The Association of Withdrawing Maintenance Renin-Angiotensin System Inhibitor on All-Cause Mortality and Intensive Care Unit Admission Among Hypertensive Patients Admitted for Mild to Moderate COVID-19 infection: A Meta-analysis of Observational Studies

Arlene Melissa T. Dychiching, MD | Erwin D. Dizon, MD
Cardinal Santos Medical Center, San Juan, Metro Manila, Philippines

Correspondence:
Email: arlenedychiching@gmail.com; eddcardio@gmail.com

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Abstract

INTRODUCTION: The pandemic caused by coronavirus disease 2019 (COVID-19) posed a serious challenge to all health care systems in the world. It has been found to be harmful in people with underlying cardiovascular diseases, particularly in patients with systemic hypertension, which may be due to upregulation of angiotensin-converting enzyme 2 (ACE2) expression, which may lead to increased severe acute respiratory syndrome coronavirus 2 virulence. Renin-angiotensin system inhibitor (RASI) acts by blocking the angiotensin-converting enzyme and angiotensin II type 1 receptors, which in turn affects the production of the ACE2 protein. Hence, there have been arguments on whether to continue or discontinue this medication. Given the widespread use of RASIs globally and the fact that they are generally cardioprotective, research into the safety of continuing these maintenance medications in patients hospitalized with mild to moderate COVID-19 is immensely needed.

METHODS: This meta-analysis involved review of observational studies among hypertensive patients on maintenance ACE inhibitor or angiotensin-receptor blocker with confirmed mild to moderate COVID-19 infection. Analyses were performed to determine the adjusted hazard ratio of each event using the raw data obtained from each study. Random-effects model and Cochran-Mantel-Haenszel method were utilized at 95% confidence interval. To check for heterogeneity, χ^2 test and I^2 statistic were calculated. Cochrane ReviewManager (RevMan version 5.3) was used for data analysis, and forest plots were generated.

RESULTS: At 95% confidence interval, the adjusted hazard ratios for all-cause mortality and intensive care unit (ICU) admission at 95% confidence interval were 1.64 (1.22, 2.21) and 1.93 (1.34, 2.79), respectively. The tests of overall estimate effect for both outcomes were $P < 0.0001$ for all-cause mortality and $P = 0.0003$ for ICU admission.

CONCLUSION: Discontinuation of maintenance RASI during hospitalization is associated with increased all-cause mortality and ICU admission among hypertensive patients with mild to moderate COVID-19 infection.

KEYWORDS: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, coronavirus, COVID-19, renin-angiotensin system inhibitor

INTRODUCTION

The world experienced a severe pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused by coronavirus disease 2019 (COVID-19). It posed a serious challenge to all health care systems in the world. It has been found to be harmful in individuals with underlying cardiovascular diseases, particularly in patients with systemic hypertension.[1,2]

Hypertension has been widely recognized as an independent risk factor for severity and mortality in COVID-19 patients. This elevated morbidity and mortality risk may be due to the upregulation of angiotensin-converting enzyme 2 (ACE2) expression that may lead to the increased SARS-CoV-2 virulence. In physiological conditions, the ACE1–angiotensin II–AT1R (angiotensin II type 1 receptor) axis (the classic RAS) is counter-regulated by the ACE2–angiotensin (1–7)–MasR axis. Thus, when the latter weakens, angiotensin II is unopposed, and its vasoconstrictor, proinflammatory, and prothrombotic actions may contribute to the pathophysiology of COVID-19.[3–6] The mechanism for SARS-CoV-2 infection requires the binding of the virus to the ACE2 receptor.[2] Thus, upregulation of ACE2 results in greater ACE2 expression, increased SARS-CoV-2 binding sites, and subsequently increased risk of COVID-19 infection.[1]

Renin-angiotensin system inhibitor (RASI) is a class of antihypertensive drugs used to treat hypertension and cardiovascular disease, which acts by blocking the ACE and AT1 receptors.[8]

Recently, a contentious debate has centered on whether utilizing RASI medications would increase patient sensitivity to viral host cell entry and propagation because of their impact on the production of the ACE2 protein.[1,2] However, withdrawing these drugs may lead to adverse health risks because of the uncontrolled blood pressure and/or untreated cardiac dysfunction.[8] Animal models indicate that RASI can increase the expression of messenger RNA or protein levels of ACE2, increasing the risk of severity when such an infection occurs.[1] As a result, many practitioners took the precautionary measure of discontinuing these medicines from patients who were still taking them.[6] Several clinical trials have found that using RASI in COVID-19 individuals with hypertension did not worsen the severity of the condition or mortality. These investigations, however, have focused on RASI use during hospitalization among hypertensive patients not on maintenance RASI. Given the widespread use of RASIs globally and the fact that they are generally cardioprotective, research into the safety of continuing these maintenance medications in patients hospitalized with mild to moderate COVID-19 infection is immensely needed.[2]

This study summarized the result of available observational studies on the effect of discontinuation of maintenance ACE inhibitor (ACEI)/angiotensin-receptor blocker (ARB) on mortality and ICU admission of hypertensive patients admitted for mild to moderate COVID-19 infection. Furthermore, this study provides an analysis of existing data regarding the effects of discontinuation of maintenance RASI among hypertensive patients admitted for mild to moderate COVID-19 infection. To the best of our knowledge, this is the first meta-analysis to investigate the relationship between maintenance RASI withdrawal with all-cause mortality and ICU admission among hypertensive patients admitted for mild to moderate COVID-19 infection.

METHODOLOGY

Study Design

This meta-analysis involved a review of retrospective observational cohort studies among hypertensive patients maintained on RASI medications admitted for mild to moderate COVID-19 infection, with the primary outcome of all-cause mortality and the secondary outcome of ICU admission. The journals selected were limited to human clinical trials and were reviewed based on the inclusion criteria, study design, intervention, and outcomes. Each study was appraised by two independent investigators. Participants in both studies were randomized to discontinuation versus continuation group. The quality and risk of bias were assessed using the Newcastle-Ottawa Quality Assessment Scale. The coauthors assessed for the risk of bias separately.

Ethical Considerations

The protocol of this study adhered to the ethical considerations and principles in relevant guidelines, including the International Conference on Harmonization Good Clinical Practice, Data Privacy Act of 2012, and the National Ethics Guidelines for Health Research. Data were obtained from retrospective observational studies.

Data Collection

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used in this study. Comprehensive literature search of cohort studies was done. The databases utilized were PubMed, Science Direct, Cochrane, and Google Scholar. Relevant cardiology journals, conference proceedings, and clinical trial databases and reference lists of relevant articles including reviews were also hand-searched. No restrictions were made about age or sex. Retrospective observational cohort studies with combinations of the following keywords were used: "COVID-19," "coronavirus," "renin-angiotensin system," "RASI," "ARBs," "ACEI," "continuation," "discontinuation," "withdrawal." Duplicate articles were removed. During the full-text screening, only those with the following criteria were included in this study: (*a*) retrospective observational cohort studies; (*b*) patients hospitalized with mild to moderate COVID-19 infection, confirmed by at least one positive result for SARS-CoV-2 on real-time polymerase chain reaction testing of nasopharyngeal samples; and (*c*) who were diagnosed with hypertension and maintained on RASI medications. Studies that reported the inflammation marker blood tests for a mixed population of COVID-19 patients who were not separated into two distinct

groups (continuation and discontinuation of maintenance RAAS inhibitor medications) were excluded, as the results were not conclusive for the purpose of this study. Furthermore, studies with the following criteria were excluded: (*a*) with patients admitted with severe to critical COVID-19 infection, articles in reaction to a journal (ie, letter, editorial, opinion, commentary); (*b*) with patients in whom the continuation or discontinuation of RASI treatment could not be properly assessed at admission, including patients transferred to another hospital from the emergency department and patients who presented the outcome (death or admission to the ICU) or were discharged within the first 3 days of hospital admission; (*c*) with patients with history of solid organ transplant, those on chronic immunosuppressive medications, and patients without a disposition (death or discharged alive); (*d*) proposed prospective trials; (*e*) reviews of published papers; (*f*) abstracts; and (*g*) case reports.

The results of search and screening are summarized in Figure 1. The PRISMA flow diagram shows the details of the protocol. After removing the duplicates, 315 of 1310 studies were selected for full-text screening. Only four studies were eligible to be included in this review. The excluded studies included 105 with wrong population, 115 with ineligible outcomes, 39 with wrong intervention, 22 that were commentaries or editorials, 15 that were not accessible, 7 that were systematic reviews, 4 that were nonclinical studies, and 4 that were retracted studies. This systematic review included a total of four studies, all of which were retrospective cohort studies.

Measurement of Outcomes

The primary outcome was in-hospital mortality, and the secondary outcome was ICU admission.

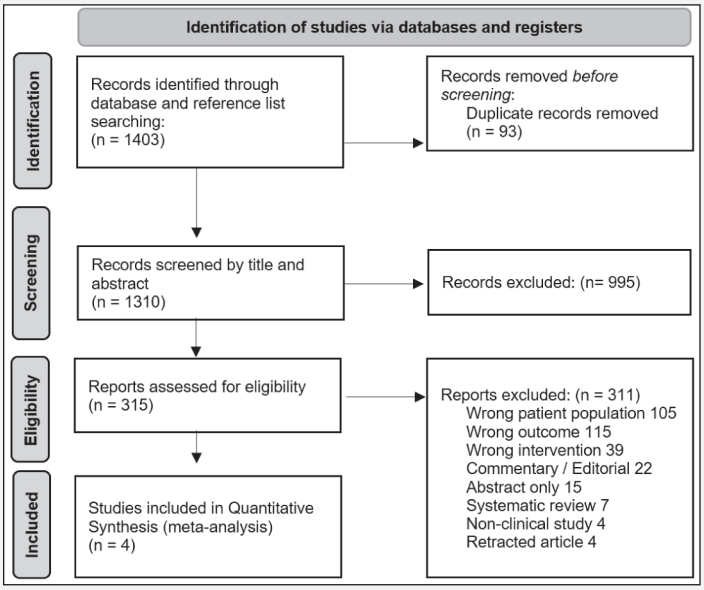

Figure 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Primary Outcome: All-Cause Mortality

Article	Discontinuation		Continuation	
	Events	Total	Events	Total
De Abajo et al,[6] 2021	94	340	79	285
Cannata et al,[3] 2020	44	157	3	56
Chaudhri et al,[4] 2020	9	31	5	49
Lam et al,[7] 2020	48	171	10	164

able 2. Secondary Outcome: ICU Admission

Article	Discontinuation		Continuation	
	Events	Total	Events	Total
De Abajo et al,[6] 2021	19	340	17	285
Cannata et al,[3] 2020	40	157	7	56
Chaudhri et al,[4] 2020	13	31	9	49
Lam et al,[7] 2020	45	171	20	164

ICU=intensive care unit.

Data Analysis

Data analysis was performed using ReviewManager (RevMan version 5.4). Forest plot was generated to describe the outcomes. Adjusted hazard ratios from dichotomous results from each study were computed at 95% confidence interval. Heterogeneity was determined using I^2, from which a value of more than 50% is considered significant. The mean difference for the clinical outcomes was determined. Summary statistics of $P < 0.05$ was considered statistically significant.

RESULTS

A total of four cohort studies were included in the study, with a total of 1253 hypertensive patients maintained on RASI (Appendix Table 1). The risk-of-bias assessments are shown in Appendix Table 2. The forest plots generated for both outcomes—mortality and ICU admission (Figures 2 and 3)—portrayed discontinuation of RASI produced an unfavorable outcome in terms of all-cause mortality and ICU admission among hypertensive patients admitted for mild to moderate COVID-19. At 95% confidence interval, the adjusted hazards ratio for all-cause mortality and ICU admission were 1.64 (1.22, 2.21) and 1.93 (1.34, 2.79), respectively, which supports increased likelihood of both outcomes with RASI withdrawal. The test of overall estimate effects for both outcomes were $P = 0.001$ for all-cause mortality and $P = 0.0004$ for ICU admission. Heterogeneity of sample populations in both outcomes was evaluated. Calculated I^2 values for all-cause mortality and ICU admission were 89% ($P < 0.00001$) and 55% ($P = 0.09$), respectively. Funnel plots (Figure 4) were also generated to look for publication bias.

DISCUSSION

The outcome of COVID-19 was assessed in most of the studies based on the all-cause mortality and ICU admission expressed

as percentages of patients in each category. Analysis for both the primary and secondary outcomes was done. Of the four studies included in this meta-analysis, three studies reported increased all-cause mortality and ICU admission between drug withdrawal and control group (Tables 2 and 3). The adjusted hazard ratios of RASI withdrawal and all-cause mortality and ICU admission were 1.64 (1.22, 2.21) and 1.93 (1.34, 2.79), respectively, at 95% confidence interval, indicating increased frequency of primary and secondary outcomes with RASI withdrawal. Multivariable analysis was done after adjusting for factors that would potentially contribute to the continuation and cessation of RASI medications in the hospitalized settings (ie, hyperkalemia, hypotension, acute kidney injury on admission) in each study included in this meta-analysis. Furthermore, the age, sex, and significantly different comorbidities between groups in each study were also included in logistic regression models as covariates for controlling confounding effects. All studies' conclusion remained true after controlling the confounders.

Funnel plot generated (Figure 4) showed asymmetry, which signified that the heterogeneity of sample populations on both outcomes was statistically significant. As in all observational studies, the possibility exists that there are some residual confounding factors. Substratification based on how long the patients were on these medications before they were discontinued was not also provided, as well as dosage, frequency, and duration. Moreover, the difference between ACEI and ARB use was not explored in this study. Although ACEIs and ARBs have similar mechanisms of action, their effects may need to be studied separately. The studies included

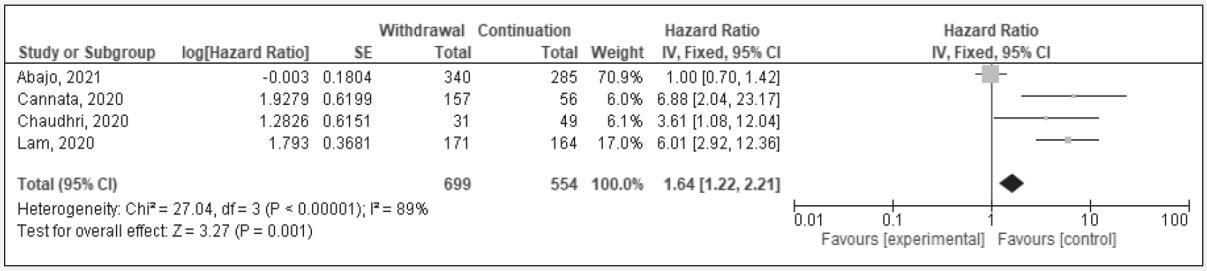

Figure 2. Adjusted hazard ratio of RASI discontinuation with all-cause mortality among hypertensive patients with confirmed COVID-19 infection.
CI=confidence interval; RASI=renin-angiotensin system inhibitor.

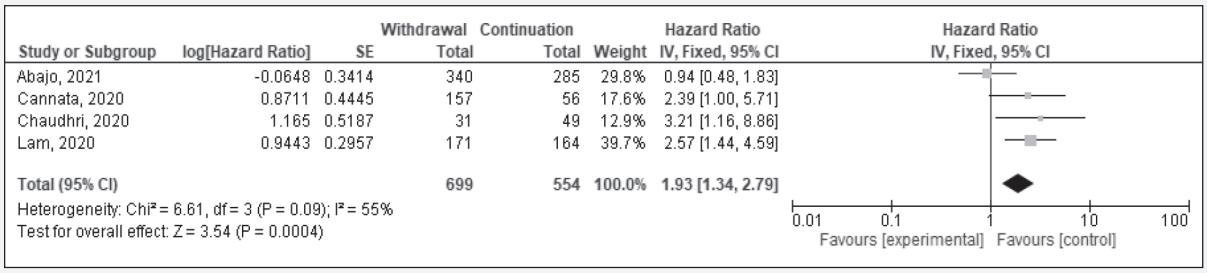

Figure 3. Adjusted hazard ratio of RASI discontinuation with ICU admission among hypertensive patients with confirmed COVID-19 infection.
CI=confidence interval; ICU=intensive care unit; RASI=renin-angiotensin system inhibitor.

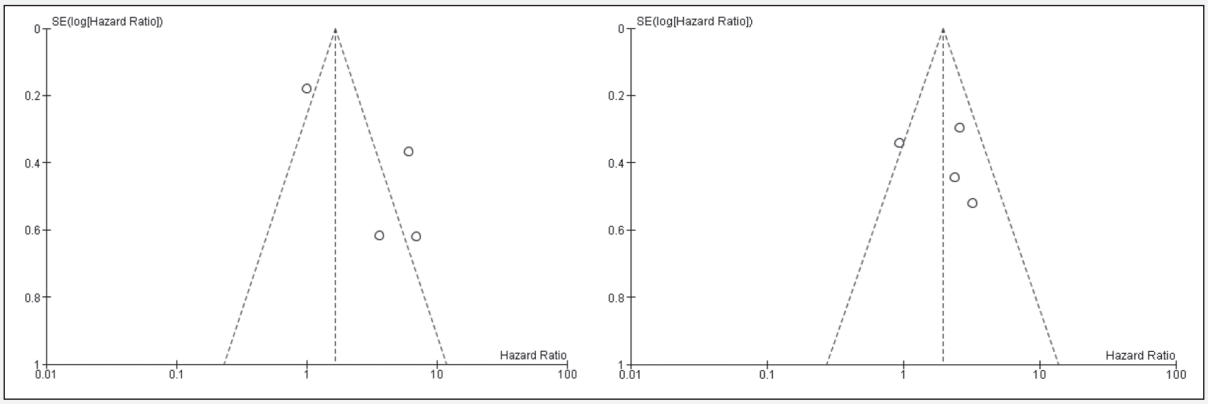

Figure 4. Funnel plots for adjusted hazard ratio of RASI use with (A) all-cause mortality and (B) ICU admission.
ICU=intensive care unit; RASI=renin-angiotensin system inhibitor.

in this meta-analysis did not account for when RASIs were discontinued for individual patients during their hospital stay.

CONCLUSION

Discontinuation of maintenance RASI was associated with a trend to an increased mortality risk and ICU admission as compared with their continuation. Therefore, it is the authors' recommendation to not discontinue maintenance RASI out of unfounded fear of increased susceptibility to infection. However, if patient developed acute renal failure or progressive renal failure due to factors other than COVID-19 (ie, hypovolemia, septic shock, etc) during the course of confinement, it is prudent to discontinue maintenance RASI.

RECOMMENDATIONS

The authors recommend further study of meta-analysis with a larger population size. Furthermore, the authors recommend substratifying the effects of ACEIs and ARBs.

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APPENDIX

Appendix 1. List of Articles Reviewed

Article	Study Design	Population	Outcome	Result
Abajo et al,[6] 2021	Observational cohort	625	Primary outcome: in-hospital death for any cause Secondary outcome: ICU admission	No significant difference
Cannata et al,[3] 2020	Observational cohort	213	Primary outcome: mortality Secondary outcome: ICU admission	Continuing ACEIs/ARBs has a lower risk of mortality compared with those discontinuing ACEIs/ARBs.
Chaudhri et al,[4] 2020	Observational cohort	80	ICU admission and final patient outcome of death vs discharge	Continuation of ACEI/ARBs during hospitalization might reduce progression of disease by lowering the severity of inflammation and admission to the ICU.
Lam et al,[7] 2020	Observational cohort	335	Primary outcome: In-hospital mortality Secondary outcome: ICU admission	COVID-19 patients who are on ACEI/ARBs should continue during admission these medications in the hospital as they may have beneficial effects.

ACEI=angiotensin-converting enzyme inhibitor; ARBs=angiotensin-receptor blockers; COVID-19=coronavirus disease 2019; ICU=intensive care unit.

Appendix 2. Newcastle-Ottawa Quality Assessment Scale

NOS Criteria	Abajo et al,[6] 2021	Cannata et al,[3] 2020	Chaudhri et al,[4] 2020	Lam et al,[7] 2020
A. Selection				
1. Representativeness of the exposed cohort	★	★	★	★
2. Selection of the nonexposed cohort	★	★	★	★
3. Ascertainment of exposure	★	★	★	★
4. Demonstration that the outcome of interest was not present at start of the study (no bone disease at start of study)	★	★	★	★
B. Comparability				
1. Comparability of cohort on the basis of the design or analysis	★☆	★☆	★☆	★☆
C. Outcome				
1. Assessment of outcome	★	★	★	★
2. Was follow-up long enough for outcomes to occur	★	★	★	★
3. Adequacy of follow-up of cohorts	★	★	★	★
Total	8	8	8	8

NOS=Newcastle-Ottawa Quality Assessment Scale.