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Use of Renin-Angiotensin-Aldosterone System Inhibitors and Severe COVID-19 Outcomes in Patients with Hypertension: A Nationwide Cohort Study

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Background: Angiotensin-converting enzyme 2 facilitates the entry of severe acute respiratory syndrome coronavirus 2 into the human body. We investigated the association of renin-angiotensin-aldosterone system (RAAS) inhibitor use with severe coronavirus disease 2019 (COVID-19) outcomes in hypertensive patients.
Methods: We identified hypertensive patients with confirmed COVID-19 from the Korean Health Insurance Review and Assessment Service from inception to May 15, 2020. The primary outcome was the composite of intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and death from COVID-19. The individual components were evaluated as secondary outcomes.
Results: Of 1,374 hypertensive patients with COVID-19, 1,076 (78.3%) and 298 (21.7%) were users and never-users of RAAS inhibitors, respectively. The RAAS inhibitor users were not associated with the risk of the primary outcome (adjusted odds ratio [aOR], 0.72; 95% confidence interval [CI], 0.46 to 1.10). The risk of ICU admission was significantly lower in the users than the never-users (aOR, 0.44; 95% CI, 0.24 to 0.84). The RAAS inhibitors were beneficial only in ICU admissions that did not require IMV (aOR, 0.28; 95% CI, 0.14 to 0.58). The risk of death from COVID-19 was comparable between the groups (aOR, 1.09; 95% CI, 0.64 to 1.85). We could not evaluate the risks of CRRT and ECMO owing to the small number of events.
Conclusion: RAAS inhibitor use was not associated with the composite of severe outcomes in the hypertensive patients with COVID-19 but significantly lowered the risk of ICU admission, particularly in patients who did not require IMV.

Keywords: Angiotensin-converting enzyme inhibitors; Angiotensin receptor antagonists; COVID-19; Hypertension; Renin-angiotensin system; Respiration, artificial

INTRODUCTION

The global pandemic of coronavirus disease 2019 (COVID-19) that began in late 2019 still threatens the health of people worldwide, causing 1,444,596 deaths by November 29, 2020 [1,2]. Hence identifying the risk factors for severe clinical outcomes of COVID-19, which include acute respiratory distress syndrome (ARDS) and death, is one of the most important issues.

However, many areas of uncertainty remain to be clarified, including the effect of renin-angiotensin-aldosterone system (RAAS) inhibitors. Several studies have been conducted on the

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hypothesis that the use of RAAS inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), affects COVID-19 susceptibility and clinical outcomes because it may alter the expression of angiotensin-converting enzyme 2 (ACE2) at the cell surface, which is known as the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3,4]. Epidemiological studies have reported inconsistent results about the use of RAAS inhibitors being harmful [5], neutral [6,7], and beneficial [8,9] to SARS-CoV-2 infection or clinical outcomes of COVID-19. This warranted the review of the existing evidence and hypothesis. ACE2 upregulation may increase the viral load via an increase in the cellular entry of SARS-CoV-2 [10]. By contrast, it may exert beneficial effects, especially on the cardiovascular and renal system via counterregulatory actions on the RAAS [11]. Meanwhile, experimental studies indicated that the effects of RAAS inhibitors on the ACE2 expression may vary according to classes or individual properties of the drugs and the tissues in which it is expressed [12,13]. These findings imply that RAAS inhibitors might have complex or mixed effects in patients with COVID-19.

Therefore, a more precise approach is needed to refine the COVID-19 outcomes related to the use of RAAS inhibitors. In this regard, we investigated the effects of RAAS inhibitors on severe outcomes of COVID-19, including respiratory failure and hemodynamic derangement, in patients with hypertension on the basis of the Korean national registry data.

METHODS

The Health Insurance Review and Assessment Service (HIRA) of South Korea is a repository of claims data generated for reimbursing providers [14]. Under the universal coverage system based on the fee-for-service payment system in Korea, HIRA data contains comprehensive information, including examinations, prescriptions, procedures, and surgeries, and covers 98% of the Korean population [14]. As the COVID-19 pandemic continues to spread, the Korean government decided to share the de-identified nationwide COVID-19 patient data with domestic and international researchers [15]. After their initial release, the data were updated with claims submitted to the HIRA by May 15, 2020 [16]. The updated data consisted of COVID-19-related items (classification, real-time polymerase chain reaction, disease, and fee codes) and information on prior use of healthcare services (Supplementary Table 1). Owing to the increased number of patients, the duration of healthcare service use history was reduced from 5 to 3 years. As the Korea Centers for Disease Control and Prevention data of confirmed cases were connected to the HIRA claims data, COVID-19 confirmation and death codes were also added. Ultimately, the claim statements of 7,590 patients among 11,018 confirmed cases were included [16].

Study population

We identified patients with prior hypertension who had confirmed COVID-19. Hypertension was defined as the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes I10, I15, O10, and O13–O16 and at least one claim in 6 months for the prescription of antihypertensive agents (identified using the Anatomical Therapeutic Chemical code). A confirmed COVID-19 case was defined as a person with laboratory-confirmed SARS-CoV-2 infection on the basis of the diagnostic testing criteria, regardless of clinical manifestations [17]. Real-time reverse transcription polymerase chain reaction tests were performed on nasopharyngeal/oropharyngeal swab or sputum samples [17]. The index date was defined as the day of diagnosis of COVID-19. All the study participants were followed up until their death or the end of the study, on May 15, 2020.

Use of RAAS inhibitors

The exposure of interest was the use of RAAS inhibitors, including ARBs and ACEIs. RAAS inhibitor users were defined as individuals with at least one prescription of ARBs or ACEIs within 6 months before the index date. RAAS inhibitor ex-users were defined as individuals who had received ARBs or ACEIs between 3 years and 6 months but not within 6 months before the index date. RAAS inhibitor never-users were defined as individuals who had never received ARBs or ACEIs within 3 years before the index date. We included both RAAS inhibitor users and never-users in the analysis.

Study outcomes

The primary outcome was defined as the composite of intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and death from COVID-19 (Supplementary Table 2). Each of the individual components was used as secondary outcomes.

Statistical analysis

The patients' characteristics and the number of events are presented as the mean±standard deviation or number (%). We performed unadjusted and adjusted (multivariable) logistic regression analyses to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for the study outcomes. For the multivariable model, the covariates of age; sex; comorbidities, including diabetes mellitus (DM), hyperlipidemia, cardiovascular disease (CVD), chronic kidney disease (CKD), chronic pulmonary disease; concomitant use of medications, including antihypertensive, glucose-lowering, lipid-lowering, and antithrombotic agents (Supplementary Table 3); and the Charlson Comorbidity Index (CCI) [18] were adjusted as confounders. Subgroup analyses were performed by age, sex, the presence of DM, hyperlipidemia, CVD, CKD, the treatment of DM, and the use of statins, antithrombotic agents, and inhaled corticosteroids. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with a two-sided test, and statistical significance was set at $\alpha=0.05$.

Ethical statement

The study protocol was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No. 2020-AN-0182). As all data were de-identified in a retrospective study, the study protocol was exempted from review and informed consent was waived.

RESULTS

Characteristics of the study participants

Of 7,590 patients with confirmed COVID-19, 1,374 with prior hypertension were included. Of the included patients, 1,076 (1,037 [96.4%] used ARBs and 39 [3.6%] used ACEIs) and 298 were RAAS inhibitor users and never-users, respectively. We excluded 17 patients who received both ARBs and ACEIs during the same period. A flow diagram of the patient selection is depicted in Fig. 1. The baseline characteristics of the study participants are shown in Table 1. Comorbidities, including DM (60.7% vs. 49.0%, $P<0.001$) and hyperlipidemia (54.0% vs. 39.6%, $P<0.001$), were more prevalent in the RAAS inhibitor users than in the never-users. Compared with the never-users, RAAS inhibitor users were more likely to have been taking antihypertensive agents (diuretics and β-blockers), glucose-lowering agents (metformin, sulfonylurea, and dipeptidyl peptidase-4 [DPP-4] inhibitors), and statins.

Severe outcomes of COVID-19

The primary composite outcome of ICU admission, IMV,

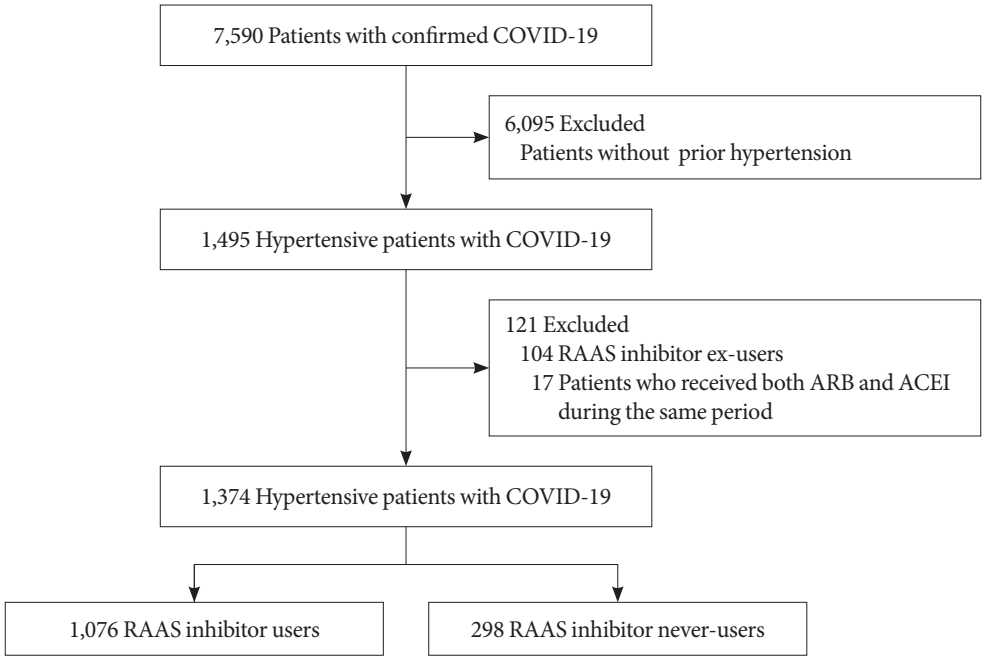

Fig. 1. A flow diagram of the patient selection. COVID-19, coronavirus disease 2019; RAAS, renin-angiotensin-aldosterone system; ARB, angiotensin-receptor blocker; ACEI, angiotensin-coverting enzyme inhibitor.

CRRT, ECMO, and death occurred in 144 patients. The RAAS inhibitor users were not associated with the risk of the composite outcome as compared with the never-users (adjusted OR [aOR], 0.72; 95% CI, 0.46 to 1.10). This finding was consistent across the ARB (aOR, 0.71; 95% CI, 0.46 to 1.10) and ACEI users (aOR, 0.81; 95% CI, 0.31 to 2.11) (Table 2).

ICU admission occurred in 52 patients. The RAAS inhibitor users were significantly associated with a lower risk of ICU admission as compared with the never-users (aOR, 0.44; 95% CI, 0.24 to 0.84). The result was attributed to the ARB users (aOR, 0.42; 95% CI, 0.22 to 0.81) rather than the ACEI users (aOR, 0.72; 95% CI, 0.21 to 2.48). The beneficial effect of RAAS inhibitors on ICU admission was observed in the patients who did not require IMV (aOR, 0.28; 95% CI, 0.14 to 0.58), but not in those who required IMV (aOR, 1.41; 95% CI, 0.39 to 5.08) (Table 2). The risk of death (n=106) was similar between the RAAS inhibitor users and never-users (aOR, 1.09; 95% CI, 0.64 to 1.85). The ORs of the other secondary outcomes, including CRRT (n=0) and ECMO (n=1), could not be calculated owing to the small number of events.

Table 1. Baseline characteristics of the study participants

Characteristic	Total (n=1,374)	RAAS inhibitor users (n=1,076)	RAAS inhibitor never-users (n=298)	P value
Age, yr	65.0±13.2	64.5±12.8	66.7±14.9	0.017
<65	727 (52.9)	599 (55.7)	128 (43.0)	
≥65	647 (47.1)	477 (44.3)	170 (57.0)	
Men	569 (41.4)	459 (42.7)	110 (36.9)	0.075
Comorbidities				
Diabetes mellitus	799 (58.2)	653 (60.7)	146 (49.0)	<0.001
Hyperlipidemia	699 (50.9)	581 (54.0)	118 (39.6)	<0.001
Cardiovascular disease[a]	594 (43.2)	454 (42.2)	140 (47.0)	0.140
Chronic kidney disease	55 (4.0)	46 (4.3)	9 (3.0)	0.328
Chronic pulmonary disease[b]	275 (20.0)	210 (19.5)	65 (21.8)	0.381
Charlson Comorbidity Index	2.00±1.57	2.01±1.56	1.95±1.58	0.813
Medications				
Diuretics	366 (26.6)	323 (30.0)	43 (14.4)	<0.001
Calcium channel blocker	705 (51.3)	539 (50.1)	166 (55.7)	0.086
β-Blocker	204 (14.9)	143 (13.3)	61 (20.5)	0.002
Metformin	326 (23.7)	279 (25.9)	47 (15.8)	<0.001
Sulfonylurea	140 (10.2)	123 (11.4)	17 (5.7)	0.004
Thiazolidinedione	35 (2.6)	29 (2.7)	6 (2.0)	0.509
DPP-4 inhibitor	199 (14.5)	174 (16.2)	25 (8.4)	0.001
SGLT2 inhibitor	31 (2.3)	28 (2.6)	3 (1.0)	0.101
GLP-1 receptor agonist	7 (0.5)	7 (0.7)	0	0.358
Insulin	26 (1.9)	23 (2.1)	3 (1.0)	0.205
Statin	654 (47.6)	542 (50.4)	112 (37.6)	<0.001
Antithrombotic agent	389 (28.3)	305 (28.4)	84 (28.2)	0.957
Inhaled corticosteroids	102 (7.4)	77 (7.2)	25 (8.4)	0.472

Values are presented as mean±standard deviation or number (%).
RAAS, renin-angiotensin-aldosterone system; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide-1.
[a]Cardiovascular disease includes ischemic heart disease, cerebral infarction, heart failure, cardiomyopathy, and arrhythmia, [b]Chronic pulmonary disease includes chronic obstructive pulmonary disease and asthma.

Table 2. Clinical outcomes of the hypertensive patients with coronavirus disease 2019 according to the use of RAAS inhibitors

Outcomes (vs. RAAS inhibitor never-users)	RAAS inhibitors (n=1,076)			ARB (n=1,037)			ACEI (n=39)		
	No. of events (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	No. of events (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	No. of events (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
Primary outcome[a] (n=144)	106 (9.9)	0.75 (0.50–1.11)	0.72 (0.46-1.10)	99 (9.6)	0.72 (0.49–1.08)	0.71 (0.46–1.10)	7 (18.0)	1.50 (0.62–3.63)	0.81 (0.31–2.11)
Secondary outcomes									
ICU admission (n=52)	34 (3.2)	0.51 (0.28–0.91)	0.44 (0.24–0.84)	30 (2.9)	0.46 (0.26–0.84)	0.42 (0.22–0.81)	4 (10.3)	1.78 (0.57–5.55)	0.72 (0.21–2.48)
Not requiring IMV (n=34)	21 (2.0)	0.35 (0.18–0.68)	0.28 (0.14–0.58)	19 (1.8)	0.33 (0.17–0.65)	0.28 (0.14–0.58)	2 (5.1)	0.96 (0.21–4.31)	0.31 (0.06–1.56)
Requiring IMV (n=17)	14 (1.3)	1.30 (0.37–4.54)	1.41 (0.39–5.08)	12 (1.2)	1.15 (0.32–4.11)	1.30 (0.36–4.76)	2 (5.1)	5.32 (0.86–32.86)	3.57 (0.52–24.71)
IMV (n=17)	14 (1.3)	1.30 (0.37–4.54)	1.41 (0.39–5.08)	12 (1.2)	1.15 (0.31–4.11)	1.30 (0.36–4.76)	2 (5.1)	5.32 (0.86–32.86)	3.57 (0.52–24.71)
CRRT (n=0)	0	NA	NA	0	NA	NA	0	NA	NA
ECMO (n=1)	1 (0.1)	NA	NA	1 (0.1)	NA	NA	0	NA	NA
Death (n=106)	82 (7.6)	0.94 (0.59–1.51)	1.09 (0.64–1.85)	79 (7.6)	0·94 (0.59–1.52)	1.12 (0.66–1.90)	3 (7.7)	0.95 (0.27–3.32)	0.62 (0.17–2.35)

RAAS, renin-angiotensin-aldosterone system; ARB, angiotensin-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; NA, not applicable; ECMO, extracorporeal membrane oxygenation.
[a]The primary outcome was defined as the composite of ICU admission, IMV, CRRT, ECMO, and death from coronavirus disease 2019, [b]Adjusted variables included age; sex; comorbidities, including diabetes mellitus, hyperlipidemia, cardiovascular disease, chronic kidney disease, and chronic pulmonary disease; medications, including antihypertensive, glucose-lowering, lipid-lowering, and antithrombotic agents; and the Charlson Comorbidity Index.

The subgroup analyses revealed that the absence of DM (aOR, 0.48; 95% CI, 0.23 to 0.99) and chronic pulmonary disease (aOR, 0.58; 95% CI, 0.37 to 0.91), the presence of hyperlipidemia (aOR, 0.50; 95% CI, 0.29 to 0.86), and the use of antithrombotic agents (aOR, 0.44; 95% CI, 0.25 to 0.77) were associated with a lower risk of the composite outcome (Supplementary Table 4).

Risk factors for the primary composite outcome and ICU admission

The multivariable analysis revealed that older age (as a continuous variable), male sex, DM, CVD, CKD, and increased CCI were associated with a higher risk of the composite outcome (Fig. 2A). Several factors, including male sex, prior CVD, and increased CCI, were also associated with a higher risk of ICU admission (Fig. 2B). On the contrary, the use of RAAS inhibitors and ARBs was associated with a lower risk of ICU admission. These findings were similar in the patients admitted to the ICU without IMV (Fig. 2C), but not in those with IMV (Fig. 2D).

DISCUSSION

In this study, we found that the use of RAAS inhibitors did not increase the risk of serious health outcomes in the hypertensive patients with COVID-19. In addition, the use of RAAS inhibitors was associated with some health benefits, including a 56% reduction in the risk of ICU admission, mostly resulted from ICU admissions not requiring IMV. This pattern was similarly observed for both ARBs and ACEIs, but statistically significant results were only observed for ARBs, not for ACEIs, which might be owing to the small number of patients and events.

Overall, the results of this study are in line with those of the existing large-scale epidemiological studies, which showed that the use of RAAS inhibitors was not harmful to COVID-19 susceptibility and outcomes [6,7,19]. The noteworthy finding in this study is that RAAS inhibitors may have different clinical effects depending on the affected organs and tissues. This is, in part, due to their different responses to altered expression of ACE2 by RAAS inhibitors or blockade per se.

ACE2 degrades angiotensin II to angiotensin-(1–7) and cleaves angiotensin I to angiotensin-(1–9), and thereby its primary action is the counterregulation of the RAAS [11]. Recent studies on the relationship between RAAS inhibitor use and the development or outcomes of COVID-19 were based on the

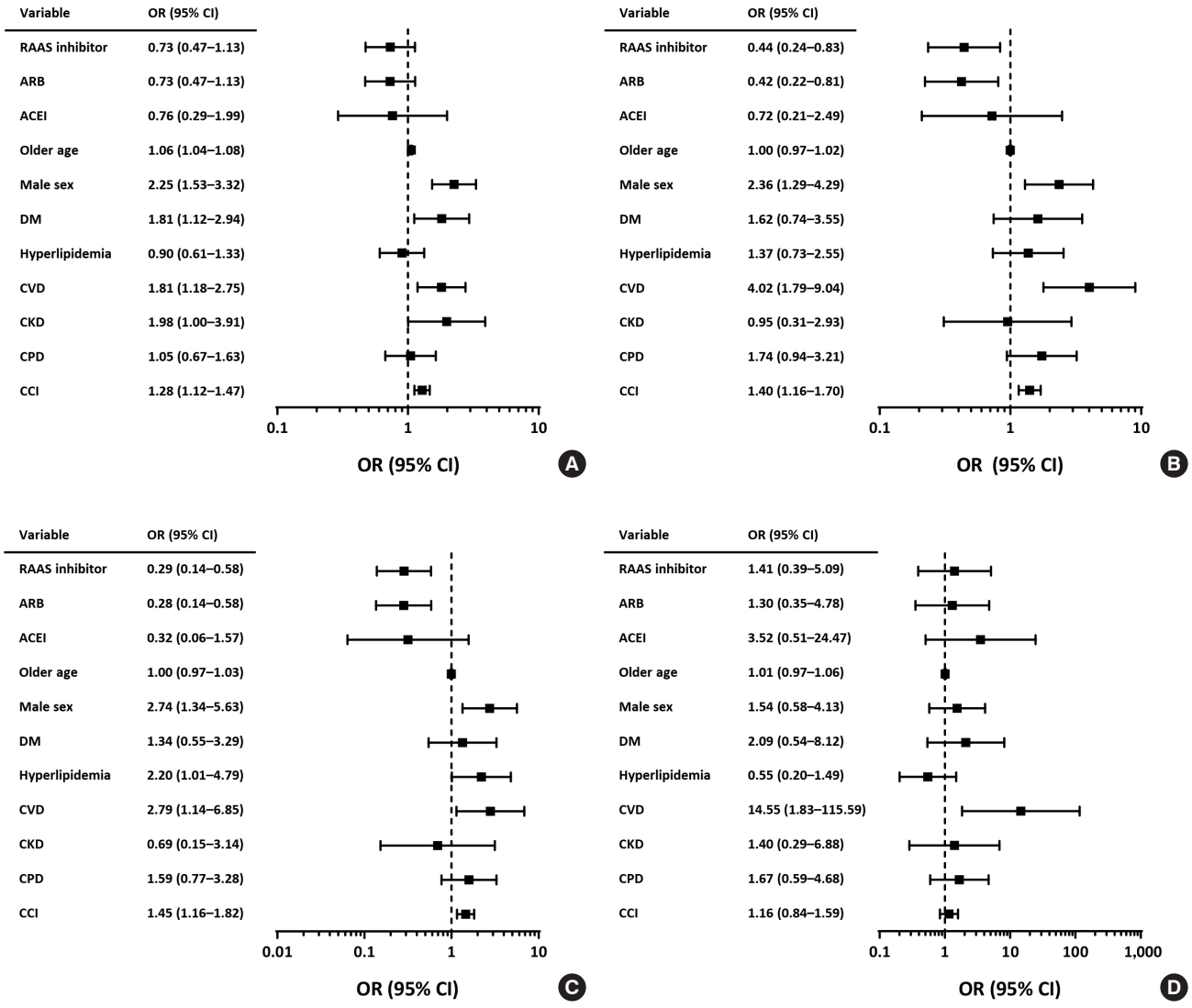

Fig. 2. Risk factors for the primary outcome and intensive care unit (ICU) admission. (A) Primary outcome. (B) ICU admission. (C) ICU admission not requiring invasive mechanical ventilation (IMV). (D) ICU admission requiring IMV. Age was regarded as a continuous variable. Separate analyses were performed to calculate odds ratio (ORs) of angiotensin-receptor blocker (ARB) and angiotensin-coverting enzyme inhibitor (ACEI). Values for ORs are plotted on a log scale. RAAS, renin-angiotensin-aldosterone system; CI, confidence interval; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease; CPD, chronic pulmonary disease; CCI, Charlson Comorbidity Index.

assumption that RAAS inhibitors would induce changes in ACE2 expression or activity. With a few exceptions [20,21], experimental studies generally supported the original assumption that RAAS inhibitor treatment induced an increase in ACE2 expression or activity [22,23]. The degree of this increase varied depending on the type of drugs and the tissues in which ACE2 was expressed. For example, losartan treatment significantly increased ACE2 activity in both heart and kidney tissues, but lisinopril treatment increased that only in kidney and not in heart tissue [12,13]. On the basis of these findings, we can speculate that changes in ACE2 and related clinical consequences would not be uniform depending on the diverse RAAS inhibitors and affected organs such as the lung, heart, or kidney.

Previous studies reported that hypertension and CVD were the major comorbidities and risk factors for COVID-19 [6,24,

25]. Similarly, in our study, CVD was identified as a significant risk factor for most outcomes. Evidence suggested that ACE2 downregulation by SARS-CoV-2 infection possibly contributed to the exacerbation of underlying CVD and even direct injury to cardiomyocytes in patients with COVID-19 [26,27]. In a previous autopsy study of severe acute respiratory syndrome coronavirus, myocardial damage was associated with the downregulation of myocardial ACE2 [28]. Thus, RAAS inhibitors, through the alteration of ACE2 activity or its own actions such as vasodilation, anti-inflammation, and anti-fibrosis, may have beneficial effects on the cardiovascular outcomes of COVID-19. In this regard, our study adds evidence of the possible benefits of RAAS inhibitors on COVID-19 outcomes. On the other hand, RAAS inhibitors had no beneficial effect on ICU admissions that required IMV. Failure to reduce the number of IMV cases, which is mainly related to severe lung injury, may be explained by the reduced benefits of RAAS inhibitors on ACE2 after acute lung injury. However, this is just a hypothesis and should be proved by further studies.

In our study, the use of metformin, DPP-4 inhibitors, and statins was higher in the RAAS users than the never-users in accordance with the prevalence of DM and hyperlipidemia. Several studies have reported that these medications are associated with clinical outcomes in patients with COVID-19. In retrospective cohort studies, metformin was significantly associated with lower inflammation in patients with type 2 diabetes mellitus (T2DM) [29] and reduced in-hospital mortality in women with T2DM and obesity [30]. In a case-control study [31] and a case series [32] from northern Italy, DPP-4 inhibitor treatment was associated with decreased mortality in patients hospitalized for COVID-19. On the other hand, in-hospital statin use was associated with a lower risk of mortality in Chinese patients with COVID-19 [33]. In this study, adding ACEIs or ARBs did not affect statin-associated outcome among patients with COVID-19 and hypertension [33]. Although these medications have anti-inflammatory and immunomodulatory effects [34-36], which might be beneficial for treating infectious diseases, there is little evidence supporting the protective or detrimental role in patients with COVID-19 [37]. In our study, RAAS inhibitor users were associated with a significantly lower risk of ICU admission in the hypertensive patients with COVID-19 after adjusting for confounders, including the use of metformin, DPP-4 inhibitors, and statins. Given the shortcomings and limitations of the retrospective nature of the study, well-designed, randomized controlled trials are required to elucidate its mechanism and potential interaction with other medications in patients with COVID-19.

This study has several limitations. First, because we approached the database retrospectively, detailed information on the in-hospital progress of the patients, including laboratory findings or imaging studies, could not be obtained. Therefore, we considered the use of IMV, CRRT, and ECMO as an indirect indicator of severe lung injury and hemodynamic derangement. Second, the dose and duration of RAAS inhibitors might affect the study outcomes. However, owing to the limitation on data availability, we could not evaluate their influence on the results. Third, information on the ACE2 expression or activity, which may have as a causal relationship between RAAS inhibitor use and COVID-19 outcomes, could not be obtained. Fourth, the number of patients who used ACEIs was insufficient. Therefore, we could not ascertain whether ACEIs have the same benefits for COVID-19 outcomes as ARBs.

This study demonstrated that the use of RAAS inhibitors did not increase serious health risks, including death, in the hypertensive patients with COVID-19. In addition, as inferred from the benefits for ICU admission without IMV, this study suggests that the use of RAAS inhibitors may exert different effects depending on the organ systems in COVID-19. The results of ongoing clinical trials of RAAS inhibitors in patients with COVID-19 may provide a clearer conclusion.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0279.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: J.H.B., J.L., S.G.K.
Acquisition, analysis, or interpretation of data: J.H.B., S.K.C., N.H.K., J.L., S.G.K.
Drafting the work or revising: J.H.B., S.K.C., N.H.K., J.L., S.G.K.
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