Original Article
Yonsei Med J 2021 Jul;62(7):577-583
https://doi.org/10.3349/ymj.2021.62.7.577
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Incidence and Mortality Associated with Cardiovascular Medication among Hypertensive COVID-19 Patients in South Korea

Tak Kyu Oh[1]*, Hyoung-Won Cho[2]*, Jung-Won Suh[2], and In-Ae Song[1]

Departments of [1]Anesthesiology and Pain Medicine and [2]Cardiology, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea.

Purpose: We aimed to investigate whether the use of cardiovascular drugs in coronavirus disease 2019 (COVID-19) patients with hypertension as a comorbidity has a significant effect on the incidence and associated mortality rate of COVID-19.

Materials and Methods: Data covering the period between January 1, 2020 and June 4, 2020 were extracted from The National Health Insurance Service-COVID-19 (NHIS-COVID-19) database in South Korea and analyzed as a population-based cohort study.

Results: A total of 101657 hypertensive adults aged 20 years or older were included for final analysis. Among them, 1889 patients (1.9%) were diagnosed with COVID-19 between January 1, 2020 and June 4, 2020, and hospital mortality occurred in 193 patients (10.2%). In a multivariable model, the use of beta-blockers was associated with an 18% lower incidence of COVID-19 [odds ratio (OR): 0.82, 95% confidence interval (CI): 0.69–0.98; p=0.029]. Among 1889 hypertensive patients diagnosed with COVID-19, the use of a calcium channel blocker (CCB) was associated with a 42% lower hospital mortality rate (OR: 0.58, 95% CI: 0.38–0.89; p=0.012). The use of other cardiovascular drugs was not associated with the incidence of COVID-19 or hospital mortality rate among COVID-19 patients. Similar results were observed in all 328374 adults in the NHIS-COVID-19 database, irrespective of the presence of hypertension.

Conclusion: In South Korea, beta-blockers exhibited potential benefits in lowering the incidence of COVID-19 among hypertensive patients. Furthermore, CCBs may lower the hospital mortality rate among hypertensive COVID-19 patients. These findings were also applied to the general adult population, regardless of hypertension.

Key Words: Hypertension, aspirin, clopidogrel, viruses, cohort studies

INTRODUCTION

On March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic.[1] As of March 9, 2021, 117537679 cases of COVID-19 and 2609805 COVID-19-related deaths have been reported globally.[2] Although vaccines are currently being administered worldwide,[3,4] the volume and speed of the production of the vaccination may hinder achieving COVID-19 herd immunity quickly.[5] Thus, COVID-19 remains a global and important health crisis.

A common comorbidity, hypertension is a known risk factor for worse outcomes among COVID-19 patients.[6-8] However, the clinical usefulness of various cardiovascular drugs that are commonly used in hypertensive COVID-19 patients is debated.[6,9-12] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of COVID-19, causes the downregulation of angiotensin-converting enzyme 2 (ACE2), thereby reducing its protective effects on various tissues. Therefore, there are concerns that angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) might increase susceptibility to SARS-CoV-2 and worsen the progno-

Received: January 14, 2021 **Revised:** March 15, 2021
Accepted: April 6, 2021
Corresponding author: In-Ae Song, MD, PhD, Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Tel: 82-31-787-7499, Fax: 82-31-787-4063, E-mail: songoficu@outlook.kr

*Tak Kyu Oh and Hyoung-Won Cho contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

sis of COVID-19.[13-15] However, other reports suggest that ACEis and ARBs may be used safely in COVID-19 patients[16] and may even result in better outcomes, including lower all-cause mortality.[17] One popular type of cardiovascular medication, namely calcium channel blockers (CCBs), has been reported to improve outcomes in COVID-19 patients by inhibiting the post-entry replication events of SARS-CoV-2.[18] Beta-blockers have also been reported to decrease the severity of COVID-19 symptoms in patients[14] because they may reduce the activity of the renin–angiotensin–aldosterone system and ACE2, which may decrease the rate of SARS-CoV-2 entry into host cells.[19] Thus, the association of cardiovascular drugs with the risk of mortality among COVID-19 patients remains controversial.

Accordingly, we aimed to investigate whether the use of cardiovascular drugs among hypertensive patients is associated with the incidence of COVID-19 and its related mortality rate in South Korea.

MATERIALS AND METHODS

Study design and ethical statement

We conducted this population-level cohort study according to the Reporting of Observational Studies in Epidemiology guidelines.[20] The need for approval of the study protocol was exempted upon deliberation by the Institutional Review Board of Seoul National University Bundang Hospital (X-2004-604-905) and the National Health Insurance Service (NHIS) (NHIS-2020-1-424). Also, the need for informed consent was waived because data analyses were performed retrospectively using anonymized data derived from the South Korean NHIS database.

Database and study population

In this study, we utilized data from the NHIS-COVID-19 cohort database, which was created for medical research in a collaborative effort between the Korea Centers for Disease Control and Prevention (KCDC) and the NHIS. The KCDC provided data on individuals who had tested positive for COVID-19 between the dates of January 1, 2020 and June 4, 2020. The data included the COVID-19 confirmation date, demographic information, and treatment results. In the NHIS-COVID-19 database, COVID-19 patients included all individuals who had tested positive to a COVID-19 polymerase chain reaction (PCR) test; therefore, the database included both COVID-19 patients with severe symptoms, such as pneumonia, who had been admitted to a hospital for treatment and COVID-19 patients with no or mild symptoms. COVID-19 patients who are currently undergoing in-hospital treatment have not been included in the database because the results of in-hospital treatment have not yet been determined.

Using stratification methods, the NHIS has also provided a control population with regard to age, sex, and place of residence as of February 2020 using the COVID-19 patients' information from the KCDC. The database contains all disease diagnoses using International Classification of Diseases (ICD)-10 codes and prescription information concerning drugs and/or procedures from 2015 to 2020. It also contains data on individuals who had undergone a COVID-19 PCR test, but tested negative. Therefore, the NHIS-COVID-19 database comprises data for three groups: COVID-19 patients, a control population, and individuals who have tested negative. For the hypertensive cohort, we included adults (20 years or older) in the NHIS database who had been diagnosed with hypertension (I10* according to ICD-10 codes) between 2015 and 2019.

Exposure variable: cardiovascular medication

The exposure variable in this cohort study was the prescription of cardiovascular drugs. To evaluate this, the prescription data from 2019 to 2020 were extracted from the NHIS database. Individuals were defined as cardiovascular drug users if they were prescribed regular cardiovascular drugs from 2019 for over 90 days until the date of diagnosis of COVID-19 in 2020 for COVID-19 patients or until June 4, 2020 for individuals who were not diagnosed with COVID-19. The cardiovascular drugs included ACEi, aspirin, ARB, beta-blocker, CCB, clopidogrel, and thiazide.

Endpoints of the study

The primary endpoint of our study was the development of COVID-19. COVID-19 positivity was evaluated by a COVID-19 PCR test during the period between January 1, 2020 and June 4, 2020. The secondary endpoint was hospital mortality among patients who were diagnosed with COVID-19. Hospital mortality was evaluated among COVID-19 patients until August 27, 2020.

Covariates

The following data were extracted and collected as confounders in this study: 1) demographic characteristics (age and sex), 2) annual income level in 2020, 3) place of residence (Seoul, Gyeonggi-do, Daegu, Gyeongsangbuk-do, and other areas), 4) underlying disabilities (mild degree and moderate-to-severe degree), and 5) comorbidity information using Charlson comorbidity index scores, which were calculated using the registered ICD-10 diagnostic codes (Supplementary Table 1, only online) from January 1, 2015 to December 31, 2019. Age in the NHIS-COVID-19 cohort was divided into seven categorical groups: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years old.

Statistical methodology

The baseline characteristics of the participants in this study are presented as numbers with percentages for categorical variables and mean values with their respective standard deviations for continuous variables. First, we fitted a multivariable logistic regression model for the diagnosis of COVID-19 among

https://doi.org/10.3349/ymj.2021.62.7.577

hypertensive individuals in the NHIS-COVID-19 cohort to investigate whether cardiovascular drug use was associated with the incidence of COVID-19. All seven cardiovascular drugs (ACEi, aspirin, ARB, beta-blocker, CCB, clopidogrel, and thiazide) were included in the multivariable logistic regression model simultaneously. In the model, the reference value for each drug was obtained from non-users of that drug. In addition, a separate multivariable logistic regression model was fitted to investigate whether the use of any of the cardiovascular drugs was associated with the incidence of COVID-19, compared to non-use of the drug. All covariates were included for multivariable adjustment, although the Charlson comorbidity index was included in the other model to avoid multicollinearity with other underlying diseases that were used to calculate the Charlson comorbidity index. Next, we fitted a multivariable logistic regression model for hospital mortality among hypertensive COVID-19 patients to investigate whether cardiovascular drug use was associated with hospital mortality among COVID-19 patients.

For sensitivity analysis, we constructed two multivariable logistic regression models for 1) COVID-19 diagnosis and 2) hospital mortality among COVID-19 patients to identify whether the results obtained from hypertensive patients in the NHIS-COVID-19 cohort were generalizable to the entire NHIS-COVID-19 cohort, including individuals without hypertension. Hosmer–Lemeshow statistics were used to confirm the goodness of fit of the multivariable models at $p>0.05$, and it was confirmed that there was no multicollinearity in any of the multivariable models, with a variance inflation factor of <2.0. The results of the logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CIs). R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses, and a p-value<0.05 was considered statistically significant.

RESULTS

Study population

A flowchart depicting participant selection in this study is presented in Fig. 1. The NHIS-COVID-19 cohort comprised 8070 COVID-19 patients, 121050 individuals in the control population, and 222257 negative-tested individuals. In total, 351377 individuals were initially reviewed. After excluding 23003 individuals aged <20 years, 328374 adults were further reviewed. Of these, 101657 adults were diagnosed with hypertension and included in the final analysis. The clinically relevant baseline characteristics of these individuals are presented in Table 1. 83215 individuals (81.9%) had been prescribed cardiovascular medication for treatment. In addition, 1889 (1.9%) were diagnosed with COVID-19 between January 1, 2020 and June 4, 2020. The incidence of hospital mortality among COVID-19 patients was 193 (10.2%).

Main analysis among hypertensive patients

Table 2 shows the results of the multivariable logistic regression model for the diagnosis of hypertensive COVID-19 patients. In multivariable model 1, the use of beta-blockers was associated with an 18% lower incidence of COVID-19 (OR: 0.82, 95% CI: 0.69–0.98; p=0.029), while other cardiovascular drugs, such as ACEi (p=0.269), aspirin (p=0.354), ARB (p=0.580), CCB (p=0.707), clopidogrel (p=0.220), and thiazide (p=0.249), were not associated with the incidence of COVID-19. In multivariable model 2, compared with non-users, the use of cardiovascular medication was not associated with the incidence of COVID-19 (p=0.215). The results of multivariable logistic regression analysis of hospital mortality among COVID-19 patients with hypertension are presented in Table 3. In multivariable model 1, among the 1889 hypertensive COVID-19 patients, CCB use was associated with a 42% lower hospital mortality (OR: 0.58, 95% CI: 0.38–0.89; p=0.012). However, other cardiovascular drugs, such as ACEi (p=0.728), aspirin (p=0.825), ARB (p=0.440), beta-blockers (p=0.793), clopidogrel (p=0.373), and thiazide (p=0.393), were not associated with hospital mortality among hypertensive COVID-19 patients. In multivariable model 2, compared to non-users, the use of cardiovascular medication was not associated with hospital mortality among hypertensive COVID-19 patients (p=0.352).

Sensitivity analysis in total NHIS-COVID-19 cohort

Table 4 shows the results of the multivariable logistic regression models for the diagnosis of COVID-19 and hospital mortality among COVID-19 patients in the entire NHIS-COVID-19 cohort. In the multivariable model, beta-blocker and aspirin use was associated with a 19% (OR: 0.81, 95% CI: 0.68–0.95; p=

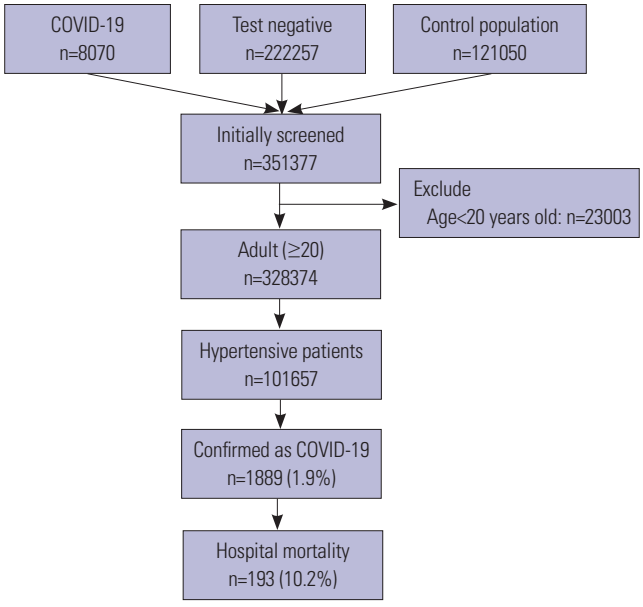

Fig. 1. Flow chart depicting the selection of hypertensive COVID-19 patients. COVID-19, coronavirus disease 2019.

Table 1. Baseline Characteristics of Hypertensive Adult Patients in the NHIS-COVID-19 Cohort (n=101657)

Variable	N (%)	Mean (SD)
Sex, male	50495 (49.7)	
Age (yr)		
20–29	1909 (1.9)	
30–39	3754 (3.7)	
40–49	7706 (7.6)	
50–59	17223 (16.9)	
60–69	24014 (23.6)	
70–79	23900 (23.5)	
≥80	23151 (22.8)	
Income in quartile		
Q1 (lowest)	27366 (26.9)	
Q2	16133 (15.9)	
Q3	20710 (20.4)	
Q4 (highest)	35984 (35.4)	
Unknown	1464 (1.4)	
Underlying disability		
Mild degree	12083 (11.9)	
Moderate to severe degree	8648 (8.5)	
Residence		
Seoul	17160 (16.9)	
Gyeonggi-do	18608 (18.3)	
Daegu	26292 (25.9)	
Gyeongsangbuk-do	10260 (10.1)	
Other area	29337 (28.9)	
Charlson comorbidity index		6.2 (3.8)
Myocardial infarction	9815 (9.7)	
Congestive heart failure	30489 (30.0)	
Peripheral vascular disease	43159 (42.5)	
Cerebrovascular disease	36899 (36.3)	
Peptic ulcer disease	62044 (61.0)	
DM without chronic complication	62946 (61.9)	
DM with chronic complication	26162 (25.7)	
Renal disease	13890 (13.7)	
Dementia	22173 (21.8)	
Hemiplegia or paraplegia	5908 (5.8)	
Rheumatic disease	18274 (18.0)	
Mild liver disease	72379 (71.2)	
Moderate to severe liver disease	2164 (2.1)	
Chronic pulmonary disease	71724 (70.6)	
Any cancer	27963 (27.5)	
Metastatic solid tumor	5441 (5.4)	
HIV/AIDS	295 (0.3)	
Any cardiovascular medication user	83215 (81.9)	
Cardiovascular medication		
ACEi	2627 (2.6)	
Aspirin	21620 (21.3)	
ARB	51572 (50.7)	
Beta-blocker	12361 (12.2)	
CCB	24790 (24.4)	
Clopidogrel	13311 (13.1)	
Thiazide	1750 (1.7)	

NHIS-COVID-19, The National Health Insurance Service-coronavirus disease 2019; DM, diabetes mellitus; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker.

Table 2. Multivariable Logistic Regression Analysis for Diagnosis of COVID-19 in South Korea

Variable	Multivariable model	*p* value
	OR (95% CI)	
Sex, male	0.94 (0.86–1.04)	0.227
Age, 10 years increase	0.99 (0.95–1.03)	0.518
Income in quartile		
Q1 (lowest)	1	
Q2	0.90 (0.78–1.04)	0.148
Q3	0.84 (0.73–0.95)	0.008
Q4 (highest)	0.72 (0.64–0.81)	<0.001
Unknown	0.84 (0.57–1.22)	0.356
Underlying disability		
Mild degree (vs. no disability)	0.98 (0.84–1.15)	0.835
Moderate to severe degree (vs. no disability)	1.36 (1.13–1.64)	0.001
Residence		
Seoul	1	
Gyeonggi-do	1.05 (0.77–1.43)	0.768
Daegu	10.33 (8.15–13.08)	<0.001
Gyeongsangbuk-do	6.97 (5.40–9.00)	<0.001
Other area	1.24 (0.94–1.64)	0.128
Charlson comorbidity index (in another model)	0.95 (0.93–0.96)	<0.001
Myocardial infarction	0.99 (0.83–1.19)	0.956
Congestive heart failure	0.94 (0.83–1.06)	0.297
Peripheral vascular disease	0.96 (0.87–1.07)	0.475
Cerebrovascular disease	0.96 (0.85–1.08)	0.460
Peptic ulcer disease	0.87 (0.79–0.96)	0.005
DM without chronic complication	1.03 (0.93–1.14)	0.595
DM with chronic complication	1.02 (0.90–1.15)	0.787
Renal disease	0.57 (0.47–0.69)	<0.001
Dementia	1.31 (1.15–1.50)	<0.001
Hemiplegia or paraplegia	1.08 (0.87–1.34)	0.482
Rheumatic disease	0.99 (0.87–1.13)	0.938
Mild liver disease	1.06 (0.95–1.18)	0.289
Moderate to severe liver disease	0.61 (0.37–1.01)	0.055
Chronic pulmonary disease	0.89 (0.80–0.98)	0.021
Any cancer	0.65 (0.56–0.75)	<0.001
Metastatic solid tumor	0.78 (0.55–1.12)	0.175
HIV/AIDS	0.47 (0.12–1.90)	0.290
Cardiovascular medication, model 1		
ACEi (vs. no ACEi use)	1.18 (0.88–1.57)	0.269
Aspirin (vs. no aspirin use)	0.94 (0.83–1.07)	0.354
ARB (vs. no ARB use)	0.97 (0.88–1.07)	0.580
Beta-blocker (vs. no beta-blocker use)	0.82 (0.69–0.98)	0.029
CCB (vs. no CCB user)	0.98 (0.88–1.09)	0.707
Clopidogrel (vs. no clopidogrel use)	0.90 (0.76–1.06)	0.220
Thiazide (vs. no thiazide use)	0.80 (0.54–1.17)	0.249
Any cardiovascular medication use (vs. no use), model 2	0.92 (0.78–1.08)	0.215

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker.

https://doi.org/10.3349/ymj.2021.62.7.577

Table 3. Multivariable Logistic Regression Analysis for Hospital Mortality among COVID-19 Patients with Hypertension (n=1889) [Mortality=193 (10.2%)]

Variable	Multivariable model OR (95% CI)	*p* value
Sex, male	2.02 (1.41–2.89)	<0.001
Age, 10 years increase	2.95 (2.37–3.67)	<0.001
Income in quartile		
Q1 (lowest)	1	
Q2	1.16 (0.66–2.05)	0.605
Q3	1.07 (0.65–1.76)	0.789
Q4 (highest)	0.80 (0.52–1.24)	0.322
Unknown	0.66 (0.13–3.37)	0.621
Underlying disability		
Mild degree (vs. no disability)	0.97 (0.60–1.59)	0.915
Moderate to severe degree (vs. no disability)	2.36 (1.32–4.22)	0.004
Residence		
Seoul	1	
Gyeonggi-do	3.92 (0.73–21.15)	0.112
Daegu	2.65 (0.56–12.54)	0.220
Gyeongsangbuk-do	2.73 (0.56–13.38)	0.216
Other area	3.20 (0.61–16.91)	0.170
Charlson comorbidity index (in another model)	1.14 (1.08–1.20)	<0.001
Myocardial infarction	0.54 (0.29–0.99)	0.046
Congestive heart failure	1.92 (1.31–2.81)	<0.001
Peripheral vascular disease	1.12 (0.78–1.60)	0.551
Cerebrovascular disease	0.90 (0.61–1.33)	0.604
Peptic ulcer disease	0.86 (0.60–1.24)	0.420
DM without chronic complication	1.08 (0.72–1.62)	0.716
DM with chronic complication	1.90 (1.29–2.81)	0.001
Renal disease	2.29 (1.34–3.90)	0.002
Dementia	1.42 (0.95–2.14)	0.090
Hemiplegia or paraplegia	1.28 (0.69–2.35)	0.432
Rheumatic disease	1.00 (0.62–1.62)	0.985
Mild liver disease	0.82 (0.54–1.22)	0.327
Moderate to severe liver disease	0.96 (0.19–4.84)	0.964
Chronic pulmonary disease	1.00 (0.68–1.49)	0.989
Any cancer	1.38 (0.86–2.20)	0.181
Metastatic solid tumor	1.76 (0.55–5.62)	0.339
HIV/AIDS	61.92 (1.08–3548.61)	0.046
Cardiovascular medication, model 1		
ACEi (vs. no ACEi use)	1.17 (0.49–2.79)	0.728
Aspirin (vs. no aspirin use)	1.05 (0.68–1.61)	0.825
ARB (vs. no ARB use)	0.87 (0.60–1.25)	0.440
Beta-blocker (vs. no beta-blocker use)	0.92 (0.49–1.72)	0.793
CCB (vs. no CCB use)	0.58 (0.38–0.89)	0.012
Clopidogrel (vs. no clopidogrel use)	1.27 (0.75–2.13)	0.373
Thiazide (vs. no thiazide use)	1.81 (0.46–7.08)	0.393
Any cardiovascular medication use (vs. no use), model 2	1.45 (0.75–2.42)	0.352

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker.

Table 4. Multivariable Logistic Regression Models for the Diagnosis of COVID-19 and Mortality among COVID-19 Patients in the Entire NHIS-COVID-19 Cohort

Variable	Multivariable model OR (95% CI)	*p* value
Diagnosis of COVID-19 among 328374 individuals		
Cardiovascular medication, model 1		
ACEi (vs. no ACEi use)	1.24 (0.95–1.63)	0.117
Aspirin (vs. no aspirin use)	0.88 (0.79–0.99)	0.041
ARB (vs. no ARB use)	0.99 (0.92–1.07)	0.761
Beta-blocker (vs. no beta-blocker use)	0.81 (0.68–0.95)	0.011
CCB (vs. no CCB use)	1.00 (0.90–1.10)	0.960
Clopidogrel (vs. no clopidogrel use)	0.88 (0.76–1.02)	0.093
Thiazide (vs. no thiazide use)	0.85 (0.59–1.22)	0.375
Any cardiovascular medication use (vs. no use), model 2	0.94 (0.88–1.04)	0.215
Hospital mortality among COVID-19 patients (n=7713)		
Cardiovascular medication, model 1		
ACEi (vs. no ACEi use)	1.49 (0.64–3.45)	0.352
Aspirin (vs. no aspirin use)	0.99 (0.65–1.50)	0.948
ARB (vs. no ARB use)	1.03 (0.74–1.44)	0.865
Beta-blocker (vs. no beta-blocker use)	1.02 (0.55–1.89)	0.951
CCB (vs. no CCB use)	0.60 (0.39–0.92)	0.019
Clopidogrel (vs. no clopidogrel use)	1.20 (0.73–1.97)	0.480
Thiazide (vs. no thiazide use)	1.99 (0.50–7.95)	0.330
Any cardiovascular medication use (vs. no use), model 2	0.94 (0.88–1.05)	0.425

COVID-19, coronavirus disease 2019; NHIS-COVID-19, The National Health Insurance Service-coronavirus disease-2019; OR, odds ratio; CI, confidence interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker.

0.011), and 12% (OR: 0.88, 95% CI: 0.79–0.99; *p*=0.041) lower incidence of COVID-19, respectively. Additionally, the use of CCB was associated with a 40% lower hospital mortality rate (OR: 0.60, 95% CI: 0.39–0.92; *p*=0.019). Compared to non-users, the use of cardiovascular medication was not associated with the incidence of COVID-19 (*p*=0.215) or hospital mortality (*p*=0.425).

DISCUSSION

In this study, we found that beta-blocker use was associated with a lower incidence of COVID-19 among hypertensive patients, while CCB use was associated with a decreased hospital mortality rate among hypertensive COVID-19 patients. These findings were also applied to the general adult population, regardless of hypertension diagnosis, in the NHIS-COVID-19 database. Since the relationship between cardiovascular drugs and the risk of COVID-19 is currently undetermined,[6] our findings have potential clinical benefits.

It was recently reported that beta-adrenergic receptors might

be involved in SARS-CoV-2 entry into the cell by acting as a co-receptor via its interaction through surface vimentin and ACE2 receptor.[21] Thus, the potential role of beta-blockers in treatment for COVID-19 was suggested in September 2020.[19] Furthermore, recent evidence has shown that treatment with beta-blockers reduces mortality in septic shock patients[22] and has beneficial effects in individuals with acute respiratory distress syndrome or respiratory failure.[23] However, at the time of writing this report, no study has described clinical effects for beta-blockers in COVID-19 patients.[14,24] We report, for the first time, that prior beta-blocker therapy might be associated with a reduced risk of COVID-19 among both hypertensive patients and the general adult population in South Korea. However, the hospital mortality rate among COVID-19 patients was not associated with beta-blocker therapy, and more clinical research is needed in this regard.

We also found that CCB use was associated with decreased mortality among both hypertensive and non-hypertensive COVID-19 patients. A previous in vitro study reported that SARS-CoV-2 requires Ca2+ ions for host cell entry[25] and that CCBs are efficacious in inhibiting the spread of SARS-CoV-2 in cell cultures.[26] CCB (amlodipine besylate) administration has been found to be associated with better outcomes among COVID-19 patients.[18] However, other studies, including a meta-analysis conducted among older COVID-19 patients[14] and a prospective cohort study in Italy, did not demonstrate benefits for CCB use on the prognosis of COVID-19 patients.[27] Notwithstanding, the sample size in the latter study was small (69),[27] while we included 101657 hypertensive adults and 328374 adults from the general population. Considering the mixed results of previous studies regarding the effect of CCB on COVID-19 patients,[14,18,27] our results might provide rationale and evidence on which to consider the administration of CCB among COVID-19 patients in the future.

Interestingly, in our sensitivity analysis, aspirin showed potential benefits in lowering COVID-19 incidence among adults in general, but not in the hypertensive population. As one of the most common and important cardiovascular drugs, aspirin has been prescribed for adults to reduce the risk of acute cardiovascular events, suggesting it has a broader indication than that of anti-hypertensive drugs.[28] Currently, there is emerging evidence on the benefits of using aspirin to treat COVID-19 patients.[29] SARS-CoV-2 is known to cause lung and systemic inflammation,[30] which can cause severe respiratory failure, multiorgan dysfunction, and mortality.[31] The main pathological features of COVID-19 are micro- and macrovascular thromboses due to the activation of the immune response with the release of pro-inflammatory cytokines and the overactivation of the coagulation cascade and platelet aggregation.[32] Therefore, aspirin has been suggested as a new treatment option for COVID-19 patients as it has anti-inflammatory, antithrombotic, and antiviral effects.[33] The potential benefits of aspirin in reducing COVID-19 incidence in our study need further research.

The current study has a few limitations. First, some clinically important variables, such as body mass index, were not included in the analysis because they were not available in the NHIS database. Second, multivariable adjustment is known to reduce known and measured confounders. Thus, there might be some residual confounders that affect the results of this study. Third, we defined comorbidities using ICD-10 codes to calculate the Charlson comorbidity index, but the diseases specified by the ICD-10 codes might not reflect actual comorbidities in our study population. Furthermore, our analysis was based on prescription data in the NHIS database; we did not assess compliance among those classified as cardiovascular drug users. Fourth, we did not consider the daily dosage of cardiovascular drugs because the NHIS database provides this prescription information with masking of type and dosage. Finally, we did not consider the possibility of combining any of the seven cardiovascular drugs in this study because there were too many possible combinations of cardiovascular drugs to reflect in the multivariable model. Therefore, combinations of cardiovascular drugs might affect the results in this study and should be interpreted carefully.

Using the NHIS-COVID-19 database cohort, we showed that beta-blockers may have potential benefits in lowering the incidence of COVID-19 in hypertensive patients in South Korea. Among these hypertensive COVID-19 patients, we also found that CCB may lower hospital mortality rates. These findings were also applied to the general adult population, regardless of the presence of hypertension as a variable, in the NHIS-COVID-19 database.

AUTHOR CONTRIBUTIONS

Conceptualization: Tak Kyu Oh and In-Ae Song. Data curation: Hyoung-Won Cho and Jung-Won Suh. Formal analysis: Tak Kyu Oh. Investigation: Hyoung-Won Cho and Tak Kyu Oh. Methodology: Tak Kyu Oh and In-Ae Song. Supervision:In-Ae Song. Validation: Tak Kyu Oh and In-Ae Song. Visualization: Hyoung-Won Cho and Jung-Won Suh. Writing—original draft: Tak Kyu Oh. Writing—review & editing: Jung-Won Suh and In-Ae Song. Approval of final manuscript: all authors.

ORCID iDs

Tak Kyu Oh https://orcid.org/0000-0002-4027-4423
Hyoung-Won Cho https://orcid.org/0000-0001-6095-8569
Jung-Won Suh https://orcid.org/0000-0002-0397-6071
In-Ae Song https://orcid.org/0000-0002-7814-4253

REFERENCES

1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. Lancet 2020;395:1015-8.
2. Johns Hopkins University & Medicine, Coronavirus Resource Center. Global map of cases and deaths by country/region/sovereignty

https://doi.org/10.3349/ymj.2021.62.7.577

[accessed on 2021 March 9]. Available at: https://coronavirus.jhu.edu/map.html.
3. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412-23.
4. Knoll MD, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet 2021;397:72-4.
5. Fontanet A, Cauchemez S. COVID-19 herd immunity: where are we? Nat Rev Immunol 2020;20:583-4.
6. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. Am J Hypertens 2020;33:373-4.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
8. Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J 2020;41:2058-66.
9. Drager LF, Pio-Abreu A, Lopes RD, Bortolotto LA. Is hypertension a real risk factor for poor prognosis in the COVID-19 pandemic? Curr Hypertens Rep 2020;22:43.
10. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res 2020;116:1688-99.
11. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. Curr Cardiol Rep 2020;22:31.
12. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol 2020;318:H1084-90.
13. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;41:1801-3.
14. Liu Y, Huang F, Xu J, Yang P, Qin Y, Cao M, et al. Anti-hypertensive angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv 2020 Mar 27 [Preprint]. Available at: https://doi.org/10.1101/2020.03.20.20039586.
15. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect 2020;53:425-35.
16. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of angiotensin II receptor blockers and ACE (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. Hypertension 2020;76:51-8.
17. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020;126:1671-81.
18. Zhang LK, Sun Y, Zeng H, Wang Q, Jiang X, Shang WJ, et al. Calcium channel blocker amlodipine besylate therapy is associated with reduced case fatality rate of COVID-19 patients with hypertension. Cell Discov 2020;6:96.
19. Vasanthakumar N. Can beta-adrenergic blockers be used in the treatment of COVID-19? Med Hypotheses 2020;142:109809.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495-9.
21. Natesan V. SARS-CoV-2 host cell entry might involve beta adrenergic receptors. OSF Preprints 2020 July 11 [Preprint]. Available at: https://doi.org/10.31219/osf.io/d2g8k.
22. Tan K, Harazim M, Tang B, Mclean A, Nalos M. The association between premorbid beta blocker exposure and mortality in sepsis-a systematic review. Crit Care 2019;23:298.
23. Noveanu M, Breidthardt T, Reichlin T, Gayat E, Potocki M, Pargger H, et al. Effect of oral β-blocker on short and long-term mortality in patients with acute respiratory failure: results from the BASEL-II-ICU study. Crit Care 2010;14:R198.
24. Rezel-Potts E, Douiri A, Chowienczyk PJ, Gulliford MC. Antihypertensive medications and COVID-19 diagnosis and mortality: population-based case-control analysis in the United Kingdom. Br J Clin Pharmacol 2021 Apr 27 [Epub]. Available at: https://doi.org/10.1111/bcp.14873.
25. Lai AL, Millet JK, Daniel S, Freed JH, Whittaker GR. The SARS-CoV fusion peptide forms an extended bipartite fusion platform that perturbs membrane order in a calcium-dependent manner. J Mol Biol 2017;429:3875-92.
26. Straus MR, Bidon M, Tang T, Whittaker G, Daniel S. FDA approved calcium channel blockers inhibit SARS-CoV-2 infectivity in epithelial lung cells. bioRxiv 2020 Jul 21 [Preprint]. Available at: https://doi.org/10.1101/2020.07.21.214577.
27. Sardu C, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, et al. Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of Southern Italy. J Am Heart Assoc 2020;9:e016948.
28. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
29. Alegbeleye BJ, Akpoveso OOP, Alegbeleye AJ, Mohammed RK, Esteban-Zubero E. The novel aspirin as breakthrough drug for COVID-19: a narrative review. Iberoam J 2020;2:335-50.
30. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
31. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
32. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020;127:104362.
33. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? Drugs 2020;80:1383-96.