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ORIGINAL RESEARCH

Renin-Angiotensin Aldosterone System Inhibitors in Primary Prevention and COVID-19

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BACKGROUND: Considering the widespread risk of collider bias and confounding by indication in previous research, the associations between renin-angiotensin aldosterone system (RAAS) inhibitor use and COVID-19 remain unknown. Accordingly, this study tested the hypothesis that RAAS inhibitors influence the summation effect of COVID-19 and its progression to severe outcomes.

METHODS AND RESULTS: This nationwide cohort study compared all residents of Sweden, without prior cardiovascular disease, in monotherapy (as of January 1, 2020) with a RAAS inhibitor to those using a calcium channel blocker or a thiazide diuretic. Comparative cohorts were balanced using machine-learning-derived propensity score methods. Of 165 355 people in the analysis (51% women), 367 were hospitalized or died with COVID-19 (246 using a RAAS inhibitor versus 121 using a calcium channel blocker or thiazide diuretic; Cox proportional hazard ratio [HR], 0.97; 95% CI, 0.74–1.27). When each outcome was assessed separately, 335 people were hospitalized with COVID-19 (HR, 0.92; 95% CI, 0.70–1.22), and 64 died with COVID-19 (HR, 1.22; 95% CI, 0.68–2.19). The severity of COVID-19 outcomes did not differ between those using a RAAS inhibitor and those using a calcium channel blocker or thiazide diuretic (ordered logistic regression odds ratio, 1.01; 95% CI, 0.89–1.14).

CONCLUSIONS: Despite potential limitations, this study is among the best available evidence that RAAS inhibitor use in primary prevention does not increase the risk of severe COVID-19 outcomes; presenting strong data from which scientists and policy makers alike can base, with greater confidence, their current position on the safety of using RAAS inhibitors during the COVID-19 pandemic.

Key Words: angiotensin II receptor blocker ■ angiotensin-converting enzyme inhibitor ■ COVID-19 ■ hypertension ■ SARS-CoV-2

SARS-CoV-2 gains entry into its target cells via angiotensin-converting enzyme (ACE) 2.[1] Renin-angiotensin aldosterone system (RAAS) inhibitors, such as ACE inhibitors and angiotensin II type-I receptor blockers (ARBs), may upregulate the expression of ACE2,[2–4] establishing a basis for the hypothesis that their use may increase the risk of a SARS-CoV-2 infection.[2]

As of February 2021, at least 118 studies have attempted to test variants of this hypothesis.[5–123] However, nearly all of them have assessed the associations between RAAS inhibitor use and COVID-19 outcomes exclusively in people with a confirmed SARS-CoV-2 infection, mainly in those hospitalized with COVID-19, introducing a high risk of collider bias.[124] Collider bias creates a spurious within-sample association between 2 variables (eg, in the context of this study: frailty caused by cardiovascular disease, with a high likelihood of being prescribed a RAAS inhibitor, and frailty caused by an adverse COVID-19 course) that affects the probability of being included in the sample (eg, being

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CLINICAL PERSPECTIVE

What Is New?

- In contrast to previous studies that have evaluated the associations between renin-angiotensin aldosterone system inhibitor use and COVID-19 outcomes, this study limits the influence of collider, indication, and confounding biases to provide the best available evidence that the use of renin-angiotensin aldosterone system inhibitors in primary prevention is not associated with COVID-19 outcomes.

What Are the Clinical Implications?

- Previously, scientists and policy makers alike were basing their current position regarding the safety of using renin-angiotensin aldosterone system inhibitors during the COVID-19 pandemic on data where the associations between renin-angiotensin aldosterone system inhibitor use and COVID-19 outcomes could be highly distorted by several types of bias.
- This study provides data where those biases have been limited, fortunately supporting advice from the authorities that antihypertensive therapies should not be altered due to of the COVID-19 pandemic.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical
RAAS	renin-angiotensin aldosterone system
TZD	thiazide diuretic

hospitalized).[124] To understand if RAAS inhibitors can increase the risk of COVID-19, a primary prevention sample of yet uninfected people using RAAS inhibitors or a relevant comparator drug class must be studied, not those already impacted by the virus.[124] Considering this, the findings of those biased studies need to be treated with caution,[124] with the total effect of RAAS inhibitors on the risk of COVID-19 remaining unknown.

Given that RAAS inhibitors are widely used in age groups where the incidence and case fatality of COVID-19 are disproportionally high,[125] there is an urgent need to provide definitive data about the safety of using these drugs during the ongoing COVID-19 pandemic. Accordingly, the present study tested the hypothesis that RAAS inhibitors influence the summation effect of a SARS-CoV-2 infection and its progression to severe COVID-19 outcomes.

METHODS

Use of the analytical methods and data that support the findings of this study can be arranged with the corresponding author upon reasonable request.

Sample

The study was set in Sweden, where all residents have universal access to health care with a negligible copayment for healthcare visits, hospitalizations, and medications.[126] Following approval by the Swedish Ethical Review Authority (approval no. 2020-01556), the 12-digit personal identity number,[127] unique to all Swedish residents, was used to link a variety of nationwide socioeconomic and health registries (classifying diagnoses using the *International Classification of Diseases, Tenth Revision* [*ICD-10*] system,[128] surgical procedures using the Nordic Medico-Statistical Committee Classification of Surgical Procedures system,[129] and filled drug prescriptions using the Anatomical Therapeutic Chemical [ATC] classification system[130]), whose only loss to follow-up was by emigration. The need for informed consent was waived.

A nationwide cohort study of all residents of Sweden in monotherapy with an antihypertensive drug as of January 1, 2020 was formed. To minimize confounding by indication, people using an ACE inhibitor (ATC code C09A), an ARB (ATC code C09C), a vascular selective calcium channel blocker (CCB; ATC code C08CA), or a thiazide diuretic (TZD; ATC codes C03AA or C03BA04) in monotherapy were included, because these are first-line choices in current European hypertension guidelines.[131] Among these, the group using a RAAS inhibitor (ie, an ACE inhibitor or an ARB) was compared with the group not using a RAAS inhibitor (ie, a CCB or TZD) in the primary analysis. Additionally, acknowledging that different classes of RAAS inhibitors do not share the same mechanistic actions, those using an ACE inhibitor and those using an ARB were also compared separately, in a secondary analysis, with the group using a CCB or TZD.

To further minimize confounding by disease severity, people using other blood pressure–lowering drugs (ATC codes C02CA04, C03DA, C07), combination pills including blood pressure–lowering drugs, or other cardiovascular drugs (ATC codes C01, C02D, C02K, C03C, C03X, C08D) were excluded. Additionally, people with preexisting cardiovascular and kidney diseases (*ICD-10* codes I20, I21, I22, I24, I25.2, Z95.1, Z95.5, I60, I61, I62, I63.0-I63.5, I63.8-I63.9, I64, I65, I66, I69.0-I69.4, G45.0-3, G45.8-9, G46.0-7, I50, I11.0, I13.0, I13.2, I25.5, I42.0, I42.6, I42.9, I43.1, Z99.4, I70.2, I73.0, I73.1, I73.9, I73.9, I74, or Z49; or procedure codes AAL10, AAL15, DF005, DF009, DF019, DF020, DR016, DR024, F, KAS, PA, PB, PC, PD, PE, PF, PG, or QF006) were excluded.

Follow-Up and Outcomes

Participants were followed in the registries from January 1, 2020 until June 23, 2020 covering the first wave of the COVID-19 pandemic in Sweden, in which around 100 to 800 new cases were recorded each day for the majority of the follow-up period, before infection rates peaked at around 1000 to 1500 cases per day in June 2020.[132] The primary outcome was defined as hospitalization and/or death with COVID-19 (*ICD-10* code U07.1 [COVID-19, virus identified] as either the main or underlying cause). A person who was hospitalized with COVID-19 and then died with COVID-19 was included in both the hospitalization and the death event counts. Mortality attributable to causes unrelated to COVID-19 was used as a negative control. An ordered outcome, reflecting the severity of the SARS-CoV-2 disease course, was defined at the end of follow-up as: (1) no event during follow-up, (2) hospitalization with COVID-19 without the need for intensive care, (3) hospitalization with COVID-19 requiring intensive care (U07.1 as the main cause as well as procedure codes DG021, DG022, and DG023), (4) death with COVID-19, and (5) death attributable to causes unrelated to COVID-19. Participants were assigned to the most severe category of disease course experienced.

Statistical Analysis

Associations between exposures and the outcomes were analyzed using an intention-to-treat approach (ie, exposure groups were defined once, January 1, 2020) and an as-treated approach. Patients were considered to have stopped or changed their RAAS inhibitor therapy if they did not refill their prescription within 120 days of their previous refill. Subsequently, in the as-treated model, those patients were censored from the analyses.

Bias-minimized models investigating total effects were identified using the directed acyclic graphs approach (Figure S1), considering subject matter knowledge and all factors listed in the Summary of Product Characteristics for the most commonly used of the studied drugs (Table S1). Potential confounding was handled by weighting patients on a propensity score and by multivariable adjustment.

The propensity score was estimated using gradient-boosted classification and regression trees to determine the probability of being prescribed a RAAS inhibitor or not. More information about the use of gradient-boosted classification and regression trees can be found in Data S1. The resulting propensity score was used to calculate an inverse probability of treatment weight for each individual:

$$w_i = \frac{Z_i}{p_i} + \frac{(1 - Z_i)}{(1 - p_i)},$$

where Z_i is a binary indicator taking the value 1 if individual i was treated with a RAAS inhibitor and 0 otherwise, and where p_i is the propensity score for individual i.

The associations between the use of RAAS inhibitors and the COVID-19 outcomes during the 6-month follow-up period were assessed in the primary analysis using Cox models weighted with this inverse probability weight, further adjusting for age, sex, income, country of birth, use of drugs affecting the immune system, diabetes mellitus, antidiabetic drug use, renal disease, hepatic disease, neoplasms, and previous RAAS inhibitor use. Proportionality of the hazards was assessed by visually examining the smoothed association of the scaled Schoenfeld residuals with time. The Aalen-Johansen estimate of the cumulative incidence function was also presented. This was repeated in the secondary analysis to evaluate the relationships between COVID-19 outcomes and the use of an ACE inhibitor or an ARB, separately.

Associations between RAAS inhibitor use and an ordinal variable indicating the severity of the outcome at the end of the 6-month follow-up period were analyzed using ordered logistic regression, using the same weights and adjustments as above.

The balance of the cohorts was assessed using the standardized mean difference between the groups, and with a falsification outcome of mortality by causes unrelated to COVID-19, which is not supposed to differ between the groups.[133] All analyses were made using R version 4.0.0 and the twang and survival add-on packages (R Foundation for Statistical Computing, Vienna, Austria).[134–136]

RESULTS

Of the 1 997 479 residents of Sweden with an active blood pressure–lowering drug prescription as of January 1, 2020, there were 165 355 people who met the inclusion criteria of this study and were eligible for inclusion in the primary analysis. After removal of missing values in the adjusted variables and nonoverlapping weights, the final sample sizes included in the regressions for the primary and secondary analyses were 164 611 and 164 655, respectively (Figure 1). Of those people included in the primary analysis, 115 684 were on monotherapy with a RAAS inhibitor, and 48 927 were on monotherapy with a CCB or a TZD. In the secondary analysis, 47 998 people were on monotherapy with an ACE inhibitor, 68 239 with an ARB, and 48 418 with a CCB or TZD. The characteristics of the cohort in the primary analysis is detailed in Table 1. Characteristics of the cohort in the secondary analysis are detailed in Tables S2 and S3. Excellent balance between the weighted study groups was achieved; the standardized mean difference for all variables was near 0, and the hazard ratio for the association of RAAS

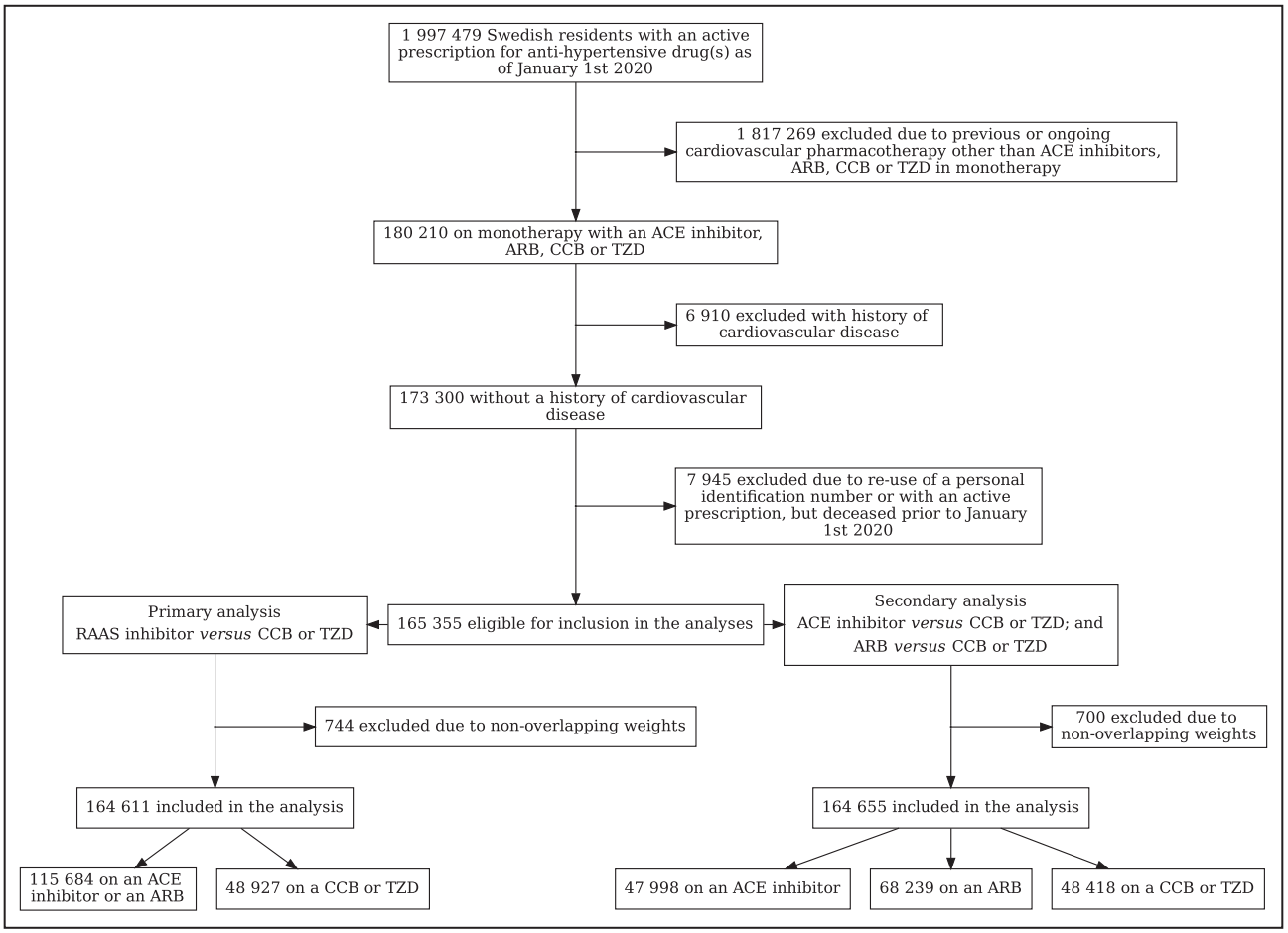

Figure 1. Flowchart detailing the identification of the study population.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; RAAS, renin-angiotensin aldosterone system; and TZD, thiazide diuretic.

inhibitor use with the falsification outcome, death by causes unrelated to COVID-19, was 1.03 (95% CI, 0.84–1.27).

Focusing on the primary analysis, 228 people using a RAAS inhibitor had been hospitalized with COVID-19, 30 had been admitted to an intensive care unit with COVID-19, 324 had died from causes unrelated to COVID-19, and 35 had died with COVID-19 at the end of the 6-month follow-up period. Of those on monotherapy with a CCB or TZD, 107 people were hospitalized with COVID-19, 15 were admitted to an intensive care unit with COVID-19, 229 died from causes unrelated to COVID-19, and 29 died with COVID-19.

There were no statistical differences in the rates of all COVID-19 outcomes between those using a RAAS inhibitor and those using a CCB or TZD (Table 2 and Figure 2). Additionally, there was no difference in the severity of the COVID-19 outcomes between these groups (odds ratio, 1.01; 95% CI, 0.89–1.14, from an ordered logistic regression). There were also no statistical differences in the rates of all COVID-19 outcomes when those using an ACE inhibitor and those using an ARB were compared separately to those using a CCB or TZD (Table 3). These findings did not change when using either an intention-to-treat or as-tread approach. Hazard ratios did not vary with adjustment (Table S4). Although the proportionality test indicated potentially nonproportional hazards, the plot of the smoothed association of the scaled Schoenfeld residuals with time revealed little (Figure S2).

DISCUSSION

In this nationwide cohort study of initially uninfected people, there is no evidence to support that RAAS inhibitor use increases the risk of severe COVID-19 outcomes including hospitalization, admission to an intensive care unit, or death.

Of the 118 previous studies of RAAS inhibition and COVID-19 associations,[5–123] at least 102 were restricted to patients who were tested for/tested positive for a SARS-CoV-2 infection or who had been hospitalized

Table 1. Baseline Characteristics of the Study Groups

	Unweighted			Weighted		
	RAAS Inhibitor, N=115 684	CCB or TZD, N=48 927	SMD	RAAS Inhibitor, N=164 358.5	CCB or TZD, N=161 041.5	SMD
Women, n (%)	56 214 (48.6)	26 316 (53.8)	0.104	82 295.6 (50.1)	81 500.2 (50.6)	0.011
Age, y, median [IQR]	62.0 [54.0–71.0]	66.0 [56.0–74.0]	0.229	63.0 [54.0–72.0]	64.0 [55.0–72.0]	0.029
Yearly income in SEK, median [IQR]	3 268 600 [207 700–443 800]	279 800 [176 200–406 200]	0.186	314 400 [197 100–433 700]	310 700 [195 300–429 200]	0.032
Education, n (%)			0.113			0.020
Elementary school	21 148 (18.4)	11 065 (22.8)		32 107.3 (19.7)	32 275.0 (20.2)	
High school	55 684 (48.5)	22 810 (47.0)		78 469.5 (48.1)	77 338.7 (48.4)	
Academic	33 802 (32.0)	14 185 (29.2)		50 880.7 (31.2)	48 782.0 (30.5)	
Postgraduate	1278 (1.1)	452 (0.9)		1720.9 (1.1)	1514.8 (0.9)	
Marital status, n (%)			0.123			0.008
Unmarried	25 511 (22.1)	9868 (20.2)		25 702.8 (15.7)	25 610.3 (15.9)	
Married	64 394 (55.7)	25 824 (52.8)		90 064.5 (54.9)	88 063.1 (54.7)	
Divorced	17 663 (15.3)	8064 (16.5)		35 352.7 (21.5)	34 359.7 (21.4)	
Widow	8006 (6.9)	5110 (10.5)		13 074.6 (8.0)	12 823.4 (8.0)	
Region of birth, n (%)			0.060			0.006
Africa	964 (0.8)	628 (1.3)		1559.3 (0.9)	1569.0 (1.0)	
Asia	4085 (3.5)	2061 (4.2)		6092.1 (3.7)	6038.4 (3.7)	
Nordic countries	3935 (3.4)	1850 (3.8)		5757.5 (3.5)	5660.3 (3.5)	
North America	275 (0.2)	121 (0.2)		405.1 (0.2)	407.1 (0.3)	
Rest of Europe	5354 (4.6)	2460 (5.0)		7718.0 (4.7)	7539.6 (4.7)	
South America	589 (0.5)	223 (0.5)		827.9 (0.5)	866.2 (0.5)	
Sweden	100 467 (86.8)	41 579 (85.0)		141 978.9 (86.4)	138 943.7 (86.3)	
Medical history, n (%)						
Angioedema	203 (0.2)	200 (0.4)	0.043	394 (0.2)	394.6 (0.2)	0.001
Diabetes mellitus	1313 (1.1)	453 (0.9)	0.021	1769.4 (1.1)	1859.3 (1.2)	0.007
Renal disease	1092 (0.9)	5571 (1.2)	0.022	1625.2 (1.0)	1452.4 (0.9)	0.009
Hepatic disease	1143 (1.0)	559 (1.1)	0.015	1672.6 (1.0)	1668.6 (1.0)	0.002
Psychiatric disease	6595 (5.7)	3401 (7.0)	0.051	9929.7 (6.0)	9847.7 (6.1)	0.003
Neuropsychiatric disease	1954 (1.7)	912 (1.9)	0.013	2838.1 (1.7)	2811.1 (1.7)	0.001
Neoplasms	6800 (5.9)	3084 (6.3)	0.018	9896.6 (6.0)	9766.0 (6.1)	0.002
Autoimmune disease	741 (0.6)	310 (0.6)	0.001	1061.1 (0.6)	1103.8 (0.7)	0.005
Obesity	3037 (2.6)	1077 (2.2)	0.028	4091.9 (2.5)	4173.6 (2.6)	0.006
Heart valve disease	1092 (0.9)	423 (0.9)	0.008	1510.6 (0.9)	1276.2 (0.8)	0.014
Hypertrophic cardiomyopathy	23 (0.0)	8 (0.0)	0.003	30.3 (0.0)	26.0 (0.0)	0.002
Pharmacotherapy, n (%)						
Antidiabetic drugs	1791 (1.5)	539 (1.1)	0.039	2333.4 (1.4)	2358.4 (1.5)	0.004
NSAID	77 917 (67.4)	32 727 (66.9)	0.010	110 422.5 (67.2)	108 776.5 (67.5)	0.008
Immune system–affecting drugs	1817 (1.6)	847 (1.7)	0.009	2682.6 (1.5)	2657.5 (1.7)	0.001
Previous ACE inhibitor/ARB	84 157 (72.7)	13 963 (28.5)	0.986	98 204.5 (59.8)	94 748.3 (58.9)	0.018

Unweighted and weighted characteristics of the study groups included in the primary analysis, composed of all Swedish residents using an antihypertensive drug in monotherapy as of January 1, 2020. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin aldosterone system; SEK, Swedish Kronor (currency of Sweden: 8.5 SEK=1.0 USD); SMD, standardized mean difference; and TZD, thiazide diuretic.

Table 2. Associations of RAAS Inhibitor Use With COVID-19 Outcomes

Outcome	Rate of Outcome With RAAS Inhibitor Use vs Use of a CCB or TZD					
	Intention-to-Treat			As-Treated		
	RAAS Inhibitor, n=115 684, No. of Events	CCB or TZD, n=48 927, No. of Events	HR (95% CI)	RAAS Inhibitor, n=115 684, No. of Events	CCB or TZD, n=48 927, No. of Events	HR (95% CI)
Hospitalization with COVID-19	228	107	0.92 (0.70–1.22)	210	100	0.93 (0.67–1.29)
Death with COVID-19	35	29	1.22 (0.68–2.19)	34	28	1.44 (0.64–3.27)
Hospitalization or death with COVID-19 combined	246	121	0.97 (0.74–1.27)	228	114	0.98 (0.72–1.34)

Swedish residents on antihypertensive monotherapy with a RAAS inhibitor were compared with those on monotherapy with either a CCB or a TZD, in both intention-to-treat and as-treated models. CCB indicates calcium channel blocker; HR, inverse probability of treatment-weighted and multivariate-adjusted Cox proportional hazard ratio; RAAS, renin-angiotensin aldosterone system; and TZD, thiazide diuretic.

because of COVID-19. Such inclusion strategies produce samples that are not representative of the general population and carry a high risk of collider bias, thus distorting any true associations between the use of RAAS inhibitors and the incidence of COVID-19 outcomes.[124] Unfortunately, even the more influential studies published to date suffer from this bias.[84,95] The most comprehensive overview of this methodological problem stresses an urgent need for COVID-19 studies that use representative population samples and

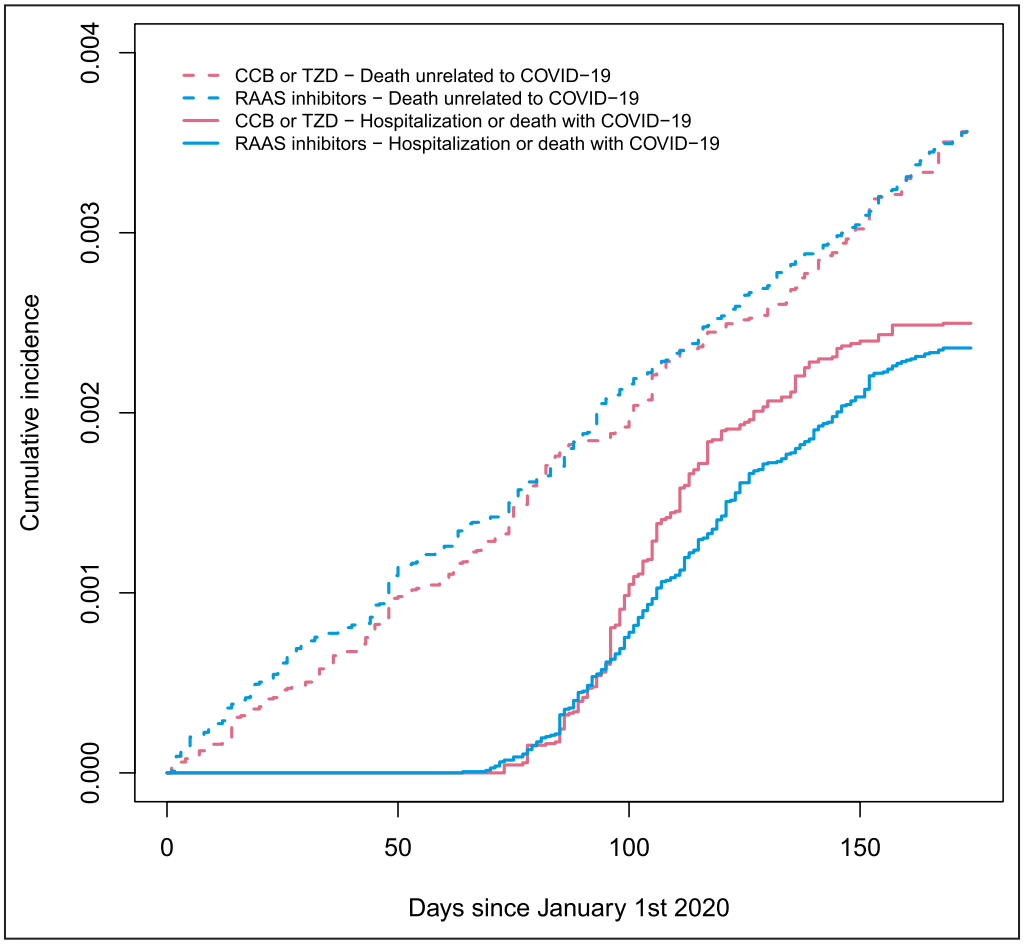

Figure 2. The Aalen-Johansen estimate of the cumulative incidence function for death unrelated to COVID-19 and for a combination of hospitalization or death with COVID-19, in people on monotherapy with a renin-angiotensin aldosterone system (RAAS) inhibitor and those on monotherapy with either a calcium channel blocker (CCB) or a thiazide diuretic (TZD).

Table 3. Associations of ACE Inhibitor or ARB Use With COVID-19 Outcomes

Outcome	Rate of Outcome With ACE Inhibitor or ARB Use vs Use of a CCB or TZD					
	Intention-to-Treat			As-Treated		
	ACE Inhibitor, n=47 998, No. of Events	CCB or TZD, n=48 418, No. of Events	HR (95% CI)	ACE Inhibitor, n=47 998, No. of Events	CCB or TZD, n=48 418, No. of Events	HR (95% CI)
Hospitalization with COVID-19	94	107	0.89 (0.64–1.23)	85	100	0.85 (0.60–1.19)
Death with COVID-19	16	26	0.97 (0.48–1.93)	15	25	0.94 (0.46–1.92)
Hospitalization or death with COVID-19 combined	104	118	0.95 (0.69–1.29)	95	111	0.91 (0.65–1.26)
	ARB, n=68 239, No. of Events	CCB or TZD, n=48 418, No. of Events	HR (95% CI)	ARB, n=68 239, No. of Events	CCB or TZD, n=48 418, No. of Events	HR (95% CI)
Hospitalization with COVID-19	135	107	0.94 (0.70–1.27)	126	100	0.93 (0.67–1.27)
Death with COVID-19	19	26	1.25 (0.63–2.49)	19	25	1.68 (0.69–2.77)
Hospitalization or death with COVID-19 combined	143	118	0.99 (0.73–1.32)	134	111	0.98 (0.72–1.33)

Swedish residents on antihypertensive monotherapy with an ACE inhibitor or an ARB were compared with those on monotherapy with either a CCB or TZD, in both intention-to-treat and as-treated models. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; HR, inverse probability of treatment weighted and multivariate adjusted Cox proportional hazard ratio; and TZD, thiazide diuretic.

thus avoid collider bias to provide reliable evidence.[124] Results from biased studies should be treated with caution by scientists and policy makers alike.[124]

Four case-control studies and 10 cohort studies provided stronger study designs than most of the other RAAS inhibitor–COVID-19 research, but each study included people with prior cardiovascular and/or renal disease, which renders them highly susceptible to confounding by indication, the main pitfall in comparative effectiveness and drug-safety studies. Considering the methodological limitations in previous studies, as well as the burden that a potential inaccurate conclusion could have on patients and healthcare systems worldwide, it was warranted that the potential associations between RAAS inhibitor use and the summation effect of SARS-CoV-2 infection and the progression to severe COVID-19 outcomes be studied further and settled.

Accordingly, Semenzato et al recognized the methodological limitations in the previous research, providing the strongest study design to date by limiting the potential for collider, indication, and confounding biases.[102] In a nationwide cohort that identified patients in France being treated for uncomplicated hypertension, they found that long-term use of an ACE inhibitor or ARB may lower COVID-19 risk when compared with those using a CCB.[102] This present study addresses a major limitation of that research, extending upon it by including an as-treated analysis. Given the similarities in study design and the event rates, it is not entirely clear why the associations between RAAS inhibitor use and COVID-19 outcomes differ from the study by Semenzato et al[102] to this present research. Potentially, the difference in the effect may be simply explained by how France and Sweden have managed the COVID-19 pandemic, with approaches that varied greatly between the 2 countries (eg, nationwide lockdowns versus no lockdowns, respectively). Nevertheless, each study provides strong data that do not indicate a harmful interaction between RAAS inhibitor use and COVID-19.

The initial doubt cast over the safety of using RAAS inhibitors was driven by the finding that SARS-CoV-2 gains entry to human cells by binding its viral spike protein to ACE2.[1,2] In brief, it was hypothesized that RAAS inhibitors could increase one's susceptibility to a SARS-CoV-2 infection, as well as potentiate a more severe disease course, by increasing the expression of ACE2 on the surface of the cell.[2] Potential protective effects of RAAS inhibition have also been proposed. RAAS inhibition may potentiate the lung protective function of ACE2.[137] Given that either of these potential effects, protective or harmful, would affect the probability of infection and the probability of symptomatic disease, the most relevant population for studying the totality of the safety of RAAS inhibition should

be noninfected people. Randomized clinical trials of RAAS inhibition in people with established COVID-19 are ongoing, but these cannot shed light on the total effect on COVID-19.

Several limitations must be considered when interpreting these data. The external validity of these findings to people on combination therapy with antihypertensive drugs, as well as to other geographic or ethnic contexts, is unknown. Given that people with preexisting cardiovascular and kidney diseases were excluded, whether these findings extend to those with underlying comorbidities is also unknown. However, exclusion of these patients was necessary to avoid collider bias and to isolate any interaction between RAAS inhibitors and COVID-19. Given that the definition for COVID-19 cases in this present study was based on admission to hospital or death (ie, a severity criterion), nonsevere cases of COVID-19 were not included in this study, meaning that the association between RAAS inhibition in primary prevention and a combination of the risk for infection and progression to severe disease was studied. However, severe COVID-19 cases are a good representation of (proportional to) all cases but are detected with much better precision because they are not subject to differences and biases in testing. Indeed, virus polymerase chain reaction testing strategies were constant in inpatient care, but changed substantially in outpatient care during follow-up, with unknown potential for bias. Furthermore, severe COVID-19 cases are more relevant considering that they are the burden to health care and that they reflect COVID-19 mortality risk in affected patients. Finally, it must be acknowledged that there was a low number of COVID-19–related events (particularly for deaths with COVID-19) in this study's sample, which limits the power to detect weak associations in each outcome of interest.

The study has several advantages, including the availability of 2 million people using antihypertensive drugs, which allowed us to select the sample least prone to several biases. Additionally, we have complete coverage of all individuals in a society with universal access to health care with a negligible copayment, we have data on both in-hospital and out-of-hospital mortality and could study the need for intensive care, and we used state-of-the-art methods for causal assumptions and development of bias-minimized models.

The importance of the findings from this study are only emphasized by the way in which much of the world is currently struggling under the burden of subsequent waves of the COVID-19 pandemic, with infection and mortality rates far surpassing those seen during the initial wave during the first half of 2020.[132] Furthermore, there is now an urgent need for research that can properly inform and support healthcare systems by providing reliable information on associations of readily modifiable factors with COVID-19 outcomes.

In conclusion, despite potential limitations in the data, this study is among the best available evidence that the use of RAAS inhibitors in primary prevention does not increase the risk of severe COVID-19 outcomes; stronger data from which scientists and policy makers alike can base, with greater confidence, their current position on the safety of using RAAS inhibitors during the COVID-19 pandemic. A corresponding randomized clinical trial is unlikely to ever be executed.

ARTICLE INFORMATION

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None.

Supplementary Material

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Supplemental Material

Data S1.

SUPPLEMENTAL METHODS

The propensity score was estimated using gradient boosted classification and regression trees (CART) to determine the probability of being prescribed a RAAS inhibitor or not. Briefly, a CART partitions the feature space into disjoint regions and assigns a constant value in these regions. While highly interpretable, a single CART has poor predictive performance. With gradient boosting, several single trees are combined by sequentially adding CARTs to predict the (pseudo) residuals from the former CARTs, creating an ensemble with a superior predictive performance.[138] Indeed, gradient boosted CARTs have many desirable properties as they handle missing covariate values, interactions and non-linear associations without the need for prior model specification. The influence of each additional CART is controlled via a shrinkage parameter and the optimal number of CARTs to include was determined by the average standardized mean differences (SMD) between the study groups. For each iteration, the SMD was calculated for every variable and averaged. The number of CARTs was then selected where the average SMD was minimized. Recommendations were followed for tuning the hyperparameters, allowing for the assessment of up to four-way interactions with the shrinkage parameter set to 0.0005.[139] Each CART was fitted in a random subsample of 50% and 50,000 iterations were run.

Table S1. Variables chosen to represent concepts in The Summary of Product Characteristics for key drugs in the studied drug classes.

	ATC codes	ICD codes	Procedure codes	Other
ACE inhibitors, ARBs and similar	C09			
Digoxin	C01A			
Drugs used in diabetes	A10			
NSAIDs	M01A			
Drugs affecting the immune system	L03, L04			
Corticosteroids	H02AB			
CYP3A4-inhibiting drugs	J05AE03, J01FA09, S01AA01, J02AB, J02AC, V03AX03, C01BD01, J01MA02, L04AD, L04AA10, L01C			
CYP3A4-inducing drugs	L02BB, N03AB02, N03AF01, N03AF02, N03AX11, J04AB02, J04AB04			
Angioedema		T78.3, D84.1		
Diabetes mellitus		E10-E14		
Renal disease		N17-N19		
Hepatic disease		K70-K77, B18		
Psychiatric disease		F20-F29, F32-F34, F41		

	ATC codes	ICD codes	Procedure codes	Other

Neuropsychiatric disease	*F40, F42, F50, F60, F61, F84.0, F84.1, F84.5, F90*		
Neoplasms	*C00-D48*		
Autoimmune disease	K900, E271, L80, D51		
Obesity	E65, E66		
Heart valve disease	I05, I06, I07, I08, I09.1, I34, I35, I36, I37, I38, I39, Q23.0, Q23.1, Q23.2, Q23.3, Z95.2, Z95.3, Z95.4	FG, FJE, FJF, FK, FM	
Hypertrophic cardiomyopathy	I42.1, I42.2		
Age			From SCB: 2020-01 minus (birth year, birth month)
Sex			From SCB
Ethnicity (own country of birth, parents' country of birth)			From SCB: FodGrEg4, FodGrFar4, FodGrMor4
Socioeconomic status (SEI, marital status, highest education)			From SCB LISA 2018: ESeG_J16, Civil, Sun2000niva_old

ACE denotes angiotensin-converting enzyme; ARBs, angiotensin II type-I receptor blockers; NSAID, nonsteroidal anti-inflammatory drug; SCB, Statistics Sweden; SEI, socio-economic index.

Table S2. Baseline characteristics of persons using an angiotensin converting enzyme inhibitor.

	Unweighted			Weighted		
	ACE inhibitor (N=47998)	**CCB or TZD** (N=48418)	**SMD**	**ACE inhibitor** (N=164053.3)	**CCB or TZD** (N=161185.2)	**SMD**
Female, N (%)	22083 (46.0)	25899 (53.5)	0.150	81684.7 (49.8)	81177.1 (50.4)	0.011
Age in years, median [IQR]	62.0 [53.0-71.0]	65.0 [56.0-74.0]	0.232	63.0 [54.0-72.0]	64.0 [55.0-72.0]	0.028
Yearly income in SEK, median [IQR]	384120 [243840-522360]	339120 [213600-489720]	0.136	377915 [237120-521520]	374640 [235920-516515]	0.027
Education, N (%)			0.053			0.011
Elementary school	9618 (20.2)	10738 (22.4)		32054.0 (19.7)	31899.6 (19.9)	
High school	23119 (48.6)	22677 (47.2)		78406.5 (48.1)	77422.9 (48.4)	
Academic	14389 (30.2)	14141 (29.5)		50731.5 (31.1)	49168.7 (30.7)	
Postgraduate	474 (1.0)	452 (0.9)		1687.9 (1.0)	1572.5 (1.0)	
Marital Status, N (%)			0.123			0.010
Unmarried	11153 (23.3)	9840 (20.3)		35619.8 (21.7)	34583.8 (21.5)	
Married	26108 (54.4)	25755 (53.3)		89915.5 (54.9)	88364.6 (54.9)	
Divorced	7336 (15.3)	7974 (16.5)		25542.7 (15.6)	25583.9 (15.9)	
Widow	3352 (7.0)	4790 (9.9)		12820.2 (7.8)	12498.6 (7.8)	
Region of birth, N (%)			0.042			0.010
Africa	504 (1.1)	624 (1.3)		1554.9 (0.9)	1579.3 (1.0)	
Asia	1919 (4.0)	2059 (4.3)		6072.1 (3.7)	6138.4 (3.8)	
Nordic countries	1820 (3.8)	1593 (3.3)		5658.7 (3.4)	5658.1 (3.5)	
North America	119 (0.2)	135 (0.3)		388.7 (0.2)	395.8 (0.2)	
Rest of Europe	2595 (5.4)	2429 (5.0)		7727.0 (4.7)	7493.9 (4.6)	
South America	269 (0.6)	221 (0.5)		845.1 (0.5)	791.4 (0.5)	
Sweden	40975 (85.4)	41141 (85.0)		139055.2 (86.3)	141841.4 (86.5)	
Medical history, N (%)						
Angioedema	64 (0.1)	194 (0.4)	0.052	350.5 (0.2)	388.9 (0.2)	0.006
Diabetes mellitus	657 (1.4)	448 (0.9)	0.042	1789.0 (1.1)	1868.0 (1.2)	0.006
Renal disease	698 (1.5)	491 (1.0)	0.040	1827.9 (1.1)	1415.9 (0.9)	0.024
Hepatic disease	528 (1.1)	552 (1.1)	0.004	1684.6 (1.0)	1685.3 (1.0)	0.002
Psychiatric disease	3316 (6.8)	2844 (5.9)	0.038	9759.6 (5.9)	9853.1 (6.1)	0.007

	Unweighted			Weighted		
	ACE inhibitor	**CCB or TZD**	**SMD**	**ACE inhibitor**	**CCB or TZD**	**SMD**
Medical history, N (%)						

Neuropsychiatric disease	937 (2.0)	911 (1.9)	0.005	2872.5 (1.8)	2884.8 (1.8)	0.003
Neoplasms	2699 (5.6)	3041 (6.3)	0.028	9796.4 (6.0)	9748.5 (6.0)	0.003
Autoimmune disease	296 (0.6)	304 (0.6)	0.001	1027.9 (0.6)	1093.7 (0.7)	0.006
Obesity	1311 (2.7)	1075 (2.2)	0.033	4124.1 (2.5)	4248.1 (2.6)	0.008
Heart valve disease	472 (1.0)	423 (0.9)	0.011	1650.1 (1.0)	1320.3 (0.8)	0.020
Hypertrophic cardiomyopathy	10 (0.0)	8 (0.0)	0.003	32.4 (0.0)	36.5 (0.0)	0.002
Pharmacotherapy, N (%)						
Antidiabetic drugs	853 (1.8)	540 (1.1)	0.055	2334.3 (1.4)	2387.0 (1.5)	0.005
NSAID	31269 (65.1)	32456 (67.0)	0.040	109853.1 (67.0)	109069.3 (67.7)	0.015
Immune system- affecting drugs	821 (1.7)	837 (1.7)	0.001	2730.6 (1.7)	2693.8 (1.7)	0.001
Previous ACE inhibitor/ARB	34888 (72.7)	13988 (28.9)	0.974	98581.5 (60.1)	95444.3 (59.2)	0.018

Unweighted and weighted characteristics of the study groups included in the secondary analysis, comprised of all Swedish residents using an angiotensin converting enzyme inhibitor in monotherapy, compared to those using a calcium channel blocker or thiazide diuretic in monotherapy; as of January 1st 2020. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SEK, Swedish Kronor (currency of Sweden: 8.5 SEK = 1.0 USD); SMD, standardized mean difference; TZD, thiazide diuretic.

Table S3. Baseline characteristics of persons using an angiotensin II type-I receptor blocker.

	Unweighted			Weighted		
	ARB (N=68239)	**CCB or TZD** (N=48418)	**SMD**	**ARB** (N=164293.3)	**CCB or TZD** (N=161185.2)	**SMD**
Female, N (%)	34245 (50.2)	25899 (53.5)	0.066	82107.3 (50.0)	81177.1 (50.4)	0.008
Age in years, median [IQR]	63.0 [54.0-71.0]	65.0 [56.0-74.0]	0.205	63.0 [54.0-72.0]	64.0 [55.0-72.0]	0.030
Yearly income in SEK, median [IQR]	398640 [253080-541320]	339120 [213600-489720]	0.202	378000 [237480-521280]	374640 [235920-516515]	0.029
Education, N (%)			0.143			0.019
Elementary school	11562 (17.0)	10738 (22.4)		31777.6 (19.5)	31899.6 (19.9)	
High school	32762 (48.3)	22677 (47.2)		78422.5 (48.1)	77422.9 (48.4)	
Academic	22684 (33.4)	14141 (29.5)		51148.9 (31.4)	49168.7 (30.7)	
Postgraduate	833 (1.2)	452 (0.9)		1765.2 (1.1)	1572.5 (1.0)	
Marital Status, N (%)			0.123			0.010
Unmarried	14680 (21.5)	9840 (20.3)		35561.6 (21.7)	34583.8 (21.5)	
Married	38507 (56.5)	25755 (53.3)		90156.4 (54.9)	88364.6 (54.9)	
Divorced	10337 (15.2)	7974 (16.5)		25512.2 (15.5)	25583.9 (15.9)	
Widow	4651 (6.8)	4790 (9.9)		12898.9 (7.9)	12498.6 (7.8)	
Region of birth, N (%)			0.101			0.011
Africa	461 (0.7)	624 (1.3)		1509.2 (0.9)	1579.3 (1.0)	
Asia	2183 (3.2)	2059 (4.3)		6081.4 (3.7)	6138.4 (3.8)	
Nordic countries	2347 (3.4)	1593 (3.3)		5709.3 (3.5)	5658.1 (3.5)	
North America	141 (0.2)	135 (0.3)		391.6 (0.2)	395.8 (0.2)	
Rest of Europe	2783 (4.1)	2429 (5.0)		7711.9 (4.7)	7493.9 (4.6)	
South America	320 (0.5)	221 (0.5)		799.0 (0.5)	791.4 (0.5)	
Sweden	59997 (87.9)	41141 (85.0)		142070.0 (86.5)	141841.4 (86.5)	
Medical history, N (%)						
Angioedema	139 (0.2)	194 (0.4)	0.036	395.7 (0.2)	388.9 (0.2)	<0.001
Diabetes mellitus	662 (1.0)	448 (0.9)	0.005	1727.9 (1.1)	1868.0 (1.2)	0.010
Renal disease	662 (1.0)	491 (1.0)	0.004	1845.1 (1.1)	1415.9 (0.9)	0.025
Hepatic disease	616 (0.9)	552 (1.1)	0.024	1621.0 (1.0)	1685.3 (1.0)	0.006
Psychiatric disease	3783 (5.5)	2844 (5.9)	0.054	9810.3 (6.0)	9853.1 (6.1)	0.006

	Unweighted			Weighted		
	ARB	**CCB or TZD**	**SMD**	**ARB**	**CCB or TZD**	**SMD**

Medical history, N (%)						
Neuropsychiatric disease	1053 (1.5)	911 (1.9)	0.026	2852.2 (1.7)	2884.8 (1.8)	0.004
Neoplasms	4113 (6.0)	3041 (6.3)	0.011	9838.5 (6.0)	9748.5 (6.0)	0.003
Autoimmune disease	452 (0.7)	304 (0.6)	0.004	1075.1 (0.7)	1093.7 (0.7)	0.003
Obesity	1758 (2.6)	1075 (2.2)	0.023	4091.8 (2.5)	4248.1 (2.6)	0.009
Heart valve disease	703 (1.0)	423 (0.9)	0.016	1597.1 (1.0)	1320.3 (0.8)	0.016
Hypertrophic cardiomyopathy	16 (0.0)	8 (0.0)	0.005	36.5 (0.0)	36.5 (0.0)	<0.001
Pharmacotherapy, N (%)						
Antidiabetic drugs	946 (1.4)	540 (1.1)	0.024	2363.6 (1.4)	2387.0 (1.5)	0.004
NSAID	46869 (68.7)	32456 (67.0)	0.035	110303.8 (67.1)	109069.3 (67.7)	0.011
Immune system- affecting drugs	1080 (1.6)	837 (1.7)	0.011	2677.9 (1.6)	2693.8 (1.7)	0.003
Previous ACE inhibitor/ARB	49826 (73.0)	13988 (28.9)	0.984	98700.6 (60.1)	95444.3 (59.2)	0.018

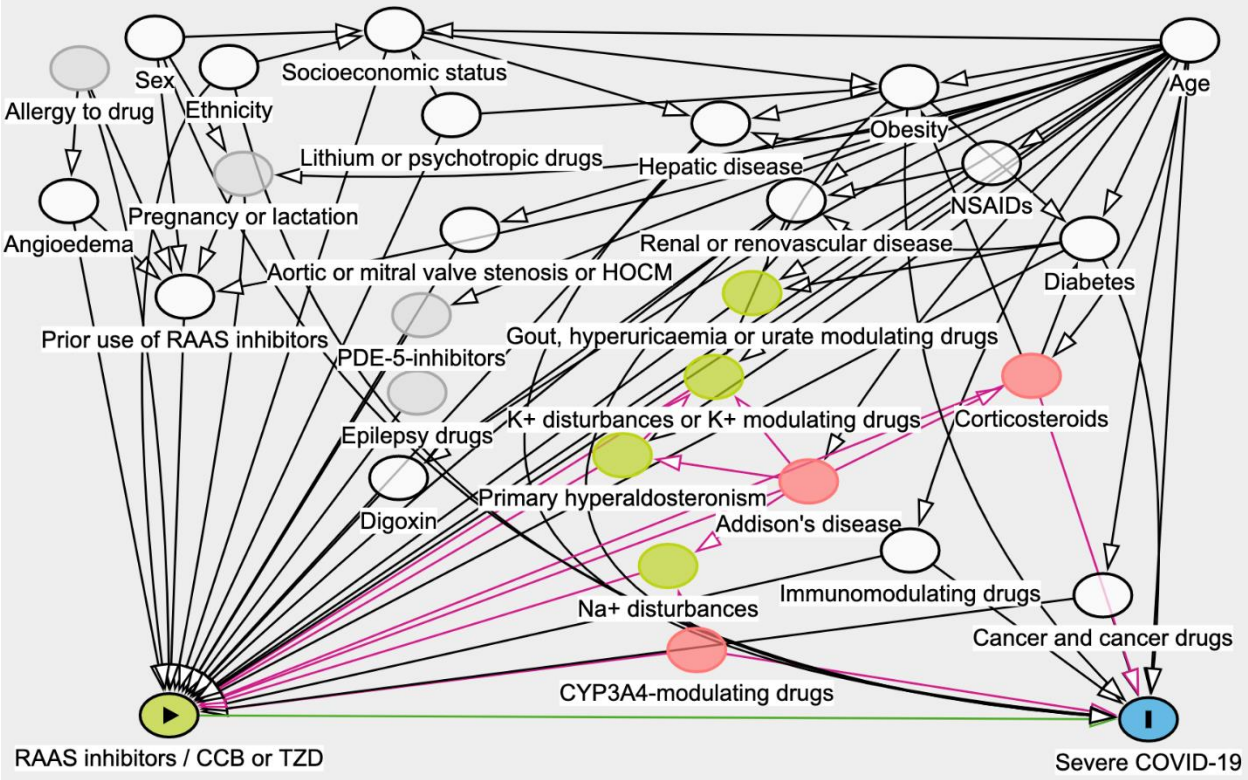
Unweighted and weighted characteristics of the study groups included in the secondary analysis, comprised of all Swedish residents using an angiotensin II type-I receptor blocker in monotherapy, compared to those using a calcium channel blocker or thiazide diuretic in monotherapy; as of January 1st 2020. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SEK, Swedish Kronor (currency of Sweden: 8.5 SEK = 1.0 USD); SMD, standardized mean difference; TZD, thiazide diuretic.

Table S4. Unadjusted and adjusted associations of RAAS inhibitor use with COVID-19 outcomes.

Outcome	**Rate of outcome with RAAS inhibitor use *versus* use of a CCB or TZD (HR and 95% CI)**			
	Intention to treat		**As treated**	
	Unadjusted	Adjusted	Unadjusted	Adjusted
RAAS inhibitor (n=115684)				
Hospitalization with COVID-19	0.92 (0.70-1.21)	0.92 (0.71-1.22)	0.89 (0.67-1.19)	0.89 (0.66-1.20)
Death with COVID-19	1.17 (0.66-2.10)	1.22 (0.68-2.19)	1.17 (0.65-2.10)	1.22 (0.69-2.31)
Hospitalization or death with COVID-19 combined	0.96 (0.74-1.25)	0.97 (0.74-1.27)	0.91 (0.70-1.19)	0.95 (0.71-1.26)
ACE inhibitor (n=47998)				
Hospitalization with COVID-19	0.89 (0.64-1.22)	0.89 (0.64-1.23)	0.84 (0.60-1.18)	0.85 (0.60-1.19)
Death with COVID-19	1.04 (0.52-2.01)	0.97 (0.48-1.93)	0.97 (0.48-1.97)	0.94 (0.46-1.92)
Hospitalization or death with COVID-19 combined	0.94 (0.69-1.27)	0.95 (0.69-1.29)	0.89 (0.65-1.23)	0.91 (0.65-1.26)
ARB (n=68239)				
Hospitalization with COVID-19	0.93 (0.69-1.26)	0.94 (0.70-1.27)	0.92 (0.67-1.26)	0.93 (0.67-1.27)
Death with COVID-19	1.28 (0.64-2.59)	1.25 (0.63-2.49)	1.35 (0.67-2.73)	1.68 (0.69-2.77)
Hospitalization or death with COVID-19 combined	0.97 (0.73-1.31)	0.99 (0.73-1.32)	0.96 (0.71-1.30)	0.98 (0.72-1.33)

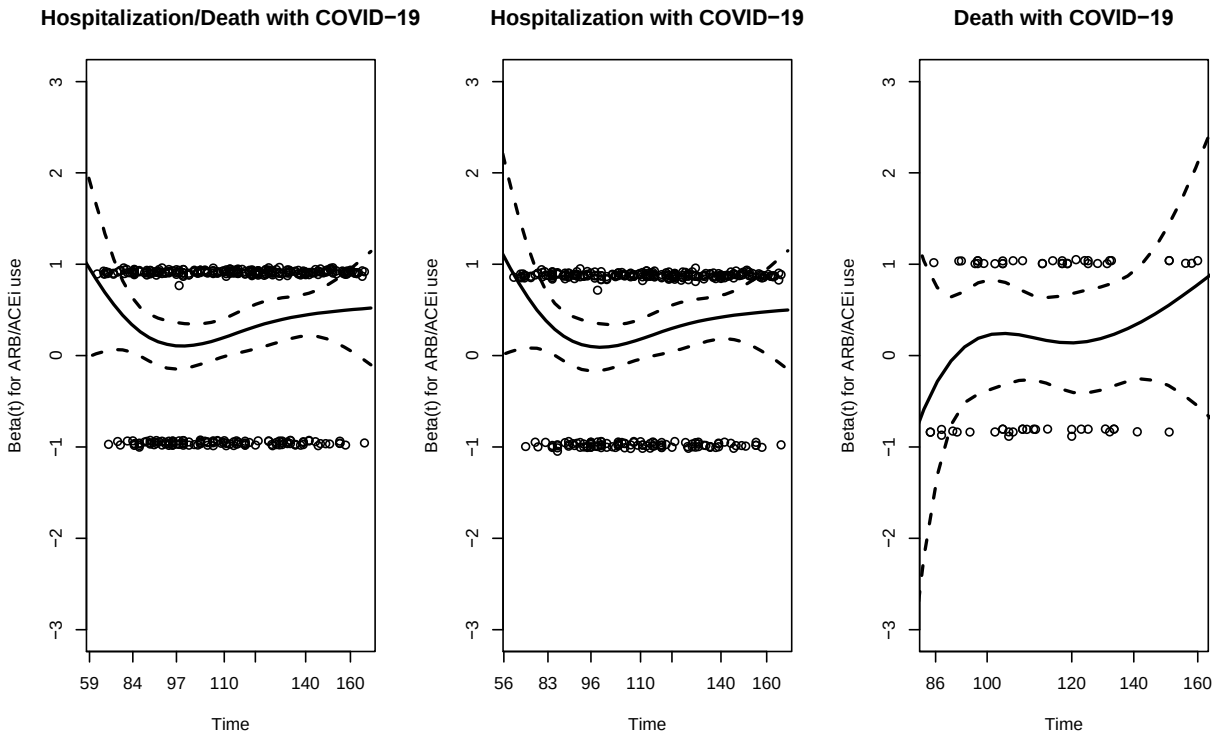
Swedish residents on antihypertensive monotherapy with RAAS inhibitor were compared to those on monotherapy with either a calcium channel blocker or thiazide diuretic, in both an intention to treat and an as treated model. In addition to assessing the associations of each RAAS inhibitor combined, the associations of ACE inhibitor and ARB use were also assessed independently of each other. RAAS denotes renin-angiotensin aldosterone system; CCB, calcium channel blocker; TZD, thiazide diuretic; HR, Cox proportional hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ACE, angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker.

Figure S1. Causal assumptions.



The directed acyclic graphs approach used to identify the bias-minimized models investigating the total effects in this study. CCB denotes calcium channel blockers; COVID-19, coronavirus disease 2019; HOCM, hypertrophic obstructive cardiomyopathy; NSAIDs, non-steroidal anti-inflammatory drugs; PDE-5-inhibitors, phosphodiesterase type 5 inhibitors; RAAS, renin-angiotensin aldosterone system; TZD, thiazide diuretic.

Figure S2. Proportionality of the hazards.



Raw (circles) and spline smoothed (solid lines) scaled Schoenfeld residuals for RAAS inhibitor use and hospitalization or death with COVID-19 (left panel), for hospitalization with COVID-19 (middle panel), and death with COVID-19 (right panel), ± 2 standard errors (broken lines). Although the test indicates non-proportional hazards, the smoothed association between the scaled Schoenfeld residuals reals little. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; COVID-19, coronavirus disease 2019; RAAS denotes renin-angiotensin aldosterone system.