Received: 13 March 2022 | Revised: 15 June 2022 | Accepted: 16 June 2022

DOI: 10.1111/bcpt.13766

ORIGINAL ARTICLE

BCPT Basic & Clinical Pharmacology & Toxicology

Initiation of antihypertensive drugs to patients with confirmed COVID-19—A population-based cohort study in Sweden

Salar Issa Mousa[1] | **Fredrik Nyberg**[2] | **Mohammadhossein Hajiebrahimi**[1,3] | **Rebecka Bertilsson**[4] | **Jonatan Nåtman**[4] | **Ailiana Santosa**[2] | **Björn Wettermark**[1,5]

[1]Pharmacoepidemiology & Social Pharmacy, Department of Pharmacy, Uppsala University, Uppsala, Sweden

[2]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Department of Statistics and Epidemiology, Public Health Faculty, Golestan University of Medical Sciences, Gorgan, Iran

[4]National Diabetes Register, Centre of Registers Västra Götaland, Gothenburg, Sweden

[5]Pharmacy Centre, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Correspondence
Björn Wettermark, Department of pharmacy, Faculty of Pharmacy, Uppsala university, Box 580, 751 23 Uppsala, Sweden.
Email: bjorn.wettermark@farmaci.uu.se

Funding information
Uppsala University; Swedish government ALF-agreement and FORMAS; NordForsk

Abstract

Purpose: Hypertension is an important risk factor for severe outcomes in patients with COVID-19, and antihypertensive drugs may have a protective effect. However, the pandemic may have negatively impacted health care services for chronic diseases. The aim of this study was to assess initiations of antihypertensive medicines in patients infected by COVID-19.

Methods: A cohort study including all Swedish residents 20–80 years old with a COVID-19 positive test compared with an unexposed group without COVID-19 matched for age, sex, and index date (date of confirmed COVID-19). Data were collected within SCIFI-PEARL, a study including linked data on COVID tests, hospital diagnoses, dispensed prescriptions, and socioeconomic data from Swedish national registers. Initiations of different antihypertensive drugs were studied from March 2020 until October 2020. Associations between COVID-19 and initiation of antihypertensives were assessed by a multivariable Cox proportional hazards model.

Results: A total of 224 582 patients (exposed and unexposed) were included. After adjusting for cardiovascular comorbidities and education level, ACEi was the most commonly initiated antihypertensive agent to patients with COVID-19. Hazard ratio and 95% confidence interval for initiation of drug therapy was 1.83 [1.53–2.19] for ACEi, followed by beta-blockers 1.74 [1.55–1.95], calcium channel blockers 1.61 [1.41–1.83], angiotensin receptor blockers 1.61 [1.40–1.86], and diuretics 1.53 [1.32–1.77].

Conclusion: All antihypertensive medicines were initiated more frequently in COVID-19 patients. This can either be associated with hypertension caused by the COVID-19 infection, more frequent diagnosis of hypertension among people with COVID-19 since they consult health care, or residual confounding factors not adjusted for in the study.

KEYWORDS
antihypertensives, COVID-19, drug utilization, pharmacoepidemiology, prescribing pattern

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was officially declared a pandemic by the World Health Organization (WHO) on 11 March 2020, and the virus rapidly spread across the world affecting the health of millions of people.[1,2] Many studies have shown that patients with cardiovascular risk factors such as hypertension, diabetes mellitus, and obesity experience more severe outcomes of the infection.[3] Consequently, cardiovascular prevention and treatment have become even more important during the pandemic.

However, the intensified focus on COVID-19, as well as lockdown measures and physical distancing restrictions, may have negatively impacted the management of patients with chronic diseases.[4,5] In May 2020, WHO conducted a survey in 155 countries on health care services for chronic diseases during the pandemic. The respondents claimed that COVID-19 negatively impacted health care delivery in all regions and three quarters of countries reported problems in the management of chronic diseases, including hypertension.[6]

There are currently five major antihypertensive drug classes available on the market: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics. All have proven to be effective in reducing the risk of myocardial infarction, stroke and heart failure in patients with hypertension,[7] but they are also used for other indications. There has been an intensive discussion on the appropriate choice of antihypertensive agent for patients with COVID-19. SARS-Cov-2 is known to use the angiotensin-converting enzyme 2 (ACE2), a component of the Renin Angiotensin Aldosterone System (RAAS), and the transmembrane serine protease 2 (TMPRS2) as co-receptors in order to gain the entry to the host cell.[8] Activation of the RAAS with a reduced expression of ACE2 leads to an increase in the inflammatory cascade, leading to cell fibrosis.[9] These mechanisms raised the debate on both harmful and beneficial effects of RAAS inhibitors (RAASi), that is, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), in patients with COVID-19.[9] To date, there are several reviews summarizing the evidence, suggesting either no risk or a benefit of using RAAS inhibitors.[10–14] One challenge, though, is the fact that most studies have included hospitalized people with a confirmed SARS-CoV-infection, thus potentially introducing bias and confounding by indication. These potential limitations were recently addressed in a large nationwide Swedish study, confirming that RAAS inhibitor use in primary prevention does not increase the risk of severe COVID-19 outcomes.[15]

Overall, the existing literature emphasizes the importance of continuing to use antihypertensive agents in patients with hypertension who develop COVID-19.[16,17] Given the challenges maintaining treatment during the pandemic, it is important to study the prescribing and use of antihypertensives. The aim of this study was to assess initiations of different antihypertensive medicines to patients infected with COVID-19 compared with matched controls from the general population.

2 | METHODS

2.1 | Study design

We conducted a cohort study to examine initiations of different antihypertensive drug classes after infection with COVID-19. The exposed group was defined as the patients who had a positive COVID-19 test, and the non-exposed group comprised patients without COVID-19, that is, either people in the general population who had not been tested for COVID-19 or those who had had been tested negative for COVID-19. The unexposed group was matched to the exposed group on age, sex, and sampling time (date of positive test in the exposed) to minimize the confounding effect as much as possible. We matched the exposed and unexposed group with a 1:1 proportion.

2.2 | Data sources

Data were collected from the database of the SCIFI-PEARL (Swedish COVID-19 Investigation for Future Insights—a Population Epidemiology Approach using Register Linkage) project.[18] Data were used from the following registers, linked through the Swedish personal identification numbers[19]:

- SmiNet: the national database of notifiable diseases - People who have positive SARS-CoV-2 polymerase chain reaction (PCR) test results (exposure)
- Swedish Prescribed Drug Register[20]—Dispensed prescriptions of antihypertensive drugs (outcome)

- National Patient Register[21]—Selected comorbidities recorded in inpatient care or during consultations in specialist ambulatory care (covariates, potential confounders) and information about hospitalization and ICU care (censoring)
- Sociodemographic registers from Statistics Sweden[22] (covariates, potential confounders)
- Cause-of-death register[23] (date of death for censoring)

2.3 | Study population

The population used in this study comprised patients aged 20–80 years, with a positive COVID-19 test. The study was restricted to this age group since most of the COVID-19-positive cases were among these ages.[18] Furthermore, hypertension is uncommon in children and multimorbidity is common in the oldest, having a substantial impact on the prescribing of antihypertensives for other indications.[24–26] Study participants had a "washout period" of 1 year before getting a positive test of COVID-19 or corresponding date in comparison group. The washout period was defined for each antihypertensive drug class as the period of not being dispensed any prescription of a drug belonging to that class. The index date for matching of the unexposed group was set to the date that a corresponding patient in the exposed group had a positive COVID-19 test. The follow-up period was between the index date and the earliest of outcome, censoring, or end of study follow-up (October 2020). Both exposed and unexposed groups were censored if receiving ICU care or hospitalized for more than 1 month, because we had no access to drug prescribing data in the inpatient setting. Furthermore, the unexposed group was censored if they tested positive for COVID-19.

2.4 | Study variables

The *exposure* in this cohort study was a positive SARS-CoV-2 polymerase chain reaction (PCR) test result recorded in the national database of notifiable diseases.

The *outcome* was the initiation of antihypertensive medicine following the exposure to COVID-19 or corresponding index date in the unexposed. Initiation was defined as claiming a first prescription at a pharmacy. The following antihypertensive drug classes were recorded (with corresponding Anatomic Therapeutic Chemical classification system [ATC] codes): angiotensin-converting enzyme inhibitors (ACE inhibitors; C09A), angiotensin receptor blockers (ARB; C09C), beta-blockers (C07), calcium channel blockers (CCB; C08), and diuretics (C03) as well as fixed combinations of ACE inhibitors/thiazides (C09B) and fixed combinations of ARB/thiazides (C09D).

The following *covariates* were used both to describe the population and as potential confounders to adjust for in the analysis. All variables were measured at or up to the index date.

- Age, sex, time (month) of COVID test (used in matching);
- Prior hospitalization(s) from January 2015 to index date (yes/no);
- Prior diagnosis of hypertension (ICD I10-I15) at least recorded once from January 2015 to index date, recorded during hospitalization or consultation in specialist ambulatory care;
- Selected comorbidities recorded at least once during hospitalization or consultation in specialist ambulatory care between January 2015 and index date; diabetes (E10,E11,E13), stroke/TIA (G45,I63), ischaemic heart disease (I20-I25), atrial fibrillation (I48), heart failure (I50), asthma, and COPD (J40-J45);
- Previous dispensing of antihypertensive drugs defined as at least one prescription dispensed (same ATC-classes as defined above, up to 365 days before index date);
- Educational level, which was subdivided into four main subgroups: Primary school <9 years, primary school 9 years, secondary school, and postsecondary school.

2.5 | Statistical analysis

Baseline characteristics are presented as frequencies and percentages for categorical variables, and as mean values and standard deviation (SD) for continuous variables. The standardized mean difference (SMD) was used to investigate the balance of covariates between the groups of the study. SMD is defined being independent to the unit of measurement; therefore, this allows it to be used in comparison between variables with different units and prevalences. We used 0.1 (10%) as the threshold for SMD indicating imbalance.

The crude cumulative proportion initiated on each drug class was assessed using Kaplan–Meier analysis. Incidence rates were expressed per 1000 person-year for the exposed and unexposed group. Crude and adjusted hazard ratios for initiation of different antihypertensive drugs were estimated using Cox regression. Models were adjusted for diabetes mellitus, stroke/TIA, hypertension, ischaemic heart disease, atrial fibrillation, asthma/COPD, prior drug usage, and education.

A sensitivity analysis was conducted to further assess potential confounding. In this analysis, we excluded patients with a prior hospitalization 1 and 5 years before index date, respectively.

To illustrate the differences, Kaplan–Meier curves were used to show the change in the prescribing patterns over time up to 200 days after index date. All analyses were conducted using R version 1.3.1073.

3 | RESULTS

We identified a total number of 112 278 patients infected with and tested positive for COVID-19 between March 2020 and October 2020. After matching for age, sex, and time of COVID-19 test, a total of 112 278 people without COVID-19 were identified for the unexposed group.

Baseline characteristics of COVID-19 test-positive subjects and the comparison group are shown in Table 1. A total of 7.8% of all study subjects who tested positive for COVID-19 and 5.7% in the comparison group, respectively, had previously been diagnosed with hypertension in specialist care. The most frequent other co-morbidity was diabetes mellitus, with 4.5% in the COVID-19 positive group and 2.8% in the comparison group. The two matched cohorts were relatively similar in terms of education, but prior use of other antihypertensive drug classes, some other comorbidities as well as the proportion being hospitalized prior to the COVID test tended to be more frequent in the test-positive group, although all SMDs were below 0.1 (Table 1).

TABLE 1 Characteristics of 112 291 persons 20–80 years old who tested positive for COVID-19 in Sweden between March and October 2020 and their comparison group matched by age, sex and calendar time

Baseline characteristics	Covid-19 positive group	Unexposed group	SMD	Missing (%)
Total number	112 291	112 291		
Age (mean (SD))	44.5 (15.6%)	44.5 (15.6%)	<0.001	0.0%
Sex = M (%)	51 284 (45.7%)	51 284 (45.7%)	<0.001	0.0%
Education level (%)			0.080	3.4%
Primary school <9 years	5017 (4.6%)	4488 (4.2%)		
Primary school 9 year	8967 (8.2%)	10 764 (10.0%)		
Secondary school	48 056 (44.1%)	49 352 (45.7%)		
Postsecondary	46 912 (43.1%)	43 368 (40.2%)		
History of medication use (%)				
Diuretics	5437 (4.8%)	4365 (3.9%)	0.047	0.0%
Betablockers	10 171 (9.1%)	9039 (8.0%)	0.036	0.0%
CCB	8055 (7.2%)	7497 (6.7%)	0.020	0.0%
ACE-inhibitors	5876 (5.2%)	5281 (4.7%)	0.024	0.0%
ACEi + thiazide (fixed comb)	835 (0.7%)	830 (0.7%)	0.001	0.0%
ARB-inhibitors	6981 (6.2%)	6569 (5.8%)	0.015	0.0%
ARB + thiazide (fixed comb)	2249 (2.0%)	2076 (1.8%)	0.011	0.0%
Comorbidities (%)				
Diabetes mellitus	5045 (4.5%)	3172 (2.8%)	0.089	0.0%
Stroke/TIA	955 (0.9%)	540 (0.5%)	0.045	0.0%
Hypertension	8782 (7.8%)	6454 (5.7%)	0.083	0.0%
Ischemic heart disease	2709 (2.4%)	1921 (1.7%)	0.049	0.0%
Atrial fibrillation	2497 (2.2%)	1745 (1.6%)	0.049	0.0%
Asthma/COPD	4036 (3.6%)	2620 (2.3%)	0.074	0.0%
Previous hospitalization (%)				
Within 1 year	10 920 (9.7%)	8125 (7.2%)	0.089	0.0%
Within 5 years	32 059 (28.5%)	28 471 (25.4%)	0.072	0.0%

Abbreviations: ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

Incidence rates of antihypertensive drugs to patients not previously dispensed any drug from that pharmacological group are shown in Table 2. Overall, incidence rates were higher in exposed group compared with unexposed group for all drugs except for ACEi in fixed combination with thiazide. Betablockers (30.4 patients per 1000 person-years) were the most commonly used drug for initiation to exposed (COVID-19 test-positive) subjects, while ACEi in fixed combination with thiazides were the least common drug used for initiation in this group (1.5 patients per 1000-person years). However, in total, RAAS inhibitors (alone or in fixed combinations) were initiated more frequently than betablockers to study subjects who had tested positive for COVID-19.

The largest absolute difference in incidence rates between subjects with COVID-19 positive test and their comparison group was observed for betablockers (13.5 patients/1000 person-years) and the smallest absolute difference was observed from ARB in fixed combination with a thiazide (0.6 patients/1000 person-years). The largest relative difference was observed for ACE inhibitors (incidence rate ratio 1.9).

3.1 | Survival analysis

Our results showed an increased proportion of people initiated on all antihypertensive drug classes after COVID-19 infection compared with a matched group without COVID-19 (Kaplan–Meier curves for all antihypertensive drug classes are found in Appendix S1). However, the increase varied between the different pharmacological groups. After adjusting for diabetes mellitus, stroke/TIA, hypertension, ischaemic heart disease, atrial fibrillation, asthma/COPD, prior drug usage, and education, the associations were persistently significant for all studied hypertensive drugs except for ACEi and ARB in fixed combinations. Hazard Ratios (95%CI) of initiation of drug consumption were 1.83 [1.53–2.19] for ACEi, followed by beta-blockers 1.74 [1.55–1.95], calcium channel blockers 1.61 [1.41–1.83], angiotensin receptor blockers 1.61 [1.40–1.86] and diuretics 1.53 [1.32–1.77] (Figure 1). The differences for the fixed ACEi/ARB and thiazide combinations were smaller and not statistically significant.

Despite some covariate imbalances in the two cohorts (although all SMDs were below 0.1), adjustment for the potential confounders did not affect the HR estimates appreciably. The sensitivity analysis excluding patients with a prior hospitalization had no major impact on the HR estimates (see Supplementary Table in Appendix S1).

4 | DISCUSSION

Our study showed that, during the initial phase of the pandemic, antihypertensives were more commonly initiated to persons with a positive test for COVID-19 compared with those who had only tested negative or were never tested. Moreover, it was slightly more likely that patients with COVID-19 received a prescription with a RAAS-active drug compared with controls. However, the differences between COVID-19 positive patients and their controls were rather similar for the different antihypertensive drug classes.

The higher proportion of patients infected with COVID-19 initiated on antihypertensive drugs is a positive sign, given that effective management of chronic diseases generally has a protective effect against severe

TABLE 2 Incidence rates of initiating different antihypertensive drug classes (cases per 1000-person-years with 95% confidence intervals), in both COVID-19-infected patients naïve to each specific antihypertensive drug class in the prior year and their matched comparison group

		Exposed group			Unexposed group			
ATC	Drugs	Initiated on treatment	Person years	Incidence rate (per 1000-person years)	Initiated on treatment	Person years	Incidence rate (per 1000-person years)	IRR
C03	Diuretics	472	27610	17.1 [15.6–18.7]	323	29658	10.9 [9.7–12.1]	1.6
C07	Betablockers	802	26361	30.4 [28.3–32.6]	480	28369	16.9 [15.4–18.5]	1.8
C08	CCB	590	26933	21.9 [20.2–23.7]	402	28705	14.0 [12.7–15.4]	1.6
C09A	ACE-inhibitors	355	27463	12.9 [11.6–14.3]	201	29372	6.8 [5.9–7.9]	1.9
C09B	ACEi/thiazide	42	28576	1.5 [1.1–2.0]	33	30501	1.1 [0.7–1.5]	1.4
C09C	ARB	511	27136	18.8 [17.2–20.5]	348	28919	12.0 [10.8–13.4]	1.6
C09D	ARB/thiazide	116	28264	4.1 [3.4–4.9]	107	30156	3.5 [2.9–4.3]	1.2

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; IRR, incidence rate ratio.

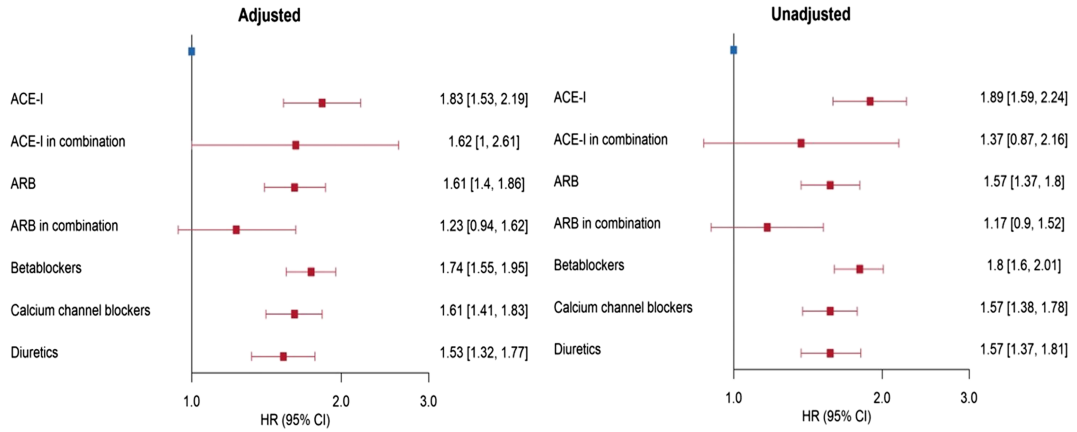

FIGURE 1 Unadjusted and adjusted hazard ratios of being initiated on different antihypertensive drugs for patients tested positive for COVID-19. Comparisons up 200 days after the date of the test with a comparison group who had tested negative or not been tested, matched by age, sex and calendar time. Adjusted for difference in prior use of other antihypertensive drugs, selected comorbidities, and educational level

outcomes of COVID-19 infection. It is not surprising that the crude proportion is higher since patients with COVID-19 had more comorbidities. However, even after adjustments for comorbidity, education and prior drug treatment, the risk of initiating treatment was higher for test-positive COVID-19 patients in our study. There are several potential reasons behind it. One potential explanation is that COVID-19 leads to hypertension.[27] A more likely reason is that patients infected with COVID-19 consult health care and have their blood pressure measured. According to the so-called "rule of halves," half of all people with hypertension are not diagnosed.[28] Therefore, there might have been people with high blood pressure in the COVID-19 positive group, identified after being infected. It could also be that too few people in the control group were initiated on antihypertensives, if they were reluctant to seek care during the first phase of the pandemic.[6] In December 2020, the EU-funded European Network to Advance Best practices & technoLogy on medication adherencE (ENABLE) COST Action conducted a survey in 39 European countries to assess barriers and facilitators for patients accessing their chronic medication during the pandemic.[29,30] The survey indicated significant disruption of chronic disease services, especially in countries with a greater number of COVID-19 cases per 100 000 inhabitants, and a large variation between countries in measures taken to ensure adequate drug management. This is of great concern, and even more critical since the pandemic may have a negative impact on blood pressure levels in the population.[31]

It is also important to acknowledge that there may be other differences between those being infected and the comparison group. Our findings showed a slight change between unadjusted and adjusted results in the HRs when we included the potential confounders in the model. The small difference between unadjusted and adjusted results and the fact that the sensitivity analysis had no major impact on the results could indicate that the effect of confounding factors is relatively small. However, we had no data for other potential confounders, such as smoking, alcohol consumption and BMI. Furthermore, we only used data on diagnoses from the national patient register including diagnoses registered in hospitals and in specialist outpatient care, while most patients with hypertension are diagnosed and treated in primary care.[24]

Our results showed differences compared with previously reported studies of antihypertensive drugs in Sweden, as betablockers and ACE-inhibitors were initiated more in our study compared with previous findings.[32] It is important to recognize that there have been several changes on the drug market since that time with, for example, new guidelines and formularies as well as changes in price after patent expiries and introduction of generics. The current prescribing patterns correspond rather well to the recent European guidelines for the treatment of hypertension.[33] Furthermore, we assessed initiation of antihypertensives for any indication, because explicit information of indication for prescription was not available. The high rate of initiations of betablockers might partly have been for the treatment of heart failure or as secondary prevention after myocardial infarction, as recommended by current guidelines.[34,35]

The fact that ACE inhibitors were the drugs with the highest likelihood of being initiated to a patient infected with COVID-19 is not surprising since according to some hypotheses, it may have some benefit compared with the other antihypertensive agents.[16,17] In a meta-analysis,

Ren et al. concluded that the mortality and severity of COVID-19 were significantly lower in patients taking ACE inhibitors/ARBs than in controls.[16] No association was found between using other antihypertensive drugs including CCBs, beta-blockers, and diuretics and the incidence and severity of COVID-19. In contrast to other reviews, Nozari and Hamidizadeh investigated the effects of antihypertensive drugs on COVID-19 only in patients with essential hypertension.[17] They suggest that ACE inhibitors and ARBs may be better choices to treat hypertension in this population. Conversely, diuretics can be considered the least effective drug in the setting of concomitant hypertension and COVID-19. It should be noted, though, that these reviews are quite recent, and most of the discussion in media focused on the RAAS inhibitors at the time of this study.

In this study, we restricted our analysis to initiations of antihypertensive therapy. It is well known from previous studies that many patients do not take their medicines as prescribed and a review found that persistence rates for antihypertensives can be as low as 35% 1 year after initiation.[36] The largest decline in persistence occurs early after initiation and in a previous study, we found that a large proportion of Swedish patients with hypertension in primary care only claimed one prescription.[37] It will be important to study if the COVID-19 pandemic has further negatively impacted patient adherence and persistence.

A major strength in our study was the large study population and nationwide coverage of our datasets. Our study was based on nationwide registers with complete coverage and high validity. The Swedish prescribed drug register is unique with 99.7% coverage, including individual patient data for all dispensed prescription drugs in the country.[20] The patient register has also showed high validity, enabling us to adjust for a range of potential confounders.[21] There were, however, some limitations. Diagnoses recorded in primary care are not available in the national patient register. Some variables such as BMI, alcohol consumption and smoking that may have been possible confounders were not included in the analysis either, due to the lack of information in the used registers. Another limitation was that COVID-19 test was not available to everyone in the beginning of the pandemic, and people with milder symptoms were never tested, likely resulting in some misclassification between the test-positive and comparison group, which may have affected the results of our study. It is also possible that patients with risk factors and chronic diseases had less access to health care in Sweden during the pandemic. This may have resulted in a general under-reporting of comorbidities in our data. Finally, it is important to acknowledge that we defined co-morbidities and drug treatment based on only one registration. This might have introduced some information bias, but it would most likely be nondifferential between groups.

In conclusion, we found that all antihypertensive medicines were more frequently initiated in people with a positive COVID-19 test compared with a matched study group from the general population. This difference may either be associated with hypertension caused by the COVID-19 infection, more people with COVID-19 diagnosed with hypertension since they consult health care, or residual confounding factors not adjusted for in this study.

ACKNOWLEDGEMENTS

This study was funded by grants for COVID research from NordForsk (Nordic COHERENCE, PI: professor Morten Andersson, Copenhagen), Swedish government ALF-agreement and FORMAS (SCIFI-PEARL-project, PI professor Fredrik Nyberg, University of Gothenburg), and Uppsala University (Faculty of Pharmacy).

CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

ORCID

Fredrik Nyberg https://orcid.org/0000-0003-0892-5668
Mohammadhossein Hajiebrahimi https://orcid.org/0000-0001-8118-4988
Björn Wettermark https://orcid.org/0000-0003-0531-2516

REFERENCES

1. CDC. *Coronavirus Disease 2019 (COVID-19)*. Centers for Disease Control and Prevention; 2020. https://www.cdc.gov/coronavirus/2019-ncov/cdcresponse/about-COVID-19.html
2. Chang AY, Cullen MR, Harrington RA, Barry M. The impact of novel coronavirus COVID-19 on noncommunicable disease patients and health systems: a review. *J Intern Med*. 2021;289:450-462. doi:10.1111/joim.13184
3. Pepera G, Tribali MS, Batalik L, Petrov I, Papathanasiou J. Epidemiology, risk factors and prognosis of cardiovascular disease in the Coronavirus Disease 2019 (COVID-19) pandemic era: a systematic review. *Rev Cardiovasc Med*. 2022;23:28. doi:10.31083/j.rcm2301028
4. Kluge HHP, Wickramasinghe K, Rippin HL, et al. Prevention and control of non-communicable diseases in the COVID-19 response. *Lancet*. 2020;395(10238):1678-1680. doi:10.1016/S0140-6736(20)31067-9
5. Lim MA, Huang I, Yonas E, Vania R, Pranata R. A wave of non-communicable diseases following the COVID-19 pandemic. *Diabetes Metab Syndr*. 2020;14:979-980. doi:10.1016/j.dsx.2020.06.050
6. WHO NCD Department. Rapid assessment of service delivery for NCDs during the COVID-19 pandemic. Available at

https://www.who.int/publications/m/item/rapid-assessment-of-service-delivery-for-ncds-during-the-covid-19-pandemic (assessed 12-02-2022)

7. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665. doi:10.1136/bmj.b1665
8. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol*. 2020;318(5):H1084-H1090. doi:10.1152/ajpheart.00217.2020
9. Wang JJ, Edin ML, Zeldin DC, Li C, Wang DW, Chen C. Good or bad: application of RAAS inhibitors in COVID-19 patients with cardiovascular comorbidities. *Pharmacol Ther*. 2020;215:107628. doi:10.1016/j.pharmthera.2020.107628
10. Wang Y, Chen B, Li Y, et al. The use of renin–angiotensin–aldosterone system (RAAS) inhibitors is associated with a lower risk of mortality in hypertensive COVID-19 patients: a systematic review and meta-analysis. *J Med Virol*. 2021;93(3):1370-1377. doi:10.1002/jmv.26625
11. Guo X, Zhu Y, Hong Y. Decreased mortality of COVID-19 with renin-angiotensin-aldosterone system inhibitors therapy in patients with hypertension: a meta-analysis. *Hypertension*. 2020;76:e13-e14. doi:10.1161/HYPERTENSIONAHA.120.15572
12. Patoulias D, Katsimardou A, Stavropoulos K, Imprialos K, Kalogirou MS, Doumas M. Renin-angiotensin system inhibitors and COVID-19: a systematic review and meta-analysis. evidence for significant geographical disparities. *Curr Hypertens Rep*. 2020;22(11):90. doi:10.1007/s11906-020-01101-w
13. Baral R, Tsampasian V, Debski M, et al. Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(3):e213594. doi:10.1001/jamanetworkopen.2021.3594
14. Bezabih YM, Bezabih A, Alamneh E, Peterson GM, Bezabhe W. Comparison of renin-angiotensin-aldosterone system inhibitors with other antihypertensives in association with coronavirus disease-19 clinical outcomes. *BMC Infect Dis*. 2021;21(1):527. doi:10.1186/s12879-021-06088-6
15. Loader J, Lampa E, Gustafsson S, Cars T, Sundström J. Renin-angiotensin aldosterone system inhibitors in primary prevention and COVID-19. *J am Heart Assoc*. 2021;10(15):e021154 doi:10.1161/JAHA.120.021154
16. Ren L, Yu S, Xu W, Overton JL, Chiamvimonvat N, Thai PN. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: a meta-analysis. *J Cardiol*. 2021;77(5):482-491. doi:10.1016/j.jjcc.2020.10.015
17. Nozari F, Hamidizadeh N. The effects of different classes of antihypertensive drugs on patients with COVID-19 and hypertension: a mini-review. *Int J Hypertens*. 2022;2022:5937802-8. doi:10.1155/2022/5937802
18. Nyberg F, Franzén S, Lindh M, et al. Swedish Covid-19 investigation for future insights—a population epidemiology approach using register linkage (SCIFI-PEARL). *Clin Epidemiol*. 2021;13:649-659. doi:10.2147/CLEP.S312742
19. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-667. doi:10.1007/s10654-009-9350-y
20. Wettermark B, Hammar N, Fored CM, et al. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16:726-735. doi:10.1002/pds.1294
21. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450. doi:10.1186/1471-2458-11-450
22. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol*. 2019;34:423-437. doi:10.1007/s10654-019-00511-8
23. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1
24. Wallentin F, Wettermark B, Kahan T. Drug treatment of hypertension in Sweden in relation to sex, age, and comorbidity. *J Clin Hypertens (Greenwich)*. 2018;20:106-114. doi:10.1111/jch.13149
25. Wallentin F, Wettermark B, Kahan T. Current antihypertensive drug therapy in 12,436 Swedish patients, 90 years and above, in relation to sex and comorbidity. *Blood Press*. 2020;29(3):168-174. doi:10.1080/08037051.2019.1707063
26. Forslund T, Carlsson AC, Ljunggren G, Ärnlöv J, Wachtler C. Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study. *Fam Pract*. 2021;38(2):132-140. doi:10.1093/fampra/cmaa056
27. Chen G, Li X, Gong Z, et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. *PLoS ONE*. 2021;16(4):e0250815 doi:10.1371/journal.pone.0250815
28. Hooker RC, Cowap N, Newson R, Freeman GK. Better by half: hypertension in the elderly and the 'rule of halves': a primary care audit of the clinical computer record as a springboard to improving care. *Fam Pract*. 1999;16:123-128. doi:10.1093/fampra/16.2.123
29. Kardas P, van Boven JFM, Pinnock H, et al. Disparities in European healthcare system approaches to maintaining continuity of medication for non-communicable diseases during the COVID-19 outbreak, ENABLE collaborators. *Lancet Reg Health Eur*. 2021;4:100099. doi:10.1016/j.lanepe.2021.100099
30. Ágh T, van Boven JF, Wettermark B, et al. A cross-sectional survey on medication management practices for noncommunicable diseases in Europe during the second wave of the COVID-19 pandemic. *Front Pharmacol*. 2021;12:685696. doi:10.3389/fphar.2021.685696
31. Laffin LJ, Kaufman HW, Chen Z, et al. Rise in blood pressure observed among us adults during the COVID-19 pandemic. *Circulation*. 2022;145:235-237. doi:10.1161/CIRCULATIONAHA.121.057075
32. Wettermark B, Godman B, Neovius M, Hedberg N, Mellgren TO, Kahan T. Initial effects of a reimbursement restriction to improve the cost-effectiveness of antihypertensive treatment. *Health Policy*. 2010;94:221-229. doi:10.1016/j.healthpol.2009.09.014
33. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021-3104. doi:10.1201/9780429199189-75

34. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
35. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Disease Prevention in Clinical Practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106
36. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract*. 2008;62(1):76-87. doi:10.1111/j.1742-1241.2007.01630.x
37. Qvarnström M, Kahan T, Kieler H, et al. Persistence to antihypertensive drug treatment in Swedish primary healthcare. *Eur J Clin Pharmacol*. 2013;69(11):1955-1964. doi:10.1007/s00228-013-1555-z

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mousa SI, Nyberg F, Hajiebrahimi M, et al. Initiation of antihypertensive drugs to patients with confirmed COVID-19—A population-based cohort study in Sweden. *Basic Clin Pharmacol Toxicol*. 2022;131(3):196-204. doi:10.1111/bcpt.13766