteristics at the time of COVID-19 diagnosis for these patients included in the analysis.

Compared with use of other antihypertensive drugs, ACEI/ARB use was not significantly associated with COVID-19 (adjusted HR, 1.05 [95% CI, 0.80-1.36]). This finding was similar for ACEI users and for ARB users analyzed separately (**Table 5**).

Table 2. Hazard Ratios for ACEI/ARB Use vs No Use and Death, Composite of Death or Severe COVID-19, and Severe COVID-19

	No. (%)		Unadjusted model		Age- and sex-adjusted model		Fully adjusted model[a]	
	ACEI/ARB users (n = 895)	ACEI/ARB nonusers (n = 3585)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Primary outcome								
Mortality	181 (20.2)	297 (8.3)	2.65 (2.18-3.23)	<.001	0.97 (0.79-1.18)	.82	0.83 (0.67-1.03)	.09
Secondary outcomes								
Mortality or severe COVID-19	292 (32.6)	526 (14.7)	2.49 (2.15-2.88)	<.001	1.17 (1.00-1.36)	.04	1.04 (0.89-1.23)	.61
Severe COVID-19	203 (22.6)	373 (10.4)	2.34 (1.97-2.77)	<.001	1.32 (1.10-1.58)	.003	1.15 (0.95-1.41)	.15

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COVID-19, coronavirus disease 2019.

[a] Fully adjusted model includes the following covariates: age; sex; highest obtained educational level; medical history of myocardial infarction, heart failure, kidney disease, stroke, peripheral artery disease, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, or malignancy; and use of the following concomitant medications: other antihypertensive drugs, lipid-lowering drugs, and anticoagulation.

Table 3. Standardized 30-Day Absolute Risks for Death, Composite of Death or Severe COVID-19, and Severe COVID-19

	Risk, % (95% CI)[a]		30-d Risk difference, % (95% CI)	*P* value
	ACEI/ARB users	ACEI/ARB nonusers		
Primary outcome				
Standardized 30-d mortality				
Unadjusted	18.2 (15.7 to 20.7)	7.3 (6.4 to 8.2)	10.9 (8.3 to 13.6)	<.001
Age- and sex-adjusted	9.4 (8.2 to 10.7)	9.7 (8.6 to 10.7)	−0.2 (−1.7 to 1.2)	.75
Fully adjusted	8.8 (7.6 to 10.1)	10.2 (9.1 to 11.3)	−1.3 (−2.9 to 0.2)	.09
Secondary outcomes				
Death or severe COVID-19				
Unadjusted	31.7 (28.8 to 34.6)	14.2 (13.0 to 15.4)	17.5 (14.3 to 20.8)	<.001
Age- and sex-adjusted	19.0 (17.1 to 20.8)	16.7 (15.5 to 18.0)	2.2 (0 to 4.5)	.05
Fully adjusted	17.8 (15.9 to 19.7)	17.2 (15.9 to 18.5)	0.6 (−1.7 to 2.9)	.62
Severe COVID-19				
Unadjusted	23.8 (20.9 to 26.8)	10.7 (9.6 to 11.7)	13.2 (10.0 to 16.3)	<.001
Age and sex-adjusted	16.0 (13.9 to 18.2)	12.4 (11.2 to 13.6)	3.6 (1.0 to 6.2)	.006
Fully adjusted	14.8 (12.7 to 16.9)	12.9 (11.7 to 14.2)	1.9 (−0.8 to 4.5)	.17

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; COVID-19, coronavirus disease 2019.

[a] ACEI/ARB users and nonusers diagnosed in the hospital system were compared.

For ACEI/ARB users compared with users of CCBs, the incidence rate of COVID-19 was not significantly different (HR, 1.23 [95% CI, 0.89-1.70]).

Sensitivity and Subgroup Analyses

For the retrospective cohort study, among patients with COVID-19, several sensitivity analyses were performed. An active comparator of CCB users was chosen, and analyses were computed for ACEI/ARB use alone vs CCB use without concurrent ACEI/ARB use. Patient characteristics are shown for the ACEI/ARB group vs the CCB users in eTable 2 in the Supplement. Groups shown in eTable 2 in the Supplement are not exclusive, but for outcomes analyses, patients represented in both groups were excluded. ACEI/ARB users were younger than CCB users (median age, 72.8 years vs 73.6 years) and were more likely to have had prior heart failure (14.6% vs 6.8%) and myocardial infarction (21.6% vs 17.9%). Analyses comparing ACEI/ARB users vs CCB users and analyses that evaluated ACEI users and ARB users separately compared with nonusers yielded HRs that were not statistically significant (**Table 6**).

The following subgroups were examined: (1) patients who required hospitalization, (2) patients with known hypertension, (3) by sex, and (4) by age groups (**Figure**). The results were similar to the overall results, and all tests for interaction with these covariates were not statistically significant ($P > .05$).

All analyses were repeated among patients with a prescription filling within 3 months of index, and results were similar to the main results. The unadjusted and adjusted HRs for death were 2.23 (95% CI, 1.80-2.75) and 0.77 (95% CI, 0.61-0.96), respectively. For the composite outcome of death or severe COVID-19, the unadjusted and adjusted HRs were 2.27 (95% CI, 1.94-2.65) and 1.01 (95% CI, 0.85-1.20). For severe COVID-19, the unadjusted and adjusted HRs were 2.23 (95% CI, 1.86-2.68) and 1.16 (95% CI, 0.95-1.42), respectively.

Discussion

Among patients diagnosed as having COVID-19, this study found no significant association between prior ACEI/ARB use and mortality or severe COVID-19 after adjusting for baseline

Table 4. Baseline Characteristics of All Danish Persons With Hypertension (and No Heart Failure or Kidney Disease) on February 1, 2020[a]

Characteristic	No. (%)		
	All persons with hypertension (N = 494 170)	ACEI/ARB use and no CCB use (n = 199 510)	CCB use and no ACEI/ARB use (n = 45 758)
Sex			
Men	242 755 (49.1)	90 223 (45.2)	18 957 (41.4)
Women	251 415 (50.9)	109 287 (54.8)	26 801 (58.6)
Age, median (IQR), y	71 (62-78)	71 (62-78)	73 (65-80)
Married	312 028 (63.1)	127 199 (36.2)	27 047 (59.1)
Living alone	181 920 (36.8)	72 218 (36.2)	18 682 (40.8)
Ethnic group			
Native Danish	463 856 (93.9)	186 897 (93.7)	42 982 (93.9)
Immigrant	29 405 (5.9)	12 248 (6.1)	2693 (5.9)
Descendant from immigrant	909 (0.2)	365 (0.2)	83 (0.2)
Medical history			
Myocardial infarction	59 732 (12.1)	24 849 (12.5)	7753 (16.9)
Heart failure	0	0	0
Hypertension	494 170 (100)	199 510 (100)	45 758 (100)
Atrial fibrillation	46 182 (9.3)	20 080 (10.1)	5871 (12.8)
Cerebrovascular disease	64 461 (13.0)	23 090 (11.6)	6688 (14.6)
Peripheral artery disease	35 573 (7.2)	12 757 (6.4)	3866 (8.4)
Diabetes	66 536 (13.5)	25 263 (12.7)	3680 (8.0)
COPD	48 327 (9.8)	19 052 (9.5)	5224 (11.4)
Cancer	79 647 (16.1)	31 625 (15.9)	8452 (18.5)
Chronic kidney disease	0	0	0
Concomitant pharmacotherapy			
β-Blocker	184 274 (37.3)	77 856 (39.0)	27 148 (59.3)
CCB	268 077 (54.2)	0	45 758 (100)
ACEI/ARB	424 019 (85.8)	199 510 (100)	0
Antiadrenergic drug	10 578 (2.1)	2886 (1.4)	1092 (2.4)
Thiazides	151 951 (30.8)	69 846 (35.0)	20 834 (45.5)
Spironolactone	25 219 (5.1)	9044 (4.5)	2717 (5.9)
Loop diuretic	37 068 (7.5)	14.144 (7.1)	4071 (8.9)
Lipid-lowering drug	242 014 (49.0)	95 518 (47.9)	21 485 (47.0)
Aspirin	96 100 (19.4)	37 151 (18.6)	10 546 (23.0)
Anticoagulation	58 760 (11.9)	25 298 (12.7)	7243 (15.8)
Socioeconomics, income quartile			
Lowest	123 542 (25.0)	48 383 (24.3)	13 737 (30.0)
Highest	123 542 (25.0)	50 628 (25.4)	8991 (19.6)
Highest obtained educational level			
Basic school	172 608 (34.9)	68 684 (34.4)	18 045 (39.4)
High school/vocational education	213 704 (43.2)	86 333 (43.3)	18 694 (40.9)
Short/medium length higher education	84 378 (17.1)	35 009 (17.5)	7232 (15.8)
Long higher education	23 480 (4.8)	9484 (4.8)	1787 (3.9)

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; COPD; chronic obstructive pulmonary disease; IQR, interquartile range.

[a] Users of both ACEI/ARBs and CCBs are not shown in the table (n = 232 807).

demographics and comorbidities. In analyses of susceptibility, ACEI/ARB use was not associated with a higher incidence rate of COVID-19 diagnosis compared with users of other antihypertensive drugs.

A recent report assessed the mechanisms of action of ACEIs and ARBs on the renin-angiotensin-aldosterone system and the rationale for why these drugs might affect COVID-19 virulence.[10] The authors concluded that there was a need for data on this subject to inform clinical guidance on the use of ACEI/ARBs. The idea[1,2,5] that ACE2 inhibition may confer worse outcomes in COVID-19 is based on suggestive mechanistic knowledge from animal studies. The ACE2 enzyme is a cell membrane protein, which the novel SARS-CoV-2 uses as a receptor to enter cells. Studies in experimental animal models have shown mixed findings,[20-27] and there does not seem to be a clear mechanistic link between ACE2 upregulation and

COVID-19 virulence and outcomes. The ACE2 enzyme is expressed widely throughout the body, including in the epithelial cells of the alveoli, the point of entry for SARS-CoV-2.[22]

In the study by Vaduganathan et al,[10] the authors also made a case for a potential beneficial effect of renin-angiotensin system inhibitors. Data from observational studies from selected patient cohorts have recently emerged. Although the results suggest that ACEI/ARB use is not associated with increased risk of COVID-19 or worse COVID-19–related outcomes, these reports have included patients from individual health care systems with quite different patient characteristics and backgrounds. Li et al[11] examined a case series from hospitals in Wuhan, China, and found no association between renin-angiotensin system inhibitors and COVID-19. Similar results using comparable designs in selected health care systems have been reported from North America[13,14] and Italy.[12] Reynolds et al[14] studied patients with COVID-19 and hypertension and found no significant difference in COVID-19 outcomes with ACEI/ARB use relative to other antihypertensive drugs. All studies reported varying patient characteristics and outcomes,

Table 5. Susceptibility Analysis Using Nested Case-Control Design for ACEI/ARB Use and Adjusted Associated Incidence Rate of COVID-19 Among Patients With Hypertension[a]

	Hazard ratio (95% CI)	*P* value
Associated incidence rate of COVID-19		
ACEI/ARB use vs use of other antihypertensives	1.05 (0.80-1.36)	.67
ACEI use vs use of other antihypertensives	0.85 (0.70-1.01)	.08
ARB use vs use of other antihypertensives	1.15 (0.96-1.37)	.11
ACEI/ARB use vs use of CCB	1.23 (0.89-1.70)	.21

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; COVID-19, coronavirus disease 2019.

[a] For the nested analysis of COVID-19 cases, 571 patients with hypertension and COVID-19 were compared with 5710 age- and sex-matched controls. Among cases, 245 (42.9%) and 48 (8.4%) used ACEI/ARBs and no CCBs and CCBs and no ACEI/ARBs, respectively, and this was 2218 (38.8%) and 545 (9.5%) among controls.

Table 6. Hazard Ratios for Death, Composite of Death or Severe COVID-19, and Severe COVID-19[a]

	No. (%)		Unadjusted model		Age- and sex-adjusted model		Fully adjusted model[b]	
	ACEI/ARB users (n = 895)	ACEI/ARB nonusers (n = 3585)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value[c]
Primary outcome								
Mortality								
ACEI/ARB nonusers (reference)								
ACEI use (n = 377)	76 (20.2)	256 (7.1)	2.79 (2.12-3.67)	<.001	1.08 (0.79-1.46)	.64	0.98 (0.71-1.35)	.97
ARB use (n = 630)	84 (15.8)	256 (7.1)	2.05 (1.58-2.65)	<.001	0.90 (0.68-1.20)	.49	0.80 (0.60-1.09)	.24
CCB use (n = 196) vs ACEI/ARB use (n = 895)	161 (18.0)	36 (18.4)	1.01 (0.69-1.46)	.99	0.94 (0.64-1.38)	.81	0.94 (0.65-1.37)	.83
Secondary outcomes								
Death or severe COVID-19								
ACEI/ARB nonusers (reference)								
ACEI use	130 (34.5)	500 (13.9)	2.80 (2.23-3.51)	<.001	1.29 (1.00-1.65)	.047	1.15 (0.89-1.49)	.29
ARB use	151 (28.5)	500 (13.9)	2.10 (1.71-2.58)	<.001	1.01 (0.81-1.27)	.91	0.90 (0.71-1.14)	.42
CCB use (n = 196) vs ACEI/ARB use (n = 895)	282 (31.5)	59 (30.1)	0.97 (0.73-1.31)	.94	0.93 (0.69-1.25)	.62	0.94 (0.70-1.25)	.74
Severe COVID-19								
ACEI/ARB nonusers (reference)								
ACEI use	90 (23.9)	370 (10.3)	2.37 (1.84-3.06)	<.001	1.34 (1.03-1.75)	.03	1.21 (0.91-1.60)	.22
ARB use	110 (20.8)	370 (10.3)	1.99 (1.58-2.50)	<.001	1.18 (0.93-1.50)	.19	1.01 (0.78-1.31)	.97
CCB use (n = 196) vs ACEI/ARB use (n = 895)	201 (22.5)	37 (18.9)	0.90 (0.62-1.29)	.61	0.86 (0.59-1.25)	.37	0.88 (0.61-1.27)	.53

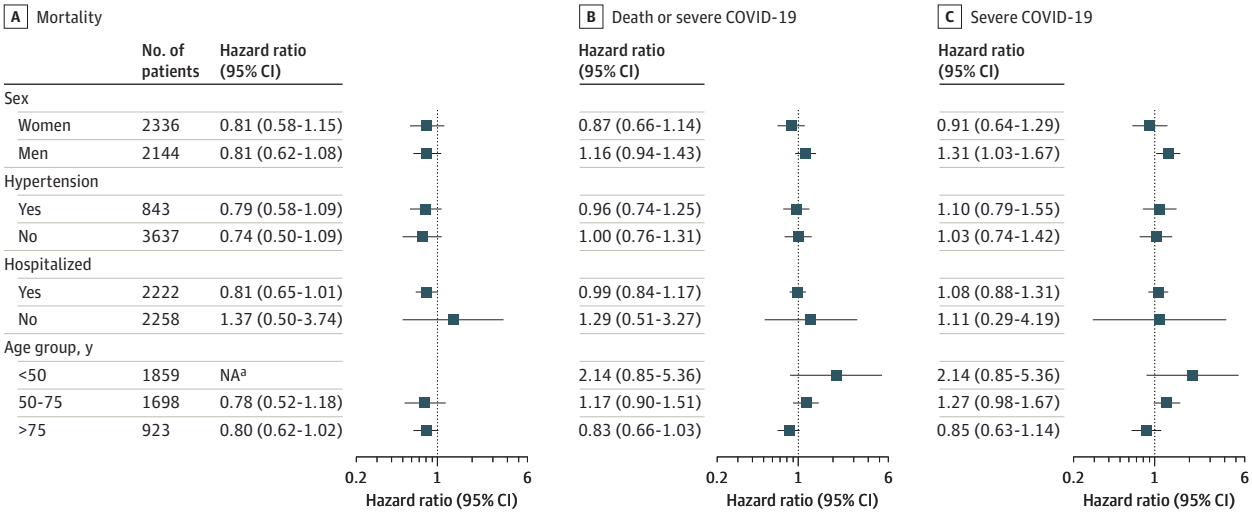
Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; COVID-19, coronavirus disease 2019.

[a] Subgroups of ACEI and ARB users separately and analysis using active control of CCB users.

[b] Fully adjusted model includes the following covariates: age; sex; highest obtained educational level; medical history of myocardial infarction, heart failure, kidney disease, stroke, peripheral artery disease, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, and malignancy; and use of the following concomitant medications: other antihypertensive drugs, lipid-lowering drugs, and anticoagulation.

[c] Fully adjusted *P* value for difference between ACEI and ARB estimate for mortality was .67, .29 for the composite outcome of death or severe COVID-19, and .37 for severe COVID-19.

Figure. Fully Adjusted Hazard Ratios for Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB) Use and Death, Composite of Death or Severe Coronavirus Disease 2019 (COVID-19), and Severe COVID-19 by Subgroups



For the primary outcome, all differences between subgroups were not statistically significant (interaction *P* value of .91 for sex, .72 for hypertension, .22 for hospitalized, and .92 for age). For secondary outcomes, all *P* values for interaction were >.05. NA indicates not available.

[a] Not enough cases and controls younger than 50 years died in order to calculate the subgroup estimate.

but ACEI/ARB use was not associated with worse prognosis. The present study represents population-based analyses of data from an entire country with comprehensive and validated databases. Furthermore, it includes analyses for susceptibility as well as outcomes, and the results suggest no association between ACEI/ARB use and COVID-19 diagnosis or in outcomes among infected patients. These findings were consistent across important subgroups and in analyses of an active comparator of CCB users.

ACEI/ARB treatment has been studied in various cardiovascular diseases and found to be efficacious in reducing death and cardiovascular end points.[28-30] In this study cohort, 21.6% of ACEI/ARB users had a history of myocardial infarction and 14.6% a history of heart failure, 2 settings in which these drugs have been proven efficacious with reduced mortality over placebo.[28-30] Clinical trials in a non-COVID-19 setting have shown worse outcomes in patients with heart failure when renin-angiotensin system inhibitors were discontinued.[31,32] The findings of the present study support that, when clinically indicated, ACEI/ARB therapy should be continued in the setting of COVID-19 unless the patient is hemodynamically unstable. Several randomized studies of ACEI/ARB discontinuation in the setting of the COVID-19 pandemic are in progress.[33-35]

The use of ACEI/ARBs in patients with COVID-19 has been controversial in part due to early reports from China showing that patients with hypertension had worse outcomes.[1-5] The analyses were crude and confounding factors were present that were also associated with hypertension, such as older age and cardiovascular disease.[3,4,36] In patients with cardiovascular disease, COVID-19 is associated with substantial mortality, and clarification of confounding by disease or indication is crucial. The present study found that hypertension and cardiovascular disease as well as ACEI/ARB use were more prevalent among patients with older age. In turn, ACEI/ARB use was associated with worse COVID-19 outcomes in unadjusted analyses. However, when accounting for age, this association was no longer significant, and this held true after further multivariable adjustment as well. Hence, this study does not support a causal link between renin-angiotensin inhibition by ACEIs or ARBs and COVID-19 susceptibility or subsequent worse outcomes of COVID-19.

Professional societies have issued position statements that ACEI/ARBs should not be discontinued[8,9]—statements that this study supports. Observational data currently support statements from relevant societies[8,9] to continue ACEI/ARB treatment, but randomized studies have been initiated in various settings of COVID-19 (hospitalized and outpatient) as well as for both ACEIs and ARBs.[33-35] Further, for patients with pneumonia, ACEI/ARB use has been associated with improved outcomes[37] and this was also recently suggested by observational data in patients with COVID-19.[11]

Limitations

This study has several limitations. First, this was an observational study; no causal inference can be made and relationships should be interpreted as associations.

Second, data were derived from a national sample of patients with COVID-19 but in a short time span. Hence, screening strategies in the beginning of the pandemic may have introduced selection bias relative to strategies at a later period.

Third, new COVID-19–specific diagnosis codes for identification of patients were used. Laboratory data were not available to specifically confirm that the patient had a positive swab

test; however, a patient sample of 98 cases with an *ICD-10* code for COVID-19 was assessed and showed that 98% of those with *ICD-10* codes for COVID-19 also had a laboratory-confirmed polymerase chain reaction test result for SARS-CoV-2.

Fourth, compared with official COVID-19 case numbers in Denmark, this study included fewer cases because *ICD-10* codes capture only those patients who were diagnosed in the hospital system (inpatient or outpatient setting and not in dedicated COVID-19 diagnostic kiosks). Hence, *ICD-10* codes had high specificity but lower sensitivity.

Fifth, study exposure of ACEI/ARB use was defined by prescription fillings. Filling data from Danish pharmacies have been shown to be complete, and a 6-month time window was used to define ACEI/ARB use. If this window was reduced to 3 months, the overall results of the study were similar. Information on in-hospital medication use was not available.

Sixth, the main analysis of this study compared ACEI/ARB users with nonusers, but confounding by indication may have influenced the results and an analysis with an active comparator (CCB users) was therefore also conducted. Results were similar for ACEI/ARB use vs nonuse and ACEI/ARB use vs CCB use.

Conclusions

Prior use of ACEI/ARBs was not significantly associated with COVID-19 diagnosis among patients with hypertension or with mortality or severe disease among patients diagnosed as having COVID-19. These findings do not support discontinuation of ACEI/ARB medications that are clinically indicated in the context of the COVID-19 pandemic.

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