Korean Circ J. 2023 Sep;53(9):606-618
https://doi.org/10.4070/kcj.2023.0035
pISSN 1738-5520·eISSN 1738-5555

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Korean Circulation Journal

Original Research

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Prognostic and Safety Implications of Renin-Angiotensin-Aldosterone System Inhibitors in Hypertrophic Cardiomyopathy: A Real-World Observation Over 2,000 Patients

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OPEN ACCESS

Received: Feb 16, 2023
Revised: May 3, 2023
Accepted: May 17, 2023
Published online: Jul 3, 2023

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AUTHOR'S SUMMARY

Despite the robust benefits of renin-angiotensin-aldosterone system inhibitors (RASi) in various cardiovascular diseases, prognostic and safety implications of RASi remain elusive in hypertrophic cardiomyopathy (HCM). With a sizable cohort of over 2,000 patients, we analyzed clinical prognosis (in terms of all-cause mortality and hospitalization for heart failure) according to the use of RASi. Despite unfavorable clinical profiles at baseline, patients taking RASi showed comparable prognosis and safety compared to those not taking RASi in all and across various subgroups, classified according to left ventricular (LV) ejection fraction, LV outflow tract obstruction, and maximal LV wall thickness. Thus, if clinically indicated, RASi can safely be administered in HCM patients.

ABSTRACT

Background and Objectives: The prognostic or safety implication of renin-angiotensin-aldosterone system inhibitors (RASi) in hypertrophic cardiomyopathy (HCM) are not well established, mainly due to concerns regarding left ventricular outflow tract (LVOT) obstruction aggravation. We investigated the implications of RASi in a sizable number of HCM patients.
Methods: We enrolled 2,104 consecutive patients diagnosed with HCM in 2 tertiary university hospitals and followed up for five years. RASi use was defined as the administration of RASi after diagnostic confirmation of HCM. The primary and secondary outcomes were all-cause mortality and hospitalization for heart failure (HHF).
Results: RASi were prescribed to 762 patients (36.2%). During a median follow-up of 48.1 months, 112 patients (5.3%) died, and 94 patients (4.5%) experienced HHF. Patients using RASi had less favorable baseline characteristics than those not using RASi, such as older age, more frequent history of comorbidities, and lower ejection fraction. Nonetheless, there was no difference in clinical outcomes between patients with and without RASi use

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Funding

This project is an investigator-initiated trial. This research was funded by a grant from HK inno.N (Seoul, Korea) (Grant number: 06-2022-4110). This research was partly funded by Seoul National University (Grant number: 800-20210548). These funding sources did not have any role in the study design, execution, analyses, interpretation of the data, or decision to submit results.

Conflict of Interest

Hyung-Kwan Kim reports research grants from HK inno.N, Johnson & Johnson, Handok Pharm, GSK, Dae-Woong Pharm, Yuhan, Hanmi, ChongKunDang Pharm, Boryung Pharm, Samjin Pharm, and JW Pharm. The remaining authors have nothing to disclose.

Data Sharing Statement

The data generated in this study is available from the corresponding author(s) upon reasonable request.

Author Contributions

Conceptualization: Park CS, Hwang IC, Kim HK; Data curation: Park CS, Rhee TM, Lee HJ, Yoon YE, Park JB, Lee SP, Kim YJ, Cho GY, Hwang IC, Kim HK; Formal analysis: Park CS, Rhee TM, Lee HJ, Park JB, Lee SP, Kim YJ, Cho GY, Kim HK; Funding acquisition: Kim HK; Investigation: Park CS, Hwang IC, Kim HK; Methodology: Park CS, Hwang IC, Kim HK; Project administration: Park CS, Hwang IC, Kim HK; Software: Park CS; Supervision: Rhee TM, Lee HJ, Yoon YE, Park JB, Lee SP, Kim YJ, Cho GY, Hwang IC, Kim HK; Validation: Park CS, Rhee TM, Lee HJ, Yoon YE, Park JB, Lee SP, Kim YJ, Cho GY, Hwang IC, Kim HK; Visualization: Park CS, Rhee TM, Lee HJ, Yoon YE, Park JB, Lee SP, Kim YJ, Cho GY, Hwang IC, Kim HK; Writing - original draft: Park CS; Writing - review & editing: Rhee TM, Lee HJ, Yoon YE, Park JB, Lee SP, Kim YJ, Cho GY, Hwang IC, Kim HK.

(log-rank p=0.368 for all-cause mortality and log-rank p=0.443 for HHF). In multivariable analysis, patients taking RASi showed a comparable risk of all-cause mortality (hazard ratio [HR], 0.70, 95% confidence interval [CI], 0.43–1.14, p=0.150) and HHF (HR, 1.03, 95% CI, 0.63–1.70, p=0.900). In the subgroup analysis, there was no significant interaction of RASi use between subgroups stratified by LVOT obstruction, left ventricular (LV) ejection fraction, or maximal LV wall thickness.

Conclusions: RASi use was not associated with worse clinical outcomes. It might be safely administered in patients with HCM if clinically indicated.

Keywords: Hypertrophic cardiomyopathy; Mortality; Prognosis; Renin-angiotensin system

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy characterized by left ventricular (LV) hypertrophy without other cardiac, systemic, or metabolic diseases.[1)2)] Most HCM patients do not have symptoms, enjoying average life expectancy without needing primary treatments. In contrast, some patients experience adverse events, including angina, heart failure (HF), stroke, and sudden cardiac death.[2)3)] The application of contemporary cardiovascular management and interventions has significantly reduced HCM-related mortality to <1.0% per year.[4)5)] Despite recent studies showing pathophysiology and prognostic factors,[6-9)] there is still an unmet need to prevent disease progression and improve prognosis in patients with HCM who live in the contemporary management era.

Renin-angiotensin-aldosterone system inhibitors (RASi), composed mainly of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), have shown prognostic benefits in various cardiovascular diseases.[10-12)] Specifically, RASi demonstrated their protective effects in reducing pressure overload-induced LV hypertrophy.[13)] It also showed decreased collagen synthesis and improved LV hypertrophy and diastolic dysfunction in several animals and small-size human HCM studies.[14)15)] However, not only is RASi discontinuation suggested for patients with obstructive HCM due to the fear of LV outflow tract (LVOT) obstruction aggravation, but its efficacy and safety also remain elusive in those with nonobstructive HCM.[2)16)] A few clinical trials evaluated the benefit of RASi in patients with HCM, but they did not compare morbidity and mortality risks between HCM patients taking and not taking RASi.[17)18)]

In this study, we aimed to investigate the prognostic and safety implications of RASi in a sizable number of patients with HCM.

METHODS

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (2013). The study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2110-131-1264) and Seoul National University Bundang Hospital (IRB No. 2004-604-409).

https://doi.org/10.4070/kcj.2023.0035

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Data availability

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. On reasonable request, the data will be made available with the approval of the corresponding authors.

Study design

From April 2007 to June 2020, 2,104 consecutive patients who underwent echocardiography and were diagnosed with HCM were enrolled in 2 tertiary university hospitals. The patients were followed up for five years. The diagnosis of HCM was made according to clinical guidelines, as previously reported.[5)16)] Baseline demographic, anthropometric, clinical, and laboratory data were collected from medical records. All echocardiographic examinations were performed according to the established guidelines.[19)]

Variables and definitions

The use of RASi was defined as the administration of either an ACEi or ARB after the diagnostic confirmation of HCM. The RASi administration before the diagnostic confirmation of HCM did not affect patient stratification into those with or without RASi. The names and doses of RASi were collected, and low-dose RASi was defined as ≤160 mg of valsartan or ≤10 mg of enalapril or equivalent doses of other ARBs or ACEIs.[20)] On echocardiography, valvular heart disease was identified as having a higher than mild degree of valvular stenosis and/or regurgitation. LVOT obstruction was defined when patients showed a peak LVOT pressure gradient of ≥30 mmHg at rest and/or with the Valsalva maneuver.[2)] For subgroup analysis according to LV ejection fraction, the patients were classified as those with LV ejection fraction <50%, 50% to 65%, and >65%.[21)] For maximal LV wall thickness, patients were stratified into those with <20 mm or ≥20 mm LV wall thickness[22)] Pathological LV hypertrophy involving only apical segments was defined as apical HCM.[23)]

The primary outcome was all-cause mortality, and the secondary outcome was hospitalization for heart failure (HHF). Mortality data were obtained and verified using a centralized death records database from the Ministry of Public Administration and Security that the Korean Government manages.

Statistical analysis

Data were presented as numbers and frequencies for categorical variables and as mean±standard deviation or median with interquartile range for continuous variables. For comparison between groups, the χ^2 or Fisher's exact test (when an expected cell count was <5 for a 2×2 table) for categorical variables and the unpaired Student's t-test for continuous variables was used. The log-rank test was used as a univariable analysis to compare the differences in clinical outcomes. A multivariable Cox proportional hazard regression analysis was used to determine the independent predictors of all-cause mortality and HHF. The chronological trend of clinical outcomes according to the use of RASi was expressed as multivariable-adjusted survival curves based on the Cox regression analysis. The proportional hazards assumption was checked using a statistical test based on Schoenfeld residuals and their plots. Time zero was defined as the date of the index echocardiography. The hazard ratio (HR) calculated using the Cox proportional hazards model was presented as a 95% confidence interval (CI) and the corresponding p-value. A multivariable Cox proportional hazard regression analysis was used to determine the independent predictors of all-cause mortality and HHF. Variables that first achieved p<0.2 in univariate Cox regression analysis or those with clinical relevance regarding RASi use were included in a multivariable model.

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The multivariable models were adjusted for covariates including age, sex, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, valvular heart disease, HF, atrial fibrillation, cancer, systolic blood pressure, and LV ejection fraction <50%. Subgroup analyses were conducted according to age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, LV ejection fraction, LVOT obstruction, maximal LV wall thickness, and apical HCM. For sensitivity analysis, a propensity score matching (PSM) analysis was performed for the following variables: age, sex, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, valvular heart disease, HF, atrial fibrillation, end-stage renal disease, cancer, systolic blood pressure, diastolic blood pressure, LV ejection fraction, maximal LV wall thickness, LV end-diastolic diameter, LV end-systolic diameter, peak LVOT pressure gradient, left atrial diameter, and apical HCM. In the PSM cohort, all variables were adjusted for with an absolute standardized difference of <0.2 in each variable (**Supplementary Table 1**). A value of 2-tailed p<0.05 was considered statistically significant. The statistical tests were performed using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and clinical characteristics

In total, 2,104 patients with HCM (mean age, 61.4±13.6 years; men, 1,421 [67.5%]) were analyzed, of whom RASi was prescribed in 762 patients (36.2%). A total of 1,145 (54.4%) patients were diagnosed with hypertension, 441 (21.0%) with diabetes mellitus, 730 (34.7%) with dyslipidemia, 93 (4.4%) with valvular heart disease, and 397 (18.9%) with atrial fibrillation.

Table 1 shows the clinical characteristics of patients according to RASi use. Generally, patients taking RASi showed more unfavorable baseline characteristics; they were older and had a more frequent history of hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation. Additionally, they had a lower LV ejection fraction and larger LV end-diastolic diameter than their counterparts, although the differences were deemed clinically negligible. In contrast, there was no significant difference in sex preponderance, a previous history of cancer, maximal LV wall thickness, LVOT obstruction, or apical HCM between patients taking and those not taking RASi.

Primary and secondary outcomes according to renin-angiotensin-aldosterone system inhibitors use

During the follow-up period (median, 48.1 months; interquartile range, 19.5–60.0 months), 112 patients (5.3%) died, and 94 patients (4.5%) experienced HHF. The patients who died were older and had a more frequent history of valvular heart disease, atrial fibrillation, and cancer; they also had larger left atrial diameters. No significant difference was observed in LV ejection fraction between the two groups (**Supplementary Table 2**).

When the clinical outcomes of patients taking and not taking RASi were compared, no prognostic difference was observed for the primary and secondary outcomes (log-rank p=0.368 for all-cause mortality and p=0.443 for HHF). In multivariable Cox regression analysis, patients taking RASi showed no significant difference in terms of all-cause mortality (HR, 0.70, 95% CI, 0.43–1.14, p=0.150) and HHF (HR, 1.03, 95% CI, 0.63–1.70, p=0.900) compared to those not taking RASi (**Figure 1**, **Supplementary Table 3**). **Figure 2** shows the clinical outcomes according to RASi use in the PSM cohort as a sensitivity analysis. In the PSM cohort, patients taking RASi showed similar risks of mortality and HHF compared to

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Table 1. Clinical characteristics according to RASi use

Variables	All population (n=2,104)	Without RASi (n=1,342)	With RASi (n=762)	p value
Demographic data				
Age (years)	61.4±13.6	60.5±14.0	63.0±12.7	<0.001
Male	1,421 (67.5)	901 (67.1)	520 (68.2)	0.604
BMI (kg/m^2)	24.9±3.4	24.6±3.2	25.4±3.8	<0.001
Past medical history				
Hypertension	1,145 (54.4)	524 (39.0)	621 (81.5)	<0.001
Diabetes mellitus	441 (21.0)	206 (15.4)	235 (30.8)	<0.001
Dyslipidemia	730 (34.7)	386 (28.8)	344 (45.1)	<0.001
Valvular heart disease	93 (4.4)	52 (3.9)	41 (5.4)	0.106
Heart failure	93 (4.4)	48 (3.6)	45 (5.9)	0.012
Atrial fibrillation	397 (18.9)	229 (17.1)	168 (22.0)	0.005
End-stage renal disease	20 (1.0)	10 (0.7)	10 (1.3)	0.198
Previous history of cancer	255 (12.1)	164 (12.2)	91 (11.9)	0.851
Physical examination				
SBP (mmHg)	129.1±17.0	127.0±15.7	133.0±18.4	<0.001
DBP (mmHg)	75.8±11.4	74.7±10.6	77.7±12.5	<0.001
Heart rate (/min)	69.3±13.5	69.1±13.1	69.7±14.2	0.406
Echocardiography				
LV ejection fraction (%)	63.7±18.2	64.1±6.4	63.0±8.1	0.002
<50%	58 (2.8)	20 (1.5)	38 (5.0)	<0.001
50% to 65%	1,153 (54.8)	745 (55.5)	408 (53.5)	
>65%	893 (42.4)	577 (43.0)	316 (41.5)	
Maximal LV wall thickness (mm)	18.2±3.9	18.2±4.0	18.1±3.8	0.556
LV end-diastolic diameter (mm)	46.3±5.4	46.0±5.3	46.9±5.5	<0.001
LV end-systolic diameter (mm)	28.1±4.9	27.8±4.5	28.7±5.5	<0.001
Peak LVOT pressure gradient (mmHg)	17.8±31.2	18.1±33.4	17.2±26.6	0.559
Left atrial diameter (mm)	44.0±7.8	43.8±7.7	44.4±7.9	0.069
Apical hypertrophic cardiomyopathy	562 (26.7)	348 (25.9)	214 (28.1)	0.283

Values are presented as number (%) or mean±standard deviation.
BMI = body mass index; DBP = diastolic blood pressure; LV = left ventricular; LVOT = left ventricular outflow tract; RASi = renin-angiotensin-aldosterone system inhibitors; SBP = systolic blood pressure.

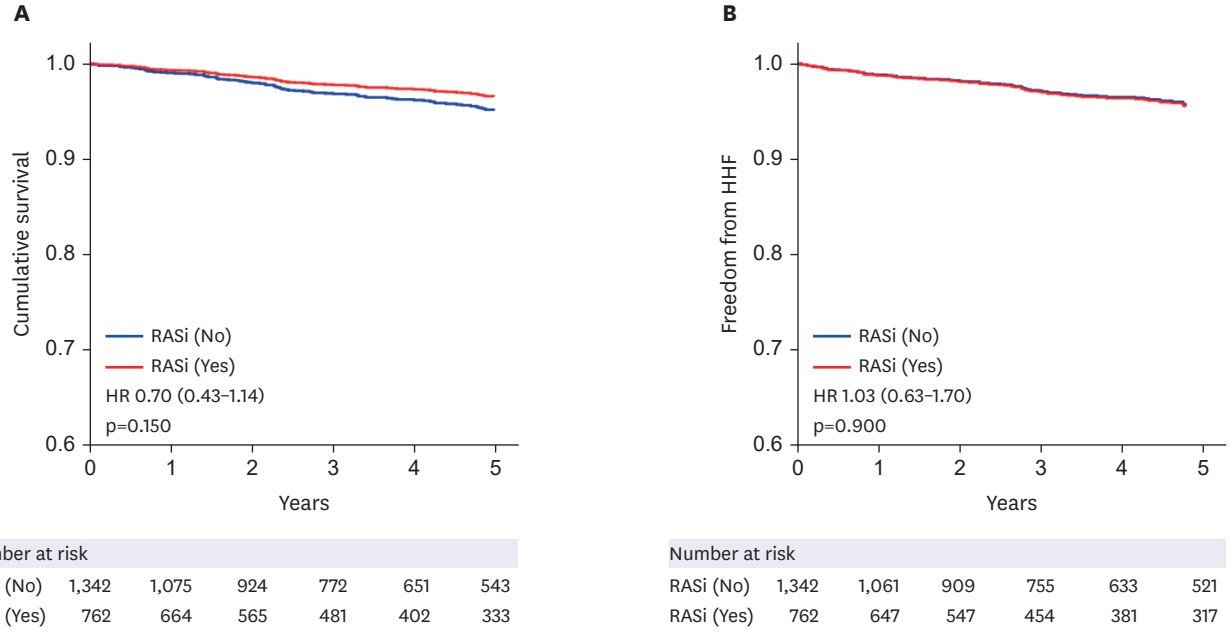

Figure 1. Clinical outcomes according to the use of RASi in the original cohort. Multivariable-adjusted survival curves demonstrating the difference in all-cause mortality (A) and HHF (B) according to the use of RASi are illustrated.
HHF = hospitalization for heart failure; HR = hazard ratio; RASi = renin-angiotensin-aldosterone system inhibitors.

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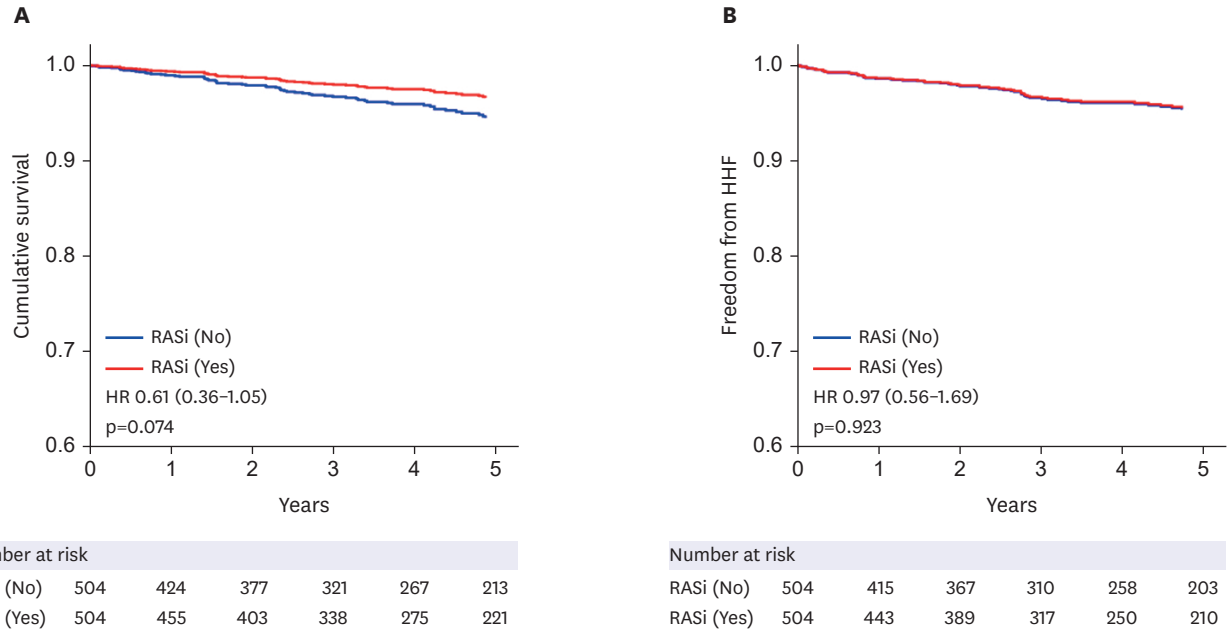

Number at risk						
RASi (No)	504	424	377	321	267	213
RASi (Yes)	504	455	403	338	275	221

Number at risk						
RASi (No)	504	415	367	310	258	203
RASi (Yes)	504	443	389	317	250	210

Figure 2. Clinical outcomes according to the use of RASi in the propensity score matching cohort. Multivariable-adjusted survival curves for all-cause mortality (A) and HHF (B) according to the use of RASi were illustrated.
HHF = hospitalization for heart failure; HR = hazard ratio; RASi, renin-angiotensin-aldosterone system inhibitors.

those not taking RASi (HR, 0.61, 95% CI, 0.36–1.05, p=0.074 and HR, 0.97, 95% CI, 0.56–1.69, p=0.923, respectively).

Again, no statistical difference in all-cause mortality and HHF was observed between patients taking ARB or ACEi (**Supplementary Figure 1**) and between patients receiving low- or high-dose RASi (**Supplementary Figure 2**).

Renin-angiotensin-aldosterone system inhibitors use and clinical outcomes according to left ventricular outflow tract obstruction, left ventricular ejection fraction, and maximal left ventricular wall thickness

When patients were classified according to LVOT obstruction, RASi use showed no survival benefits in patients with and without LVOT obstruction (log-rank p=0.544 and log-rank p=0.501, respectively). Similarly, patients receiving RASi showed an equivalent risk of HHF compared to their counterparts, irrespective of the presence or absence of LVOT obstruction (log-rank p=0.248 and log-rank p=0.700, respectively). Of note, in patients without LVOT obstruction, RASi use tended to show survival benefits without statistical significance after adjusting for covariates (HR, 0.60, 95% CI, 0.34–1.07, p=0.085) (**Figure 3A**). However, RASi use did not decrease the risks of HHF (HR, 1.00, 95% CI, 0.57–1.79, p=0.988). As shown in **Figure 3B**, RASi use was not associated with clinical outcomes in multivariable analysis in patients with LVOT obstruction. Similar results were observed in the PSM cohort (**Supplementary Figure 3**).

We stratified the patients according to their LV ejection fraction. Patients taking RASi showed no differences in all-cause mortality compared to their counterparts across all LV ejection fraction categories (log-rank p=0.957 for LV ejection fraction >65% group, log-rank p=0.150 for LV ejection fraction 50% to 65% group, and log-rank p=0.868 for LV ejection fraction <50% group). Moreover, for HHF, a statistically significant difference was not observed between the two groups. In the Cox regression analysis, no prognostic difference

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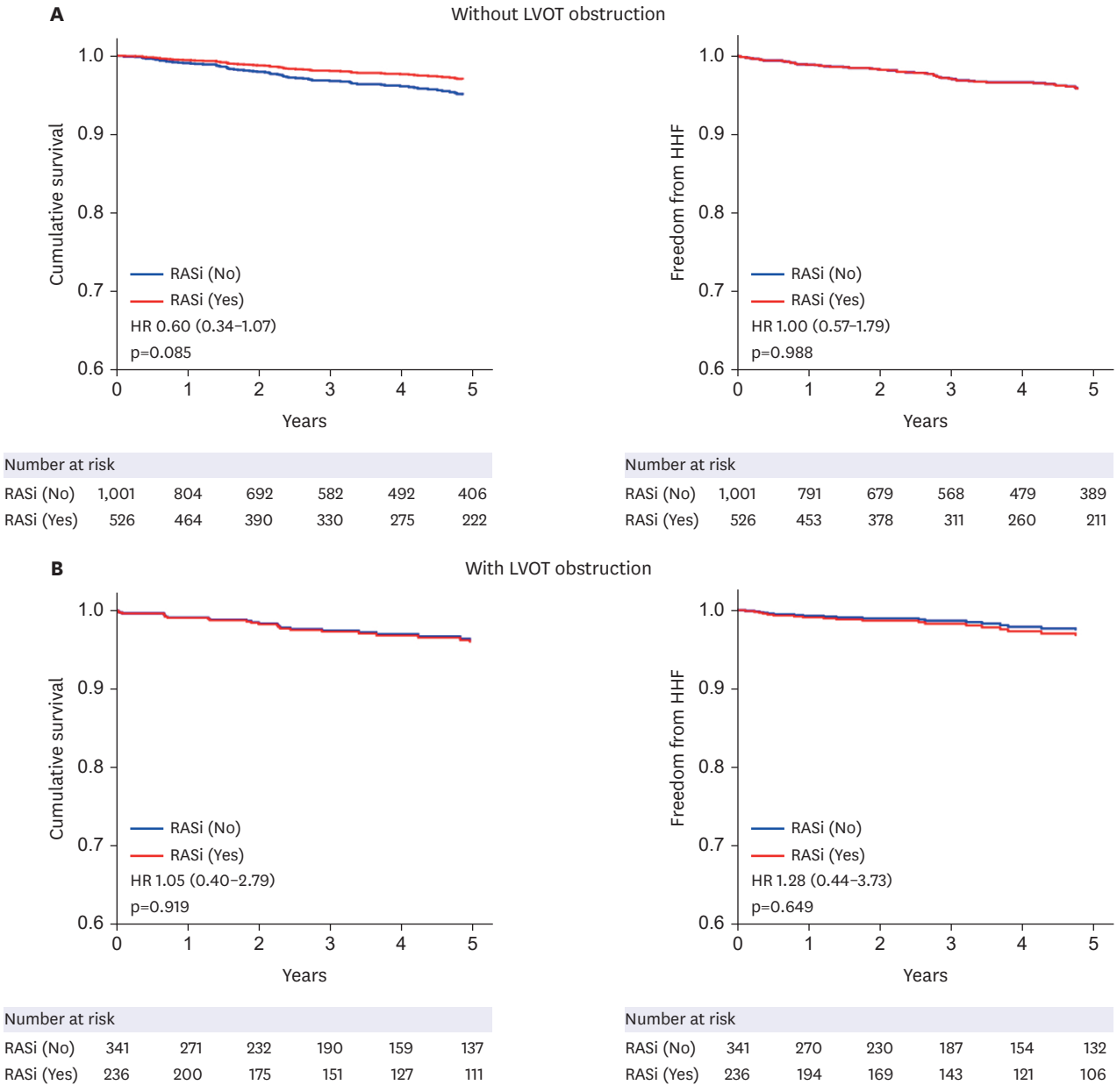

Figure 3. Impact of RASi according to LVOT obstruction. Patients without LVOT obstruction (A) and with LVOT obstruction (B) were categorized according to the use of RASi. Multivariable-adjusted survival curves demonstrating the difference in each group are illustrated.
HHF = hospitalization for heart failure; HR = hazard ratio; LVOT = left ventricular outflow tract; RASi = renin-angiotensin-aldosterone system inhibitors.

was observed between the groups across all LV ejection fraction categories (**Figure 4**). In the PSM cohort, there was no prognostic difference between those who took and those who did not take RASi across the LV ejection fraction categories (**Supplementary Figure 3**).

For both subgroups with a maximal LV wall thickness of <20 mm and ≥20 mm, RASi use did not provide a survival benefit (log-rank p=0.717 and log-rank p=0.273, respectively). Similar findings were observed for HHF. In multivariable analysis, RASi use did not result in survival differences in each subgroup (**Figure 4**). **Supplementary Figure 3** shows the clinical outcomes according to RASi use in the PSM cohort.

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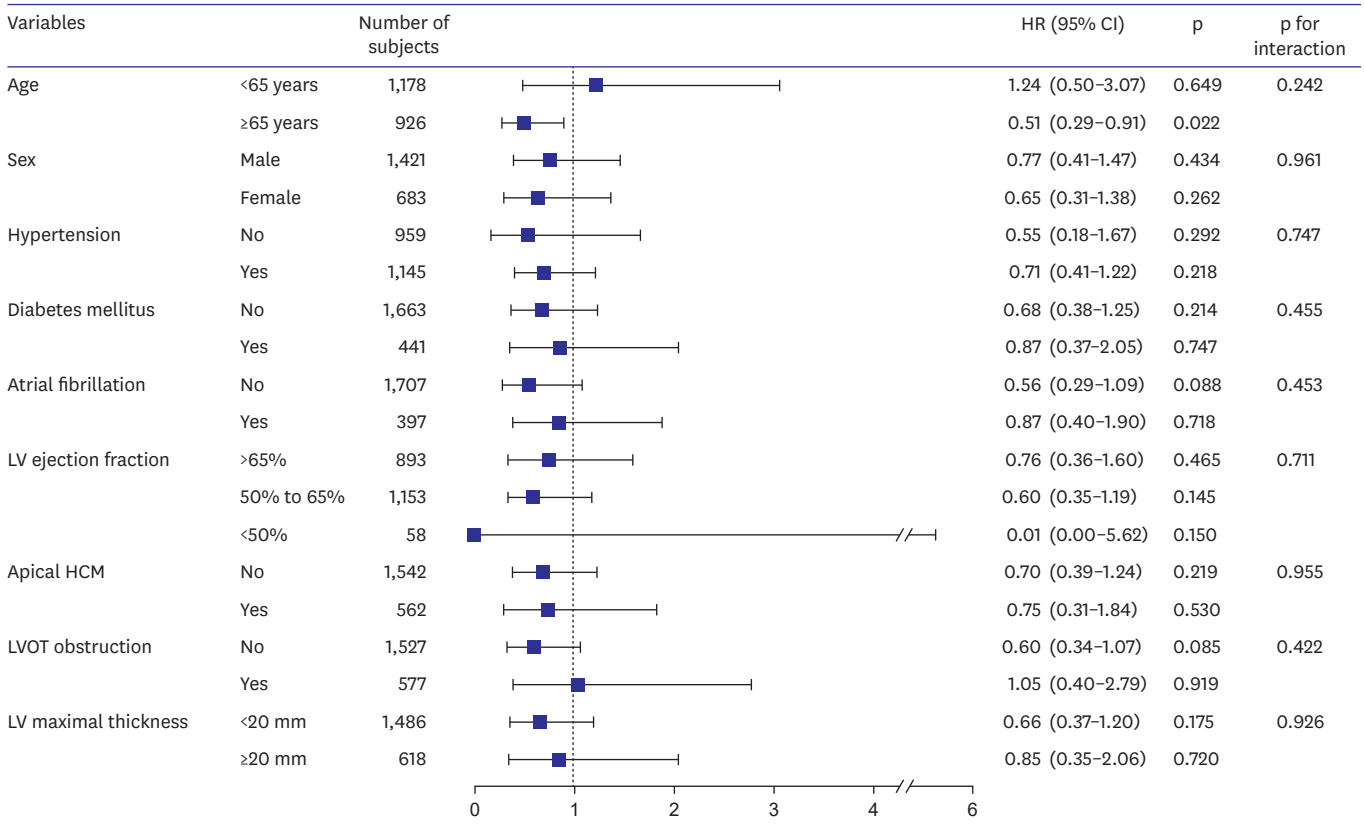

Figure 4. Association between all-cause mortality and use of RASi. The effects of RASi on all-cause mortality in exploratory subgroups were analyzed.
CI = confidence interval; HCM = hypertrophic cardiomyopathy; HR = hazard ratio; LV = left ventricular; LVOT = left ventricular outflow tract; RASi = renin-angiotensin-aldosterone system inhibitors.

Outcome in patients according to renin-angiotensin-aldosterone system inhibitors use for variable subgroups

Figure 4 shows a forest plot according to variable subgroups. Compared with patients not taking RASi, those taking RASi showed similar survival probability across various subgroups. Statistically significant prognostic interaction was not observed in relation to the RASi use within each subgroup.

DISCUSSION

In this study, we investigated the prognostic and safety implications of RASi use in real-world HCM patients. The main findings were 2-fold: (1) approximately one-third of HCM patients were prescribed RASi in real-world practice for various reasons, and they had more unfavorable clinical characteristics compared with those not taking RASi, and (2) patients taking RASi, despite unfavorable clinical profiles at baseline, showed comparable prognosis (in terms of all-cause mortality and HHF) and safety, compared with those not taking RASi across various subgroups, irrespective of LV ejection fraction categories, the presence or absence of LVOT obstruction, and maximal LV wall thickness.

Since the introduction of captopril and losartan into the clinical arena, RASi has been widely prescribed and has proven its benefits in hypertension, coronary artery disease, and HF.[6-9]

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RASi also showed their prognostic benefits in patients with fixed LVOT obstruction, such as aortic stenosis.[24)25)] Thanks to studies attempting to determine the mechanism of action of RASi, various protective roles of RASi, such as lowering blood pressure, modulating neurohumoral activation, and reducing proteinuria, have been revealed.[8)9)] HCM is a common genetic cardiomyopathy characterized by intrinsic LV hypertrophy, although unhealthy metabolic profiles can lead to earlier and unfavorable clinical manifestations.[26)] Notably, RASi use reduces LV hypertrophy in patients with hypertensive heart disease.[13)] Therefore, there was hope that patients with HCM may also receive similar benefits from RASi use.

In several preclinical and pilot studies, RASi use showed some promise by decreasing collagen synthesis and LV hypertrophy and improving LV diastolic function.[14)15)] Despite substantial reduction in blood pressure, two earlier randomized trials showed less promising results in LV hypertrophy reduction.[17)18)] In the INHERIT trial, Axelsson et al.[17)] randomized 133 patients with HCM to the placebo or the losartan arm and compared LV mass at a 12-month follow-up, reporting no significant difference between the two groups. In the VANISH trial, 178 patients with HCM and without LVOT obstruction were randomized and followed up for two years. The primary endpoint was the Z-score, composed of 9 clinical risk factors. Although the Z-score decreased in a valsartan-taking group, valsartan did not show a decrease in LV wall thickness or LV mass index.[18)] Indeed, these trials had relatively small sample sizes and short follow-up durations. Moreover, the researchers compared surrogate markers rather than hard endpoints between the control and placebo groups; therefore, the efficacy and safety profiles of RASi use remain unresolved. This issue has been described as 'unanswered' in current clinical guidelines.[2)16)] In the present study of real-world data, patients with HCM taking RASi showed comparable outcomes and safety despite worse baseline clinical and echocardiographic characteristics. In addition, we found the potential benefit of RASi use in HCM patients without LVOT obstruction.

Noteworthily, contrary to the general belief that RASi use may aggravate LVOT obstruction in patients with obstructive HCM, we observed that RASi use was not associated with adverse outcomes, which is in line with the results of the INHERIT trial.[17)] The outcomes and safety profile of RASi use in HCM patients with LVOT obstruction were comparable between those taking and not taking RASi, particularly regarding morbidity and mortality, which have not been comprehensively evaluated in previous reports. Although current clinical guidelines suggest discontinuation of RASi use in patients with obstructive HCM because of its vasodilating effects,[2)16)] we propose, based on the present study, that the careful RASi use with close monitoring for symptomatic aggravation can be a safe option in selected patients with HCM if clinically indicated, even in those with LVOT obstruction.

Furthermore, RASi use tended to show survival benefits in patients without LVOT obstruction, although statistical significance was marginally diminished (HR, 0.60, 95% CI, 0.34–1.07, p=0.085 in the original cohort; HR, 0.55, 95% CI, 0.32–1.01, p=0.054 in PSM cohort). We hypothesize that the innate pharmacologic effects of RASi may provide better survival benefits in patients with HCM and without LVOT obstruction. Patients with HCM are known to have an overactivated neurohumoral status.[27)] Previous studies have reported that RASi use reduced the B-type natriuretic peptide level in these patients.[15)18)] We speculate that neurohumoral modulation by RASi may provide potential benefits in these patients. In addition, some reports imply another beneficial role of RASi. In contrast to controls and patients with hypertensive LV hypertrophy,[28)] signaling pathways associated with myocyte hypertrophy,[29)] i.e., Ras/mitogen-activated protein kinase or transforming growth factor

https://doi.org/10.4070/kcj.2023.0035

β pathways, were upregulated in patients with HCM, causing LV hypertrophy. RASi was suggested to have the potential to ameliorate these signaling pathways,[28] supporting their potential benefits in HCM treatment. However, this concept requires further investigation.

If the pharmacologic effects of RASi could be demonstrated even in patients with HCM, it can be assumed that these effects will be more prominent in patients with an LV ejection fraction <50%. Indeed, current clinical guidelines recommend RASi use in HCM cases with LV ejection fraction <50%.[2][16] However, in the present study, RASi failed to show clinical benefits in HCM cases with LV ejection fraction <50%. This observation does not imply that RASi does not exert a beneficial effect on these patients. Instead, this may be due to a small number of HCM patients with an LV ejection fraction <50%, warranting more extensive prospective studies to determine the prognostic implications of RASi use in this critical HCM subgroup.

This study has several limitations. First, this is a retrospective observational cohort study. Therefore, although we performed a multivariable analysis adjusting for various confounding factors, this study was not free from bias caused by residual confounding factors. We also could not control the initiation or discontinuation of RASi during the follow-up. Well-designed randomized controlled trials would be required to consolidate our findings. Second, we did not investigate sarcomeric or non-sarcomeric gene mutations. However, there is still controversy regarding the general use of genetic testing in all patients with HCM, mainly because genetic mutations and/or genetic etiology do not reliably predict clinical course or outcome, including sudden cardiac death.[30] Third, as we enrolled only Asian patients in this study, the results should be validated in other races before generalization. Lastly, although we enrolled a sizable number of patients, the number of patients with LV ejection fraction <50% was small; therefore, this study could not investigate the role of RASi use in end-stage HCM. For an adequate evaluation of RASi use in patients with HCM who are at high risk of morbidity and mortality, a more significant number of patients should be enrolled using a multicenter study design.

We suggest that RASi might be safely used in patients with HCM without serious concerns about the aggravation of LVOT obstruction or other worse outcomes. RASi use in patients with an LV ejection fraction <50% (end-stage HCM population) requires further investigation, enrolling a larger number of this HCM subgroup.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Clinical characteristics according to the use of RASi in the propensity score matching cohort

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Supplementary Table 2

Clinical characteristics according to all-cause mortality during follow-up

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https://doi.org/10.4070/kcj.2023.0035

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Supplementary Table 3

Multivariable Cox-proportional hazard regression analysis for all-cause mortality and hospitalization for heart failure

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Supplementary Figure 1

Clinical outcomes according to the use of ARB or ACEi. Multivariable-adjusted survival curves demonstrating the difference in all-cause mortality (A) and HHF (B) according to the use of ARB or ACEi were illustrated.

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Supplementary Figure 2

Clinical outcomes according to a dose of RASi. Multivariable-adjusted survival curves demonstrate the difference in all-cause mortality (A) and HHF (B) according to a dose of RASi.

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Supplementary Figure 3

Association between all-cause mortality and use of RASi in the propensity score matching cohort. The effects of RASi on all-cause mortality in exploratory subgroups were analyzed.

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