Association Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 Infection in South Korea

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Abstract—The severe acute respiratory syndrome coronavirus 2 is known to infect host cells by interacting with ACE2 (angiotensin-converting enzyme 2) expressed in the respiratory epithelium. There have been concerns on whether alterations of ACE2 expression by renin-angiotensin-aldosterone system (RAAS) inhibitors would contribute to the infectivity and severity of coronavirus disease 2019 (COVID-19). We performed a case-control study to investigate the association between RAAS inhibitors and risk and severity of COVID-19 infection in South Korea using the population-based data provided by the Korean National Health Insurance System. Of 16 281 subjects with hypertension, there were 950 (5.8%) confirmed COVID-19 cases. After case-control matching, multivariable-adjusted conditional logistic regression analysis was performed. The adjusted odds ratio and 95% CIs for COVID-19 infection and long-term hospitalization comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors was 1.161 (0.958–1.407) and 0.863 (0.533–1.397), respectively. When comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors for intensive care unit admission, high-flow oxygen therapy, and death, the adjusted odds ratios (95% CIs) were 1.515 (0.402–5.701), 0.663 (0.272–1.619), and 1.363 (0.513–3.662), respectively. In all analyses, *P* values were not significant ($P>0.05$). The present study demonstrates the absence of an identifiable association between the exposure to RAAS inhibitors and risk and severity of COVID-19 infection, supporting the current medical guidelines and recommendations that patients should not discontinue RAAS inhibitors out of a concern that they are at increased risk for infection or severe illness of COVID-19. **(*Hypertension*. 2020;76:742-749. DOI: 10.1161/HYPERTENSIONAHA.120.15464.)** ● **Data Supplement**

Key Words: antihypertensive agents ■ COVID-19 ■ hypertension ■ Republic of Korea ■ renin-angiotensin system

On March 11, 2020, the World Health Organization has upgraded the status of the current coronavirus disease 2019 (COVID-19) outbreak from epidemic to pandemic. As of May 5, 2020, a total of 3 517 345 cases have been confirmed worldwide with 243 401 deaths, according to the World Health Organization.[1] The culprit of the disease, severe acute respiratory syndrome coronavirus 2, is known to infect host cells by interacting with membrane-bound ACE2 (angiotensin-converting enzyme 2) expressed in the respiratory epithelium.[2,3] Given the importance of the renin-angiotensin-aldosterone system (RAAS) in orchestrating the human cardiovascular, respiratory, and immune systems, with ACE2 being part of the RAAS, there have been concerns on whether alterations of ACE2 expression by ACE inhibitors or angiotensin receptor blockers (ARBs) would contribute to the infectivity and severity of illness in the current COVID-19 pandemic.[4–6]

Keeping in mind that ACE2 differs from ACE, in which the latter is the enzyme inhibited by an ACE inhibitor, the question of how exactly RAAS blockade by ACE inhibitors or ARBs might influence the degree of ACE2 expression and thereby impact severe acute respiratory syndrome coronavirus 2 virulence is at the core of the current topic. Although there is evidence from several animal studies that ARBs may upregulate membrane-bound ACE2, evidence of the ACE inhibitory effect on ACE2 expression is weak.[7] Moreover, it has been postulated that the upregulation of ACE2 itself might have both beneficial and detrimental effects on patients with COVID-19.[8]

Given the necessity of further mechanistic studies in humans, recent debate and media coverage on the urgent discontinuation of antihypertensive drugs in patients with hypertension with COVID-19 have prompted the call for an investigation on whether these patients indeed have increased risk for infectivity and more serious outcomes of COVID-19 in the empirical setting.[9] Although there have been studies utilizing data from countries, including the United States, Italy, and China, to date, no studies have investigated the abovementioned subject on COVID-19 cases in South Korea.[10–12] Using the data provided by the Korean National Health Insurance System, we conducted a case-control study to investigate the association between the exposure to RAAS inhibitors and risk and severity of COVID-19 infection in the South Korean population.

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Specific considerations regarding the distinct epidemiology of the COVID-19 outbreak in South Korea should be noted. Characteristics of the South Korean situation are the cluster outbreaks, with Shincheonji-related cases leading the percentage by 48% (5212 cases), in a total of 10 793 confirmed cases, as of May 3. In addition to the Shincheonji-related cases, 2 other cluster infections of Chungdo Daenam hospital and pilgrimage tour to Israel are all based in the Daegu and Gyeongbuk regions, 150 miles southeast of Seoul, making it the epicenter of the COVID-19 outbreak in South Korea (regional cases sum up to 76.2% of total cases).[13,14] In our study, we have taken several statistical measures to account for the possible biases that may be associated with such unequal distributions of the COVID-19 outbreak.

Methods

Data Source

Data obtained from the national health insurance claims of South Korea were analyzed. Because of the sensitive nature of data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Health Insurance Review and Assessment at https://hira-covid19.net/. Datasets were collected and processed promptly by the Korean National Health Insurance System, which covers the entire population across the nation. The current dataset, based on the insurance benefit claim sent to the Health Insurance Review and Assessment on April 8, 2020, is population based and comprised of all tested cases of COVID-19, including suspicious cases, confirmed cases, and history of medical service use for the past 5 years. Data were fully anonymized and did not contain any identifiable information. This study was approved, and informed consent was waived by the Institutional Review Board of the Gwangju Institute of Science and Technology (20200413-EX-02-02).

Study Population

Figure presents an overview of this case-control study. The study was conducted on 69 793 subjects, all of whom were tested for COVID-19. Of the participants, we analyzed 16 281 subjects aged ≥19 years who had hypertension. The presence of hypertension was defined based on tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* codes for hypertension (I10, I11) with at least one claim per year for prescription of an antihypertensive drug.[15,16] The laboratory diagnosis of COVID-19 in South Korea was based on the guidelines provided by the Korea Centers for Disease Control and Prevention and World Health Organization, which recommend polymerase chain reaction amplification of the viral E gene as a screening test and amplification of the RdRP (RNA-dependent RNA polymerase) region of the *orf1b* gene as a confirmatory test.[17] Confirmed cases were defined as subjects with diagnosis codes of B34.2, B97.2, U18, U18.1, and U07.1 according to the Korean Standard Classification of Diseases. Among the selected hypertensive groups, there were 950 (5.8%) confirmed cases of COVID-19 infection, which were designated as the case group. There were 15 331 (94.2%) uninfected cases, which were designated as the control group. Cases and controls were matched up to 1:2 based on multiple covariates. Several variables were identified for the matching procedure. In South Korea, because the number of patients was unequally distributed as a result of the explosive outbreak in Daegu and Gyeongbuk regions,[14] subjects were classified into Daegu and Gyeongbuk regions and other regions as binary variables. The hospitals where subjects had been tested were classified into tertiary hospitals and etc. The matching was exact in sex, region, and tested hospital, but greedy nearest neighbor matching was performed on age with a caliper of 0.1 of the propensity scores. After matching, the final number of subjects was 950 and 1897 for the case and control groups, respectively. The standardized mean differences between the groups are shown in Figure S1 in the Data Supplement.

To analyze the association between RAAS inhibitors and severity of COVID-19 infection, we evaluated 4 severity indices in the case group: presence of long-term hospitalization (≥7 days), intensive care unit (ICU) admission, high-flow oxygen therapy, and death.[18] Because severe illness in COVID-19 infection usually begins ≈1 week after symptom onset, long-term hospitalization was defined as ≥7 days based on the number of days of hospitalization.[19,20] ICU admission was identified by claim codes, including AJ. High-flow oxygen therapy was identified by claim codes, including mechanical ventilation (M5850, M5857, M5858, M5860) and high-flow nasal cannula therapy (M0046).[18] The index of death was identified by the classification code of treatment result. In the COVID-19 infection group, the numbers of subjects for long-term hospitalization, ICU admission, high-flow oxygen therapy, and death were 221 (23.3%), 22 (2.3%), 47 (4.9%), and 38 (4.0%), respectively. In each index group, case and control matching up to 1:2 was performed in the infection group in the same manner as described above, except for long-term hospitalization (1:1 matching). The standardized mean differences between the groups are shown in Figure S2.

Classification of Exposure to RAAS Inhibitors

Exposure to RAAS inhibitors was defined as the type of drug administered within 1 year, which encompasses both single and combination drugs. RAAS inhibitors were classified as ACE inhibitors and ARBs. Regarding the exposure to RAAS inhibitors, classification was performed based on nonexposure to RAAS inhibitors, exposure to RAAS inhibitors, exposure to ACE inhibitors, and exposure to ARBs. To verify the robustness of our findings, we performed 2 additional analyses. With at least one claim within 6 months and 3 months for prescription of an antihypertensive drug, we classified these according to the exposure to RAAS inhibitors and performed additional analyses.

Definition of Covariates

Covariate diseases were determined based on the diagnosis codes of the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems*. The covariates considered were diabetes mellitus, dyslipidemia,[15] myocardial infarction, stroke,[21] liver disease, cancer, chronic obstructive pulmonary disease,[22] asthma,[23] end-stage renal disease (ESRD) with dialysis,[16] and immunocompromised status including autoimmune disease and HIV infection.[24] The definition of each comorbidity is presented in Table S1. The Charlson comorbidity index, which is the most widely used for a measuring total comorbidity burden,[25] was also used as a covariate and classified as 0, 1, and ≥2.

Statistical Analysis

Baseline characteristics of groups were presented as mean with SD for continuous variables and number with percentage (%) for categorical variables. Comparisons between case and control groups were performed using Student *t* test for continuous variables and χ^2 test or Fisher exact test for categorical variables. After matching, the odds ratio (OR) and 95% CI were calculated using conditional logistic regression analysis. The multivariable-adjusted conditional logistic regression analysis was adjusted for the presence of diabetes mellitus, dyslipidemia, myocardial infarction, stroke, liver disease, cancer, chronic obstructive pulmonary disease, asthma, ESRD with dialysis, immunocompromised status, and Charlson comorbidity index in the outcome of infection and long-term hospitalization. Because of the small number of participants in the evaluation of the outcomes of ICU admission, high-flow oxygen therapy, and death, a logistic regression model was adjusted for presence of ESRD with dialysis and Charlson comorbidity index.[26] To evaluate risk stratification, a subgroup analysis of COVID-19 infection according to age and region was performed. In the subgroup analysis, age was divided into 2 groups with an age threshold of 65 years, which was defined as the high-risk group for severe COVID-19 infection by the Centers for Disease Control and Prevention. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC). A $P<0.05$ was considered statistically significant.

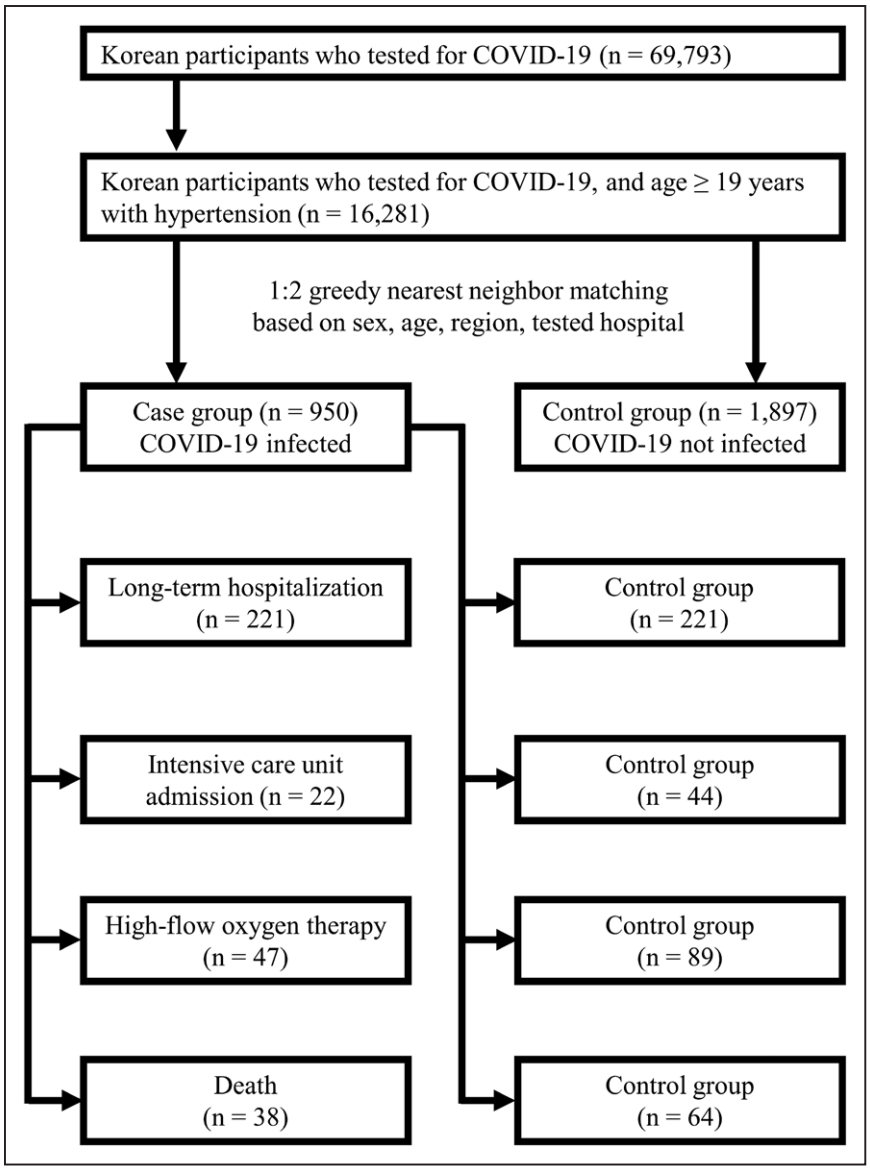

Figure. Flow of study participants. COVID-19 indicates coronavirus disease 2019.

Results

Baseline Characteristics

Before matching, the control and case groups consisted of 15 331 and 950 subjects, respectively, and the proportions of exposure to RAAS inhibitors and ARBs were significantly higher in the case group. The baseline characteristics before matching are shown in Table S2. After matching, a total of 2847 subjects were enrolled and analyzed. The mean age was 64.0 years, and 1449 (50.9%) subjects were male. The baseline characteristics of the case and control groups are presented in Table 1. There were no significant differences in sex, age, region, and tested hospital between the 2 groups. The proportions of diabetes mellitus, dyslipidemia, myocardial infarction, stroke, liver disease, chronic obstructive pulmonary disease, immunocompromised status, and Charlson comorbidity index were not significantly different, but those of cancer, asthma, and ESRD with dialysis were significantly different between both groups. The proportion of exposure to RAAS inhibitors was 77.5% in the case group and 74.4% in the control group (P=0.0707). In the 4 severity indices, there was no significant difference in death (P=0.8436), but the proportions of long-term hospitalization, ICU admission, and high-flow oxygen therapy were significantly higher in the case group (P<0.0001). Baseline characteristics of the case and control groups for the four severity indices are shown in Tables S3 through S6. There were no significant differences in the exposure to RAAS inhibitors between the case and control groups for all severity indices.

Association Between Exposure to RAAS Inhibitors and Risk and Severity of COVID-19 Infection

Table 2 shows the results of the logistic regression analysis for COVID-19 infection and its severity indices in accordance with exposure to RAAS inhibitors. The adjusted OR (95% CI) for COVID-19 infection comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors was 1.161 (0.958–1.407). When comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors based on long-term hospitalization and ICU admission, the adjusted ORs (95% CI) were 0.863

Table 1. Baseline Characteristics of Subjects With Hypertension According to COVID-19 Infection

Total (n=2847)	Control (n=1897)	Case (n=950)	*P* Value
Sex (male), %	966 (50.9)	483 (50.8)	0.9677
Age, y, mean (SD)	64.1 (14.2)	64.0 (14.3)	0.8597
Age over 65 y, %	948 (50.0)	474 (49.9)	0.9683
Age under 65 y, %	949 (50.0)	476 (50.1)	
Region of diagnosis			
Daegu and Gyeongbuk, %	697 (36.7)	350 (36.8)	0.9584
Etc, %	1200 (63.3)	600 (63.2)	
Tested hospital			
Third, %	701 (36.9)	352 (37.0)	0.9586
Etc, %	1196 (63.1)	598 (63.0)	
Comorbidities			
Diabetes mellitus, %	675 (35.6)	322 (33.9)	0.3734
Dyslipidemia, %	417 (22.0)	215 (22.6)	0.6942
MI and stroke, %	663 (35.0)	311 (32.7)	0.2405
Liver disease, %	1272 (67.1)	626 (65.9)	0.5364
Cancer, %	346 (18.2)	142 (15.0)	0.0280
COPD, %	715 (37.7)	352 (37.1)	0.7400
Asthma, %	795 (41.9)	355 (37.4)	0.0199
ESRD with dialysis, %	148 (7.8)	154 (16.2)	<0.0001
Immunocompromised status, %	283 (14.9)	121 (12.7)	0.1158
Charlson comorbidity index			
0, %	196 (10.3)	91 (9.6)	0.4361
1, %	277 (14.6)	155 (16.3)	
≥2, %	1424 (75.1)	704 (74.1)	
Exposure to RAAS inhibitors			
RAAS inhibitors, %	1411 (74.4)	736 (77.5)	0.0707
ACE inhibitors, %	98 (5.2)	47 (5.0)	0.8024
ARBs, %	1346 (71.0)	702 (73.9)	0.0996
Outcomes			
Admission date, d, mean±SD	2.2±4.2	4.9±7.0	<0.0001
Long-term hospitalization, %	144 (7.6)	233 (24.5)	<0.0001
Intensive care unit admission, %	8 (0.4)	22 (2.3)	<0.0001
High-flow oxygen therapy, %	5 (0.3)	47 (5.0)	<0.0001
Death, %	73 (3.9)	38 (4.0)	0.8436

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; MI, myocardial infarction; and RAAS, renin-angiotensin-aldosterone system.

(0.533–1.397) and 1.515 (0.402–5.701), respectively. When comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors based on high-flow oxygen therapy and death, the adjusted ORs (95% CIs) were 0.663 (0.272–1.619) and 1.363 (0.513–3.662), respectively. In all analyses, *P* values were not significant (*P*>0.05). In the additional analyses incorporating at least one claim within 6 months and 3 months for exposure to RAAS inhibitors, the crude ORs (95% CIs) for COVID-19 infection between exposure to RAAS inhibitors and nonexposure to RAAS inhibitors were 1.222 (1.010–1.477) and 1.028 (0.649–1.627), respectively. However, after multivariable adjustment, the ORs (95% CIs) were adjusted to 1.180 (0.971–1.434) and 1.299 (0.974–1.733), respectively. Most analyses did not show significant differences with *P*>0.05 (Table S7).

Subgroup Analysis of COVID-19 Infection Based on Exposure to RAAS Inhibitors

To evaluate risk stratification, subgroup analyses on age and region were performed in the same manner as mentioned above (Table 3). All analyses did not show significant differences,

Table 2. OR and 95% CI for Outcome of COVID-19 According to Exposure to RAAS Inhibitors

Outcomes	Control Group, %	Case Group, %	Crude OR (95% CI)	*P* Value	Adjusted OR* (95% CI)	*P* Value
Infection	1897 (100)	950 (100)				
Nonexposure to RAAS inhibitors	486 (25.6)	214 (22.5)	1.000		1.000	
Exposure to RAAS inhibitors	1411 (74.4)	736 (77.5)	1.188 (0.986–1.433)	0.0702	1.161 (0.958–1.407)	0.1277
Exposure to ACE inhibitors	98 (5.2)	47 (5.0)	0.956 (0.667–1.371)	0.8077	0.927 (0.639–1.344)	0.6878
Exposure to ARBs	1346 (71.0)	702 (73.9)	1.161 (0.972–1.387)	0.1005	1.140 (0.950–1.369)	0.1587
Long-term hospitalization	221 (100)	221 (100)				
Nonexposure to RAAS inhibitors	43 (19.5)	52 (23.5)	1.000		1.000	
Exposure to RAAS inhibitors	178 (80.5)	169 (76.5)	0.785 (0.498–1.238)	0.2979	0.863 (0.533–1.397)	0.5489
Exposure to ACE inhibitors	11 (5.0)	4 (1.8)	0.352 (0.110–1.123)	0.0776	0.640 (0.175–2.334)	0.4987
Exposure to ARBs	171 (77.4)	166 (75.1)	0.883 (0.569–1.368)	0.5766	0.906 (0.567–1.448)	0.6795
Intensive care unit admission	44 (100)	22 (100)				
Nonexposure to RAAS inhibitors	11 (25.0)	4 (18.2)	1.000		1.000	
Exposure to RAAS inhibitors	33 (75.0)	18 (81.8)	1.500 (0.417–5.397)	0.5349	1.515 (0.402–5.701)	0.5392
Exposure to ACE inhibitors	1 (2.3)	2 (4.6)	2.048 (0.122–34.368)	0.6185	2.235 (0.132–37.884)	0.5775
Exposure to ARBs	32 (72.7)	18 (81.8)	1.687 (0.474–6.010)	0.4197	1.703 (0.459–6.324)	0.4265
High-flow oxygen therapy	89 (100)	47 (100)				
Nonexposure to RAAS inhibitors	16 (18.0)	11 (23.4)	1.000		1.000	
Exposure to RAAS inhibitors	73 (82.0)	36 (76.6)	0.717 (0.302–1.704)	0.4517	0.663 (0.272–1.619)	0.3675
Exposure to ACE inhibitors	10 (11.2)	2 (4.3)	0.351 (0.074–1.674)	0.1890	0.358 (0.074–1.734)	0.2020
Exposure to ARBs	66 (74.2)	35 (74.5)	1.016 (0.452–2.283)		0.972 (0.424–2.226)	0.9464
Death	64 (100)	38 (100)				
Nonexposure to RAAS inhibitors	17 (26.6)	8 (21.0)	1.000		1.000	
Exposure to RAAS inhibitors	47 (73.4)	30 (79.0)	1.356 (0.521–3.532)	0.5325	1.363 (0.513–3.662)	0.5342
Exposure to ACE inhibitors	6 (9.4)	1 (2.6)	0.261 (0.030–2.258)	0.2226	0.260 (0.030–2.247)	0.2206
Exposure to ARBs	41 (64.1)	30 (79.0)	2.104 (0.828–5.343)	0.1179	2.132 (0.829–5.485)	0.1163

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COVID-19, coronavirus disease 2019; OR, odds ratio; and RAAS, renin-angiotensin-aldosterone system.

*Adjusted for diabetes mellitus, dyslipidemia, myocardial infarction, stroke, liver disease, cancer, chronic obstructive pulmonary disease, asthma, end-stage renal disease with dialysis, immunocompromised status, and Charlson comorbidity index in outcome of infection and long-term hospitalization; adjusted for end-stage renal disease with dialysis and Charlson comorbidity index in outcome of intensive care unit admission, high-flow oxygen therapy, and death.

with $P>0.05$. Regardless of age and region, COVID-19 infection was not associated with exposure to RAAS inhibitors.

Discussion

Among the 2847 subjects with hypertension tested for COVID-19, after matching for major confounders, such as sex, age, region, and tested hospital, our case-control analysis showed similar baseline characteristics between the case and control groups, with no significant difference in the risk and severity of COVID-19 infection regarding the exposure to RAAS inhibitors. Subgroup analyses of RAAS inhibitors and other drugs based on age and region also showed no significant difference between groups. Taken together, our study shows no evidence of significant associations between exposure to RAAS inhibitors and risk and severity of COVID-19 infection.

To date, several studies have taken similar measures in approaching the subject of debate. A case-control study from Italy by Mancia et al[11] analyzed a total of 6272 patients matched to 30 759 controls according to sex, age, and municipality of residence. Although their initial comparison between case and control groups showed worse clinical profile and increased use of RAAS inhibitors in the case group, after adjusting for covariates, subsequent analyses showed no evidence of an independent relationship between RAAS inhibitors and susceptibility to COVID-19. Our study included patients with hypertension as the primary subject of investigation, and our matched analysis showed similar baseline characteristics between the case and control groups. Therefore, similar implications could be elicited from both studies. However, few variables, including cancer (18.2% versus 15.0%; $P=0.0280$), asthma (41.9% versus 37.4%; $P=0.0199$), and ESRD with dialysis (7.8% versus 16.2%, $P<0.0001$), were shown to have statistically significant differences between the case and control groups; thus, multivariable logistic regression was performed. The results, as shown in Table 2,

Table 3. Subgroup Analysis for Infection of COVID-19 According to Exposure to RAAS Inhibitors

Subgroup	Control Group, %	Case Group, %	Crude OR (95% CI)	*P* Value	Adjusted OR* (95% CI)	*P* Value
Age over 65 y	948 (100)	474 (100)				
Nonexposure to RAAS inhibitors	267 (28.2)	124 (26.2)	1.000		1.000	
Exposure to RAAS inhibitors	681 (71.8)	350 (73.8)	1.113 (0.862–1.438)	0.4120	1.122 (0.862–1.460)	0.3937
Exposure to ACE inhibitors	60 (6.3)	27 (5.7)	0.894 (0.560–1.427)	0.6396	0.899 (0.558–1.449)	0.6631
Exposure to ARBs	636 (67.1)	331 (69.8)	1.142 (0.895–1.457)	0.2863	1.154 (0.899–1.482)	0.2602
Age under 65 y	949 (100)	476 (100)				
Nonexposure to RAAS inhibitors	219 (23.1)	90 (18.9)	1.000		1.000	
Exposure to RAAS inhibitors	730 (76.9)	386 (81.1)	1.279 (0.973–1.682)	0.0781	1.179 (0.885–1.569)	0.2603
Exposure to ACE inhibitors	38 (4.0)	20 (4.2)	1.058 (0.600–1.865)	0.8460	1.044 (0.566–1.923)	0.8912
Exposure to ARBs	710 (74.8)	371 (77.9)	1.183 (0.911–1.536)	0.2065	1.082 (0.822–1.425)	0.5729
Daegu and Gyeongbuk	697 (100)	350 (100)				
Nonexposure to RAAS inhibitors	178 (25.5)	78 (22.3)	1.000		1.000	
Exposure to RAAS inhibitors	519 (74.5)	272 (77.7)	1.202 (0.879–1.646)	0.2494	1.030 (0.725–1.465)	0.8677
Exposure to ACE inhibitors	53 (7.6)	29 (8.3)	1.105 (0.686–1.782)	0.6812	0.899 (0.523–1.544)	0.6986
Exposure to ARBs	482 (69.2)	251 (71.7)	1.127 (0.846–1.501)	0.4125	1.070 (0.776–1.476)	0.6779
Etc	1200 (100)	600 (100)				
Nonexposure to RAAS inhibitors	308 (25.7)	136 (22.7)	1.000		1.000	
Exposure to RAAS inhibitors	892 (74.3)	464 (77.3)	1.181 (0.936–1.490)	0.1615	1.253 (0.986–1.593)	0.0647
Exposure to ACE inhibitors	45 (3.8)	18 (3.0)	0.794 (0.456–1.384)	0.4162	0.835 (0.475–1.470)	0.5326
Exposure to ARBs	864 (72.0)	451 (75.2)	1.182 (0.942–1.484)	0.1483	1.252 (0.990–1.584)	0.0601

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COVID-19, coronavirus disease 2019; OR, odds ratio; and RAAS, renin-angiotensin-aldosterone system.

*Adjusted for diabetes mellitus, dyslipidemia, myocardial infarction, stroke, liver disease, cancer, chronic obstructive pulmonary disease, asthma, end-stage renal disease with dialysis, immunocompromised status, and Charlson comorbidity index.

demonstrate no significant association between the exposure to RAAS inhibitors and risk and severity of COVID-19 infection. Such observations are in line with recent findings reported by United States and Chinese investigators.[12,27]

In an observational analysis based in New York City with a cohort of 12 594 patients tested for COVID-19, no adverse effects of the use of RAAS inhibitors on the likelihood of a positive test for COVID-19 and its severity could be identified.[27] A Chinese single-center study on 1178 hospitalized patients with confirmed COVID-19 infection have demonstrated no difference in the percentage of patients using RAAS inhibitors between severe and nonsevere infections and between survivors and nonsurvivors, rejecting the theorized association between either severity or mortality of COVID-19 infection in patients using RAAS inhibitors.[12]

Worth noting are the results from previous analyses, including the aforementioned Chinese study, which demonstrated increased mortality and severity of COVID-19 infection in patients with hypertension compared with those without.[12,28,29] Considering the overall mortality rate of 2.3% in patients with COVID-19 in South Korea, the mortality rate of 4.0% in the hypertensive group of this study implies concordance in regard to the previous analyses.[13] However, in the control group, the mortality rate of patients with hypertension without confirmed COVID-19 infection was not significantly different from that of the case group (3.9% versus 4.0%; *P*=0.8436). Few explanations could be provided regarding the relatively high mortality rates in the control group, granted that they were not infected by severe acute respiratory syndrome coronavirus-2. The first explanation would be that because all subjects were candidates for COVID-19 testing, which indicates that they had symptoms such as fever, cough, sputum, active upper respiratory infection or diseases, such as pneumonia, might have led to an increase in their mortality rate, which could be considered as a potent bias. However, speculation on the secondary casualties inflicted by the COVID-19 pandemic is also possible, which suggests that fulminant concentration of healthcare resources for the control of COVID-19 pandemic might have led to relatively poor recognition and failure to determine problems on the peripheries of COVID-19, leading to increased mortality rate of patients without COVID-19 infection.[30] Regarding the allegations from the international media that a certain proportion of mortalities might have been due to infected-but-not-tested cases, aggressive testing policy applied by the South Korean government mitigates the indictment.[31] Another bias in action might be the overall delay and, therefore, underestimation of mortality cases. Considering the increasing mortality rate from 0.9% on March 15 to 2.3% as of May 6, a lead-time bias may be in effect by overlooking the fatal cases that are yet to be concluded.[32] Further investigations regarding the consequences of

the COVID-19 pandemic should be conducted to validate these embryonic hypotheses.

Our subgroup analysis was performed to investigate the possible effects of age and region on the results of this study, regarding the clustered characteristics of the outbreak in South Korea and abrupt increase in mortality rate in those aged ≥60 years in the general South Korean population. Considering the definition of patients with a high risk of COVID-19 infection by the Centers for Disease Control and Prevention, which uses the age threshold of 65 years, we performed our analysis accordingly. After adjusting for multiple covariates, no evidence of association between COVID-19 infection and exposure to RAAS inhibitor could be identified in the 2 subgroups. Thus, even after considering the major confounding factors, our analysis presents a coherent conclusion.

There were notable limitations in this study. First, because data from the national health insurance claims were used, there could be possible discrepancies between the actual therapeutic practices and insurance claim itself. However, for the validation of our study, we used widely accepted definitions of clinical outcomes and covariates from many previously performed studies.[15,16,18,21–24] In addition, because the diagnosis of COVID-19 and hypertension and prescription of drugs, such as antihypertensive drugs, outside the domain of the national health insurance system in South Korea is extremely rare, results are not likely to be confounded. Second, although optimal adjustments were attempted for the diverse confounding factors, possibility of unaccounted factors remains. Especially, according to the Centers for Disease Control and Prevention, body mass index above 40 is considered as high risk along with the current smoking status.[33] Our dataset did not include factors such as body mass index or smoking status to employ as confounder factors in our analysis. In addition, a weak point in our study is that most cases were exposed to ARBs, whereas the proportion of those exposed to ACE inhibitors was small. According to the Korean fact sheet published by the Korean Society of Hypertension, the majority of hypertension treatment consists of calcium channel blockers and ARBs, whereas the use of ACE inhibitors in monotherapy only accounts for 1.9%.[34] Thus, our study reflects such weakness regarding the preference for antihypertensive medication in South Korea. Lastly, despite implementing multiple variables and applying advanced statistical methods, such as propensity score matching to reduce the effect of confounders, we cannot eliminate the biases from residual confounding by physicians' treatment decisions and unmeasurable factors, which is an inherent limitation for observational studies. This limitation restricts the implication of this study only to the extent of association between the 2 compared matters, not to date as to the cause-and-effect relationship.

Perspectives

The strength of this study lies in the large number of case subjects and the thoroughly matched, sizable control group. Without the extensive background of data, reliable interpretation of collected data would have been arduous. Therefore, the present study demonstrates the absence of an identifiable association between the use of RAAS inhibitors and risk and severity of COVID-19 infection, supporting the current medical guidelines and recommendations that patients should not discontinue RAAS inhibitors out of a concern that they are at increased risk or severity of COVID-19 infection.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This case-control study demonstrates no identifiable association between exposure to renin-angiotensin-aldosterone system inhibitors and risk and severity of coronavirus disease 2019 (COVID-19) infection in South Korea, regardless of age and region.

What Is Relevant?

- Considering that severe acute respiratory syndrome coronavirus 2 is known to infect host cells via membrane-bound angiotensin-converting enzyme 2 in the respiratory epithelium, renin-angiotensin-aldosterone system inhibitors may affect the risk and severity of COVID-19 infection.

Summary

Our study demonstrates the absence of an identifiable association between exposure to renin-angiotensin-aldosterone system inhibitors and COVID-19 infection in South Korea, supporting the current recommendations against discontinuation of antihypertensive drugs.