Kidney Diseases

Research Article

Kidney Dis
DOI: 10.1159/000532055

Received: March 14, 2023
Accepted: July 11, 2023
Published online: October 13, 2023

# Long-Term Impact of Renin-Angiotensin System Inhibitors for Secondary Prevention in Patients with Chronic Kidney Disease Who Underwent Percutaneous Coronary Intervention

Tatsuya Fukase[a] Tomotaka Dohi[a] Ryota Nishio[a] Mitsuhiro Takeuchi[a] Norihito Takahashi[a] Yuichi Chikata[a] Hirohisa Endo[a] Shinichiro Doi[a] Hiroki Nishiyama[a] Iwao Okai[a] Hiroshi Iwata[a] Shinya Okazaki[a] Katsumi Miyauchi[a] Hiroyuki Daida[a, b] Tohru Minamino[a, c]

[a]Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; [b]Department of Radiological Technology, Faculty of Health Science, Juntendo University, Tokyo, Japan; [c]Japan Agency for Medical Research and Development-Core Research for Evolutionary Medical Science and Technology (AMED-CREST), Japan Agency for Medical Research and Development, Tokyo, Japan

**Keywords**
Renin-angiotensin system inhibitor · Chronic kidney disease · Heart failure · Cardiovascular events · Percutaneous coronary intervention

**Abstract**
***Introduction:*** The long-term impact of renin-angiotensin system (RAS) inhibitors for secondary prevention in patients with chronic kidney disease (CKD) and coexisting coronary artery disease remains unclear. ***Methods:*** Altogether, 1,160 consecutive patients with CKD (mean age, 70 ± 9 years; 78% men) who underwent their first percutaneous coronary intervention (PCI) between 2000 and 2018 were included and analyzed. Based on their RAS inhibitor use, 674 patients (58%) were allocated to the RAS inhibitor group, and 486 patients (42%) were allocated to the non-RAS inhibitor group. This study evaluated the incidence of 3-point major adverse cardiovascular events (3P-MACE), including cardiovascular death, nonfatal acute coronary syndrome and nonfatal stroke, admission for heart failure (HF), target vessel revascularization (TVR), and all-cause death. ***Results:*** During a median follow-up duration of 7.8 years, 280 patients (24.1%) developed 3P-MACE, 134 patients (11.6%) were hospitalized for HF, 171 patients (14.7%) underwent TVR, and 348 patients (30.0%) died of any causes. The cumulative incidence rate of 3P-MACE in the RAS inhibitor group was significantly lower than in the non-RAS inhibitor group (31.7% vs. 39.0%, log-rank test, $p = 0.034$); however, that of admission for HF in the RAS inhibitor group was significantly higher than in the non-RAS inhibitor group (28.1% vs. 13.3%, log-rank test, $p < 0.001$). The subgroup of preserved ejection fraction, non-acute myocardial infarction, and non-proteinuria tended to promote the onset of HF rather than cardiovascular prevention by RAS inhibitors. ***Conclusion:*** The long-term RAS inhibitor use for patients with CKD after PCI might prevent cardiovascular events but increase the risk of HF.



karger@karger.com
www.karger.com/kdd



Correspondence to:
Tomotaka Dohi, tdohi@juntendo.ac.jp

## Introduction

In the renin-angiotensin system (RAS), angiotensin-II activation results in harmful effects and targeted organ damage due to tissue remodeling, endothelial dysfunction, and fibrosis [1]. RAS inhibitors, such as angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers, act by decreased the generation of angiotensin-II or blocking angiotensin-II from binding to its receptors. These medications are widely used to treat hypertension, coronary artery disease (CAD), heart failure (HF), and chronic kidney disease (CKD) in the clinical practice [2–5]. However, the benefits of these medications need to be weighed against the side effects, such as hyperkalemia, acute kidney injury, and a reduction in an estimated glomerular filtration rate (GFR) [6]. In addition, the incidence rates of end-stage kidney disease, myocardial infarction (MI), HF, and mortality are especially relevant in patients with lower estimated GFR [7]. In the nephrology, many studies on the clinical outcomes affected by RAS inhibitors have recently been reported [8–12]. Both studies showed that RAS inhibitors for patients with CKD significantly prevented the adverse cardiovascular events, but the progression to end-stage kidney disease and introduction of kidney replacement therapy caused by RAS inhibitors were inconsistent, whereas RAS inhibitor use has been recommended for purpose of myocardial protection even when coexisting CAD [13, 14]. However, it is unclear how the relationship between RAS inhibitors and renal parameters influences prognosis in patients with CKD and coexisting CAD. Thus, this study aimed to investigate whether RAS inhibitor use for secondary prevention after percutaneous coronary intervention (PCI) affects the long-term clinical outcomes in patients with CKD.

## Materials and Methods

*Study Population*

We conducted a single-center, observational, retrospective cohort study at our institution, identifying patients who met the criteria of CKD out of 4,840 patients who underwent their first PCI between January 2000 and February 2018. The enrolled patients were divided into two groups based on their RAS inhibitor use, after patients with unknown ejection fraction (EF) and receiving hemodialysis were excluded.

*Ethics*

The Ethics Committee of our institution approved this study, and all participants provided written informed consent. The study conformed to the "*Declaration of Helsinki*" [15].

*Data Collection and Definitions*

We collected patients' characteristic data from an institutional database. Blood samples were collected in the morning, 1 day before the intervention, and after an overnight fast. All blood tests were performed in the same laboratory.

All patients were diagnosed as CKD by the presence of either kidney damage (mainly proteinuria) or decreased kidney function (estimated GFR of <60 mL/min/1.73 $m^2$) for three or more months. The presence of proteinuria was defined as proteinuria ≥0.15 g/gCr or dipstick proteinuria (1+ or greater), and an estimated GFR was measured based on the Modification of the Diet in Renal Disease equation modified using the baseline serum creatinine level [5, 16]. Patients with a blood pressure of >140/90 mm Hg or those receiving antihypertensive drugs were considered hypertensive [17]. Dyslipidemia was defined as a triglyceride level of ≥150 mg/dL, a low-density lipoprotein cholesterol level of ≥140 mg/dL, a high-density lipoprotein cholesterol level of <40 mg/dL, or lipid-lowering therapy administration [18]. Diabetes mellitus was defined as a hemoglobin A1c level of ≥6.5% or oral hypoglycemic agent administration or insulin injection [19]. Anemia was defined based on the hemoglobin level recommended by the World Health Organization (<12.0 g/dL in women and <13.0 g/dL in men) [20]. A family history of premature CAD was defined as the presence of any first-degree relative with premature cardiovascular disease (age <55 years for men and <65 years for women) [21]. The coronary artery lesion type (A, B1, B2, or C) was defined based on the American Heart Association/American College of Cardiology classification [22].

*Study Endpoint*

The endpoints of this study were 3-point major adverse cardiovascular events (3P-MACE), defined as a composite of cardiovascular death, nonfatal acute coronary syndrome (ACS) and nonfatal stroke, admission for HF, target vessel revascularization (TVR), and all-cause death. Cardiovascular death was defined as death resulting from MI, sudden cardiac death, HF, stroke, cardiovascular procedures, cardiovascular hemorrhage, and other cardiovascular causes. Stroke was defined as ischemic stroke, symptomatic intracerebral hemorrhage, symptomatic subarachnoid hemorrhage, and not otherwise specified according to the classification proposed by Neurologic Academic Research Consortium, because we considered it important to clearly distinguish between clinically meaningful and incidental findings in clinical practice. Patients requiring unscheduled hospital admission for a primary diagnosis of HF with typical signs, symptoms, and diagnostic testing results of HF for a length of stay exceeded 24 h or crossing one calendar day were classified as being admitted for HF. Any admission for HF was defined as the first onset of HF in each patient. TVR was defined as any repeated PCI or surgical bypass of any segment of the target vessel, including the target lesion [23–25].

Clinical follow-up data were collected from the patients' medical records or by contacting the patients or their families if the follow-up did not occur at our institution. Information about the circumstances and date of death was obtained from the families of the patients who died at home and by the staff of other hospitals or clinics where the patient had been admitted. Blinded investigators collected all the data.

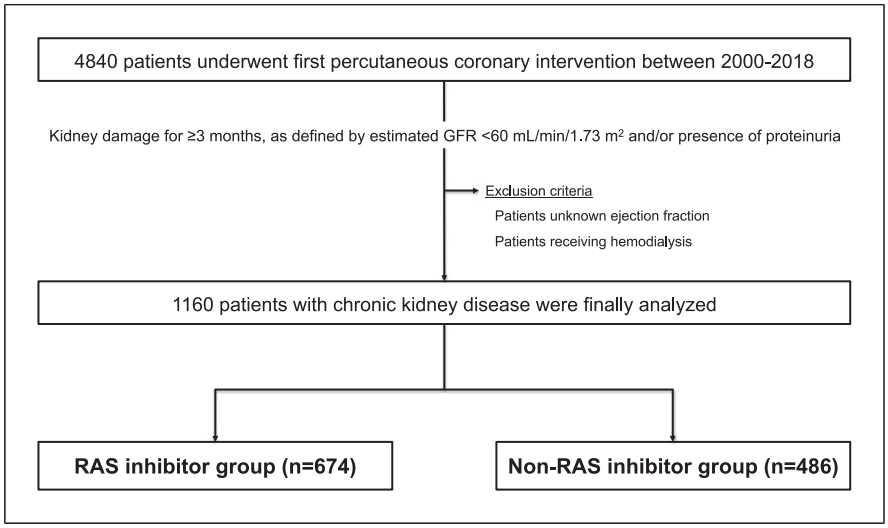


**Fig. 1.** Study flowchart. Among 4,840 patients who have undergone first intervention between 2000 and 2018, this study targeted patients who were diagnosed as CKD by the presence of either kidney damage (mainly proteinuria) or decreased kidney function (estimated GFR of <60 mL/min/1.73 $m^2$) for three or more months. After exclusion of patients with unknown EF and receiving hemodialysis, 1,160 patients were finally analyzed. These patients were divided into two groups based on the presence or absence of RAS inhibitor use. 674 patients (58%) were allocated to the RAS inhibitor group, and 486 patients (42%) were allocated to the non-RAS inhibitor group. GFR, glomerular filtration rate; RAS, renin-angiotensin system.

*Statistical Analysis*

Categorical data were presented as numbers and percentages and were compared using the $\chi^2$ test. Continuous variables were expressed as means±standard deviations or as medians and interquartile ranges (IQR) and were compared using a one-way analysis of variance or the Kruskal-Wallis test. The Kolmogorov-Smirnov test was used to determine if the scores were likely to follow a specific distribution in all patients. If the $p$ value <0.05, then the variable did not follow a normal distribution. Kaplan-Meier analyses for the cumulative incidence of 3P-MACE, admission for HF, TVR, and all-cause death were used to compare the two groups based on the presence or absence of RAS inhibitor; between-group differences were assessed using the log-rank test. Furthermore, the multivariable analysis was performed using a Cox proportional hazard model and evaluated the independent predictors and prognostic impacts of RAS inhibitors for 3P-MACE and admission for HF after adjusting for risk factors, comorbidities, and medications related to cardiovascular disease.

All probabilities were expressed as two-tailed values, with statistical significance at $p < 0.05$. All confidence intervals (CIs) were computed at 95% level. All data were analyzed using JMP version 14.2 for Macintosh (SAS Institute, Cary, NC, USA).

## Results

*Study Population*

We included 1,160 patients with CKD after PCI, excluding patients with an unknown EF and those who received hemodialysis. In total, 674 patients (58%) were allocated to the RAS inhibitor group, and 486 (42%) were allocated to the non-RAS inhibitor group (Fig. 1). Of those taking RAS inhibitors, 31% took angiotensin-converting enzyme inhibitors, and 71% took angiotensin-II receptor blockers. The median duration of oral administration of RAS inhibitor in the RAS inhibitor group was 6.8 years, although 66 patients discontinued RAS inhibitor due to 8 hyperkalemia, 14 renal function exacerbation, 42 decrease in blood pressure, and 2 others. While 105 patients newly added RAS inhibitor due to 92 increase in blood pressure, 2 HF, 13 CAD, and 2 others in the non-RAS inhibitor group.

*Baseline Clinical and Procedural Characteristics*

Baseline clinical characteristics are summarized in Table 1. The mean age was 70 ± 9 years, and 78% of the patients were men. Overall, the prevalence of hypertension, dyslipidemia, diabetes mellitus, current smoker, a family history of premature CAD, and atrial fibrillation was 94%, 86%, 31%, 17%, 27%, and 11%, respectively. The median estimated GFR was 54.4 [IQR: 47.9–57.8] mL/min/1.73 $m^2$, and the proportion of mild, moderate, and severe renal impairment was 81%, 16%, and 4%, respectively. The RAS inhibitor group had a significantly higher body mass index, systolic blood pressure, diabetic markers, and proportion of hypertension, statin use, calcium channel blocker use and oral hypoglycemic agent use, as well as a lower proportion of male and aspirin use, and EF than the non-RAS inhibitor group (all $p < 0.05$). Regarding baseline lesion and procedural characteristics, the RAS inhibitor group had a significantly longer stent length and lesion length, and a higher proportion of drug-eluting stent use, as well as a smaller stent diameter and lesion diameter, and proportion of bare metal stent use than the non-RAS inhibitor group (all $p < 0.05$).

**Table 1.** Patients' baseline clinical characteristics

| | Overall, *n* = 1,160 | RAS inhibitor group, *n* = 674 (58%) | Non-RAS inhibitor group, *n* = 486 (42%) | *p* value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Age, years | 70±9 | 71±10 | 70±9 | 0.380 |
| Male, *n* (%) | 908 (78) | 505 (75) | 403 (83) | 0.001 |
| Body mass index, kg/m$^2$ | 24.2±3.4 | 24.5±3.5 | 23.9±3.4 | 0.011 |
| Systolic BP, mm Hg | 135±24 | 137±25 | 131±23 | <0.001 |
| Diastolic BP, mm Hg | 72±14 | 73±15 | 71±13 | 0.060 |
| Total cholesterol level, mg/dL | 178±38 | 177±39 | 179±37 | 0.278 |
| Triglyceride level, mg/dL | 131±74 | 131±73 | 129±76 | 0.663 |
| HDL-C level, mg/dL | 44±13 | 44±12 | 44±13 | 0.652 |
| LDL-C level, mg/dL | 108±32 | 107±33 | 110±32 | 0.223 |
| Estimated GFR, mL/min/1.73 m$^2$ | 54.4 (47.9, 57.8) | 54.0 (47.5, 57.7) | 55.0 (48.2, 58.0) | 0.128 |
| 45 ≤estimated GFR <60, *n* (%) | 934 (81) | 539 (80) | 395 (81) | 0.579 |
| 30 ≤estimated GFR <45, *n* (%) | 183 (16) | 111 (16) | 72 (15) | 0.445 |
| Estimated GFR <30, *n* (%) | 43 (4) | 24 (4) | 19 (4) | 0.757 |
| Hemoglobin level, g/dL | 12.8±1.8 | 12.7±1.8 | 12.8±1.7 | 0.281 |
| FBG level, mg/dL | 113±44 | 116±47 | 110±40 | 0.019 |
| HbA1c level, % | 6.3±1.0 | 6.3±1.1 | 6.2±1.0 | 0.028 |
| Hs-CRP level, mg/dL | 0.14 (0.06, 0.39) | 0.14 (0.06, 0.38) | 0.14 (0.06, 0.39) | 0.783 |
| BNP level, pg/mL | 72 (30, 182) | 76 (28, 203) | 65 (30, 139) | 0.149 |
| Presence of proteinuria, *n* (%) | 289 (25) | 198 (29) | 91 (19) | <0.001 |
| EF, % | 61±13 | 59±14 | 63±12 | <0.001 |
| Reduced EF, *n* (%) | 81 (7) | 55 (8) | 26 (5) | 0.060 |
| Acute MI, *n* (%) | 138 (12) | 99 (15) | 39 (8) | <0.001 |
| Comorbidity | | | | |
| Hypertension, *n* (%) | 1,094 (94) | 674 (100) | 420 (86) | <0.001 |
| Dyslipidemia, *n* (%) | 992 (86) | 582 (86) | 410 (84) | 0.344 |
| Diabetes mellitus, *n* (%) | 365 (31) | 227 (34) | 138 (28) | 0.055 |
| Current smoker, *n* (%) | 197 (17) | 114 (17) | 83 (17) | 0.965 |
| Family history of premature CAD, *n* (%) | 309 (27) | 174 (26) | 135 (28) | 0.456 |
| Atrial fibrillation, *n* (%) | 126 (11) | 80 (12) | 46 (9) | 0.191 |
| Medication | | | | |
| ACE inhibitor, *n* (%) | 207 (18) | 207 (31) | 0 (0) | <0.001 |
| ARB, *n* (%) | 480 (41) | 480 (71) | 0 (0) | <0.001 |
| Statin, *n* (%) | 748 (64) | 456 (68) | 292 (60) | 0.008 |
| Aspirin, *n* (%) | 1,102 (96) | 637 (95) | 465 (97) | 0.043 |
| Calcium channel blocker, *n* (%) | 521 (45) | 329 (49) | 192 (40) | 0.002 |
| β-Blocker, *n* (%) | 602 (52) | 342 (51) | 260 (54) | 0.354 |
| MRA, *n* (%) | 89 (8) | 59 (9) | 30 (6) | 0.100 |
| Diuretics, *n* (%) | 186 (16) | 120 (18) | 66 (14) | 0.051 |
| Oral hypoglycemic agent, *n* (%) | 352 (30) | 221 (33) | 131 (27) | 0.032 |
| Insulin, *n* (%) | 73 (6) | 45 (7) | 28 (6) | 0.525 |
| Lesion characteristics | | | | |
| Lesion site | | | | |
| Right coronary artery, *n* (%) | 345 (30) | 202 (30) | 143 (30) | 0.841 |
| Left main coronary trunk, *n* (%) | 47 (4) | 24 (4) | 23 (5) | 0.321 |
| Left anterior descending artery, *n* (%) | 510 (44) | 307 (46) | 203 (42) | 0.200 |
| Left circumflex artery, *n* (%) | 229 (20) | 131 (19) | 98 (20) | 0.759 |
| Lesion classification | | | | 0.401 |
| Type A, *n* (%) | 68 (6) | 36 (5) | 32 (7) | |
| Type B1, *n* (%) | 166 (14) | 89 (13) | 77 (16) | |
| Type B2, *n* (%) | 339 (29) | 197 (29) | 142 (29) | |
| Type C, *n* (%) | 587 (51) | 352 (52) | 235 (48) | |

**Table 1** (continued)

| | Overall, *n* = 1,160 | RAS inhibitor group, *n* = 674 (58%) | Non-RAS inhibitor group, *n* = 486 (42%) | *p* value |
|---|---|---|---|---|
| CTO lesion, *n* (%) | 60 (6) | 30 (5) | 30 (6) | 0.239 |
| Multi vessel disease, *n* (%) | 717 (62) | 427 (64) | 290 (61) | 0.286 |
| Lesion length, mm | 17.5±8.7 | 18.2±8.9 | 16.6±8.4 | 0.005 |
| Lesion reference diameter, mm | 2.90±0.49 | 2.88±0.50 | 2.94±0.48 | 0.047 |
| Procedural characteristics | | | | |
| Use of BMS, *n* (%) | 419 (37) | 219 (34) | 200 (41) | 0.008 |
| Use of DES, *n* (%) | 605 (52) | 377 (56) | 228 (47) | 0.002 |
| Stent length, mm | 20.2±6.9 | 20.9±7.2 | 19.2±6.6 | <0.001 |
| Stent diameter, mm | 3.03±0.42 | 3.01±0.43 | 3.05±0.41 | 0.089 |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMS, bare metal stent; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CTO, chronic total occlusion; DES, drug-eluting stent; FBG, fasting blood glucose; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system.

*Clinical Outcomes*

The median follow-up duration was 7.8 [IQR: 3.7–12.4] years, and the prognostic data were fully documented during the entire follow-up period. During the follow-up, 280 patients (21.4%) developed 3P-MACE; there were 141 cardiovascular deaths, 98 nonfatal ACSs, and 71 nonfatal strokes. In addition, 134 patients (11.6%) developed HF, 171 patients (14.7%) underwent TVR, and 348 patients (30.0%) died of any cause.

Kaplan-Meier analysis showed that the cumulative incidence rate of 3P-MACE in the RAS inhibitor group was significantly lower than in the non-RAS inhibitor group (31.7% vs. 39.0%, log-rank test, $p = 0.034$; Fig. 2a). Regarding specific 3P-MACE, the cumulative incidence rate of cardiovascular death and nonfatal ACS in the RAS inhibitor group was significantly lower than in the non-RAS inhibitor group (16.4% vs. 24.5%, log-rank test, $p = 0.007$, and 9.0% vs. 14.9%, log-rank test, $p = 0.009$, respectively), but the Kaplan-Meier curves for nonfatal stroke between both groups were not significantly different (11.2% vs. 7.8%, log-rank test, $p = 0.178$) (data not shown). In addition, the cumulative incidence rate of admission for HF in the RAS inhibitor group was significantly higher than in the non-RAS inhibitor group by Kaplan-Meier analysis (28.1% vs. 13.3%, log-rank test, $p < 0.001$; Fig. 2b). However, the analysis showed that there was no significant difference between both groups for TVR (21.6% vs. 21.0%, log-rank test, $p = 0.979$; Fig. 2c) and all-cause death (42.6% vs. 43.8%, log-rank test, $p = 0.433$; Fig. 2d).

*Impacts of RAS Inhibitor on 3P-MACE and Admission for HF*

Tables 2–4 show results of multivariable Cox hazard analysis; average annual percent change in estimated GFR (5% decrease) (hazard ratio [HR], 1.18; 95% CIs: 1.10–1.26; $p < 0.001$), age (1-year increase) (HR: 1.03; 95% CIs: 1.01–1.05; $p < 0.001$), acute MI (HR: 1.72; 95% CIs: 1.21–2.46; $p = 0.003$), RAS inhibitor use (HR: 0.71; 95% CIs: 0.55–0.93; $p = 0.011$), statin use (HR: 0.72; 95% CIs: 0.56–0.93; $p = 0.011$), and presence of proteinuria (HR: 1.37; 95% CIs: 1.02–1.84; $p = 0.037$) were strong independent predictors of 3P-MACE (Table 2), whereas diuretics use (HR: 4.29; 95% CIs: 2.94–6.26; $p < 0.001$), age (1-year increase) (HR: 1.04; 95% CIs: 1.02–1.07; $p < 0.001$), presence of proteinuria (HR: 1.99; 95% CIs: 1.36–2.91; $p < 0.001$), reduced EF (HR: 2.78; 95% CIs: 1.61–4.81; $p < 0.001$), average annual percent change in estimated GFR (5% decrease) (HR: 1.19; 95% CIs: 1.08–1.30; $p = 0.002$), family history of premature CAD (HR: 1.65; 95% CIs: 1.14–2.40; $p = 0.009$), atrial fibrillation (HR: 1.73; 95% CIs: 1.08–2.77; $p = 0.023$), and RAS inhibitor use (HR: 1.59; 95% CIs: 1.07–1.37; $p = 0.023$) were strong independent predictors of admission for HF (Table 3).

Furthermore, Table 4 reveals the impacts of RAS inhibitors by multivariable Cox proportional hazard analysis after adjustment for various confounders; the RAS inhibitor group was significantly associated with a reduced risk of 3P-MACE (HR: 0.68; 95% CIs: 0.50–0.93;

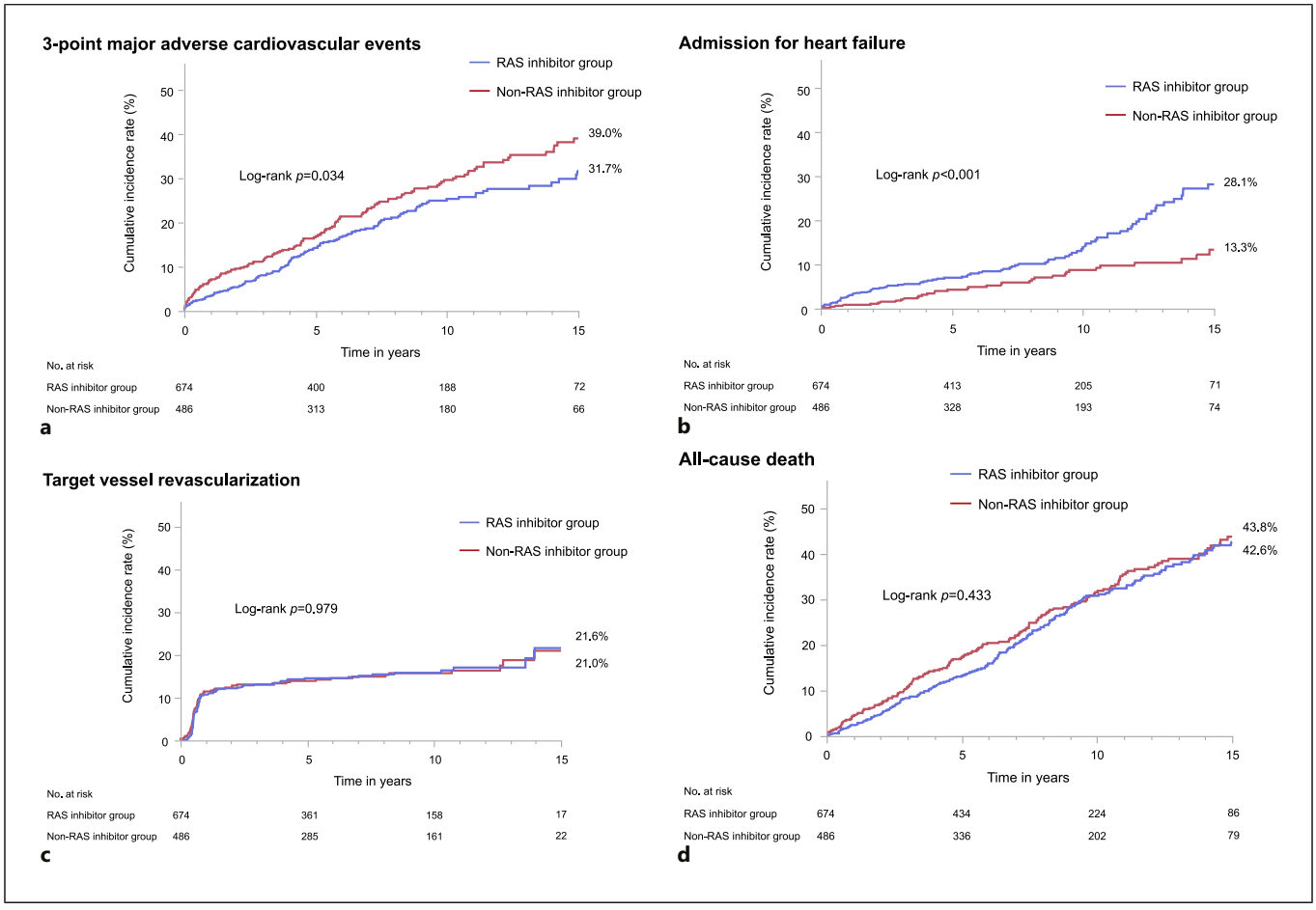


**Fig. 2.** Kaplan-Meier curves for endpoints between RAS inhibitor group and non-RAS inhibitor group. **a** Cumulative incidence of 3P-MACE. **b** Cumulative incidence of admission for HF. **c** Cumulative incidence of TVR. **d** Cumulative incidence of all-cause death. RAS, renin-angiotensin system.

$p = 0.014$) and an increased risk of admission for HF (HR: 1.68; 95% CIs: 1.05–2.67; $p = 0.029$), compared with the non-RAS inhibitor group.

*Subgroup Analysis for 3P-MACE and Admission for HF*

Figure 3 shows subgroup analysis of 3P-MACE and admission for HF, including age, EF, acute MI, diabetes mellitus, CKD stage, and presence of proteinuria. Lower risk for 3P-MACE in the RAS inhibitor use compared with non-RAS inhibitor use was observed in the elderly, impaired EF, acute MI, proteinuria, whereas higher risk for admission for HF in the RAS inhibitor use compared with non-RAS inhibitor use was observed across strata of age and diabetes mellitus, and in preserved EF, non-acute MI, mild renal impairment, non-proteinuria.

## Discussion

The major findings of this study are as follows: (1) RAS inhibitor group had a significantly lower incidence of adverse cardiovascular events and a significantly higher incidence of hospitalization for HF, compared to the non-RAS inhibitor group in patients with CKD and coexisting CAD; (2) even after adjustments for pertinent covariates, long-term oral administration of RAS inhibitors was an independent predictor of a reduced risk of 3P-MACE and an increased risk of admission for HF; and finally, (3) patients with preserved EF, and without acute MI and proteinuria tended to promote the onset of HF rather than cardiovascular prevention by RAS inhibitors.

CKD is widely known to be a strong risk factor for cardiovascular disease including HF, and decreased

**Table 2.** Cox proportional hazard regression analysis for prediction of 3P-MACE

| Covariate | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CIs) | *p* value | HR (95% CIs) | *p* value |
| Average annual percent change in estimated GFR, 5% decrease | 1.21 (1.13–1.29) | <0.001 | 1.18 (1.10–1.26) | <0.001 |
| Age, 1-year increase | 1.03 (1.02–1.05) | <0.001 | 1.03 (1.01–1.05) | <0.001 |
| Acute MI | 1.91 (1.39–2.63) | <0.001 | 1.72 (1.21–2.46) | 0.003 |
| RAS inhibitor use | 0.77 (0.61–0.98) | 0.035 | 0.71 (0.55–0.93) | 0.011 |
| Statin use | 0.67 (0.53–0.86) | 0.001 | 0.72 (0.56–0.93) | 0.011 |
| Presence of proteinuria | 1.70 (1.31–2.21) | <0.001 | 1.37 (1.02–1.84) | 0.037 |
| Reduced EF | 2.49 (1.70–3.65) | <0.001 | | |
| Baseline estimated GFR <45 mL/min/1.73 $m^2$ | 1.68 (1.27–2.22) | <0.001 | | |
| Anemia | 1.58 (1.21–2.06) | <0.001 | | |
| Body mass index, 1 kg/$m^2$ increase | 0.95 (0.91–0.98) | 0.004 | | |
| Multi vessel disease | 1.44 (1.11–1.87) | 0.006 | | |
| Atrial fibrillation | 1.62 (1.14–2.30) | 0.008 | | |
| Diabetes mellitus | 1.29 (1.00–1.66) | 0.046 | | |

Average percent change in estimated GFR = (Follow-up − Baseline estimated GFR)/Baseline estimated GFR. Average annual percent change in estimated GFR = Average percent change in estimated GFR/Follow-up years (up to 5 years). 3P-MACE, 3-point major adverse cardiovascular events; CIs, confidence intervals; GFR, glomerular filtration rate; HR, hazard ratio; RAS, renin-angiotensin system.

**Table 3.** Cox proportional hazard regression analysis for prediction of admission for HF

| Covariate | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CIs) | *p* value | HR (95% CIs) | *p* value |
| Diuretics use | 6.21 (4.35–8.87) | <0.001 | 4.29 (2.94–6.26) | <0.001 |
| Age, 1-year increase | 1.05 (1.03–1.07) | <0.001 | 1.04 (1.02–1.07) | <0.001 |
| Presence of proteinuria | 2.37 (1.63–3.44) | <0.001 | 1.99 (1.36–2.91) | <0.001 |
| Reduced EF | 5.41 (3.36–8.72) | <0.001 | 2.78 (1.61–4.81) | <0.001 |
| Average annual percent change in estimated GFR, 5% decrease | 1.30 (1.21–1.39) | <0.001 | 1.19 (1.08–1.30) | 0.002 |
| Family history of premature CAD | 1.46 (1.01–2.11) | 0.044 | 1.65 (1.14–2.40) | 0.009 |
| Atrial fibrillation | 2.95 (1.90–4.59) | <0.001 | 1.73 (1.08–2.77) | 0.023 |
| RAS inhibitor use | 2.07 (1.40–3.07) | <0.001 | 1.59 (1.07–2.37) | 0.023 |
| Male | 0.46 (0.31–0.67) | <0.001 | | |
| Baseline estimated GFR <45 mL/min/1.73 $m^2$ | 2.11 (1.41–3.15) | <0.001 | | |
| Anemia | 1.80 (1.22–2.65) | 0.003 | | |
| Diabetes mellitus | 1.57 (1.10–2.26) | 0.014 | | |

Average percent change in estimated GFR = (Follow-up − Baseline estimated GFR)/Baseline estimated GFR. Average annual percent change in estimated GFR = Average percent change in estimated GFR/Follow-up years (up to 5 years). CAD, coronary artery disease; CIs, confidence intervals; GFR, glomerular filtration rate; HR, hazard ratio; RAS, renin-angiotensin system.

GFR and proteinuria have been reported as risk factors for cardiovascular disease through independent mechanism [26, 27]. Few studies have considered the presence of proteinuria and decrease of GFR in patients with CKD and coexisting CAD; thus, this study mentions the effects of RAS inhibitors on onset of cardiovascular events and HF, and the relationship between RAS inhibitors, and estimated GFR and proteinuria, based on the nephrological findings. A report on the association between CKD progression based on the estimated GFR slope per year and the risk of cardiovascular disease has shown that a greater decline in estimated GFR slope was strongly associated with an increase in cardiovascular events, including

**Table 4.** Impacts of RAS inhibitor on 3P-MACE and admission for HF

| | 3P-MACE | | Admission for HF | |
|---|---|---|---|---|
| | HR (95% CIs) | *p* value | HR (95% CIs) | *p* value |
| RAS inhibitor group versus non-RAS inhibitor group | | | | |
| Model 1 | 0.76 (0.60–0.97) | 0.027 | 1.90 (1.28–2.82) | 0.001 |
| Model 2 | 0.76 (0.59–0.97) | 0.027 | 1.82 (1.22–2.72) | 0.003 |
| Model 3 | 0.68 (0.50–0.93) | 0.014 | 1.68 (1.05–2.67) | 0.029 |

RAS inhibitor group ($n$ = 673). Non-RAS inhibitor group ($n$ = 487). Model 1 was adjusted for age, sex, and BMI. Model 2 was adjusted for age, sex, BMI, systolic BP, β-blocker use, CCB use, diabetes mellitus, statin use, current smoker, family history of premature CAD, and baseline estimated GFR <45 mL/min/1.73 $m^2$. Model 3 was adjusted for age, sex, BMI, systolic BP, β-blocker use, CCB use, diabetes mellitus, statin use, current smoker, family history of premature CAD, baseline estimated GFR <45 mL/min/1.73 $m^2$, presence of proteinuria, average annual percent change in estimated GFR, reduced EF, AMI, aspirin use, diuretics use, MVD, AF, and anemia. Average percent change in estimated GFR = (Follow-up − Baseline estimated GFR)/Baseline estimated GFR. Average annual percent change in estimated GFR = Average percent change in estimated GFR/Follow-up years (up to 5 years). 3P-MACE, 3-point major adverse cardiovascular events; AF, atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CIs, confidence intervals; EF, ejection fraction; GFR, glomerular filtration rate; HR, hazard ratio; MVD, multi vessel disease; RAS, renin-angiotensin system.

hospitalization for HF and developing MI [28]. Our study evaluated estimated GFR at baseline and after one, three, and five years, respectively. The baseline estimated GFR did not differ between the both groups (54.0 [IQR: 47.5–57.7] mL/min/1.73 $m^2$ vs. 55.0 [IQR: 48.2–58.0] mL/min/1.73 $m^2$, $p$ = 0.128); however, the estimated GFR in the RAS inhibitor group was significantly lower than in the non-RAS inhibitor group after 5 years (46.1 [IQR: 35.0–53.7] mL/min/1.73 $m^2$ vs. 49.9 [IQR: 40.8–56.9] mL/min/1.73 $m^2$, $p$ < 0.001) (Fig. 4). In addition, there was already a significant difference in average percent change in estimated GFR 1 year later, and this difference gradually widened. On multivariable Cox hazard analysis, average annual percent change in estimated GFR was shown as an independent predictor of 3P-MACE and admission for HF.

Considering the long-term progression of renal dysfunction, we feared that RAS inhibitors might increase CAD recurrence, stroke development, and hospitalization for HF. However, the RAS inhibitor group was significantly associated with a reduced risk of 3P-MACE, compared with the non-RAS inhibitor group. Other studies have also reported on this paradoxical relationship between renal dysfunction exacerbation and cardiovascular events [12, 29]. RAS inhibitors have actions that enhance the nitric oxide concentration, decrease oxidants/antioxidant imbalance, and inhibit RAS-induced inflammation. These biochemical alterations eventually improve the endothelium activities and vascular system pathophysiology in atherosclerosis [30]. Furthermore, several studies have shown vascular benefits beyond antihypertensive action which was most important in renal dysfunction, and the preventive effects of RAS inhibitor beyond exacerbation factor for cardiovascular events could be explained [31, 32].

There are several possible reasons why hospitalization for HF correlated with oral administration of RAS inhibitors. A previous study included patients with estimated GFR between 30 and 59 mL/min/1.73 $m^2$ demonstrated that the accelerated progression of renal dysfunction within 2 years affected approximately 1 in 4 patients with diabetes and 1 in 7 without diabetes, and hospitalization for HF significantly strongly correlates with the CKD progression [33]. In our study, estimated GFR in the RAS inhibitor group decreased more over time than in the non-RAS inhibitor group. Furthermore, more patients taking RAS inhibitors were hospitalized for HF than patients not taking RAS inhibitors. This difference in hospitalization for HF between the both groups gradually widened over time (shown in Fig. 2b), perhaps partly due to the long-term progression of renal dysfunction [31, 33].

In addition, this study evaluated the subgroup analysis; CKD patients with proteinuria could benefit from prevention of adverse cardiovascular events by RAS

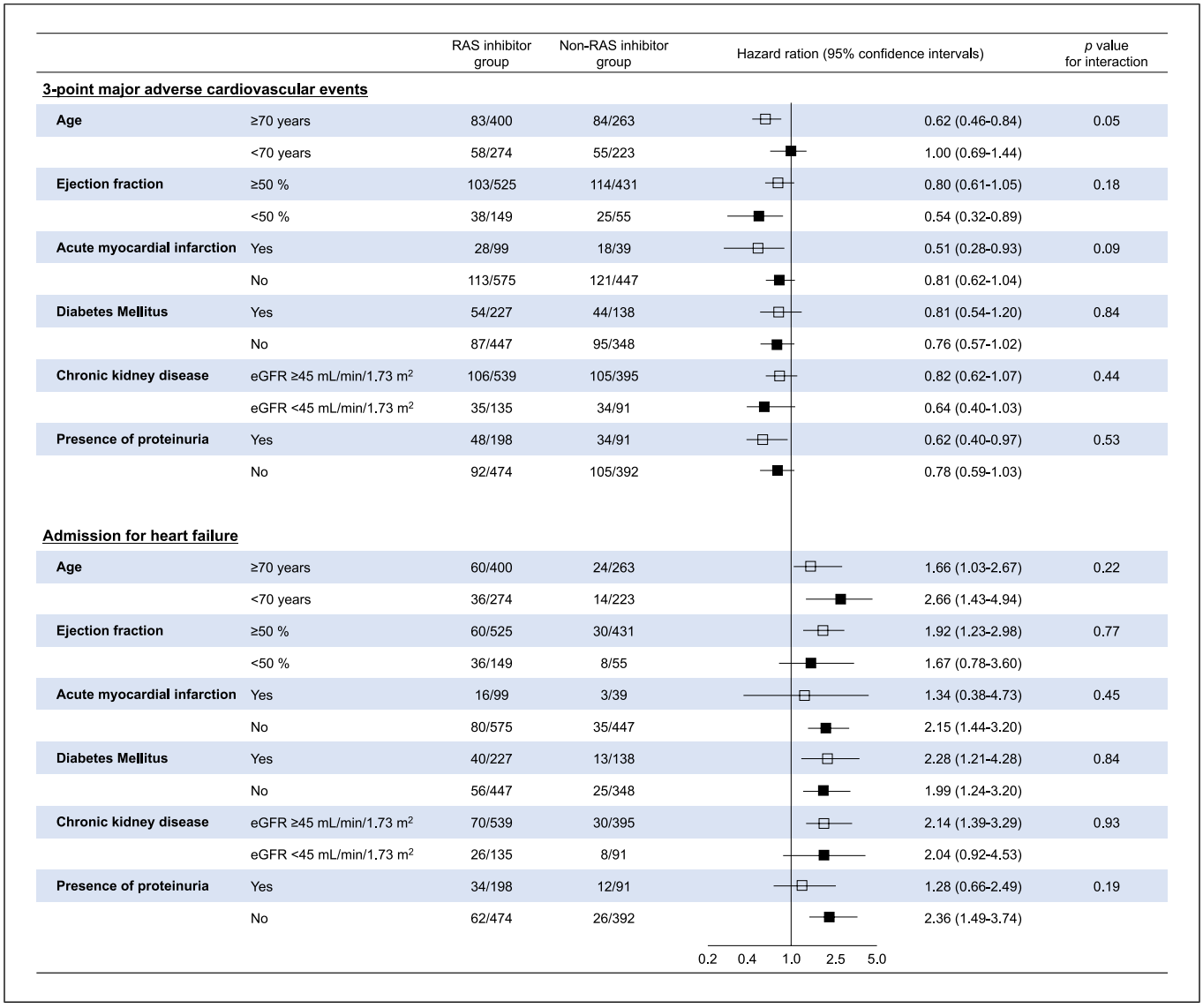


**Fig. 3.** Subgroup analysis of 3P-MACE and admission for HF. Number of events/patients, HR for 3P-MACE, and admission for HF compared between the RAS inhibitor group and the non-RAS inhibitor group, according to subgroups of age, EF, acute MI, CKD, and presence of proteinuria. GFR, glomerular filtration rate; RAS, renin-angiotensin system.

inhibitors; however, CKD patients without proteinuria might have risk of admission for HF by RAS inhibitors. It has been reported that RAS inhibitors are effective at reducing proteinuria, and reduction in proteinuria is associated with a reduction in rate of progression of kidney disease [34–36]. In this study, a significant difference in estimated GFR was observed between the both groups after 1 year in patients without proteinuria, but there was no significant difference in estimated GFR between the both groups even after 5 years in patients with proteinuria, suggesting that RAS inhibitors had an inhibitory effect on proteinuria. Also, the subgroup of preserved EF and non-acute MI tended to promote the onset of HF rather than cardiovascular prevention by RAS inhibitors, whereas it has been established that RAS inhibitors suppressed hospitalization for HF and improved prognosis for patients with left ventricular dysfunction and MI [37, 38]. Thus, we should pay close attention to prescription of RAS inhibitors for patients with CKD who underwent PCI, after considering the risk

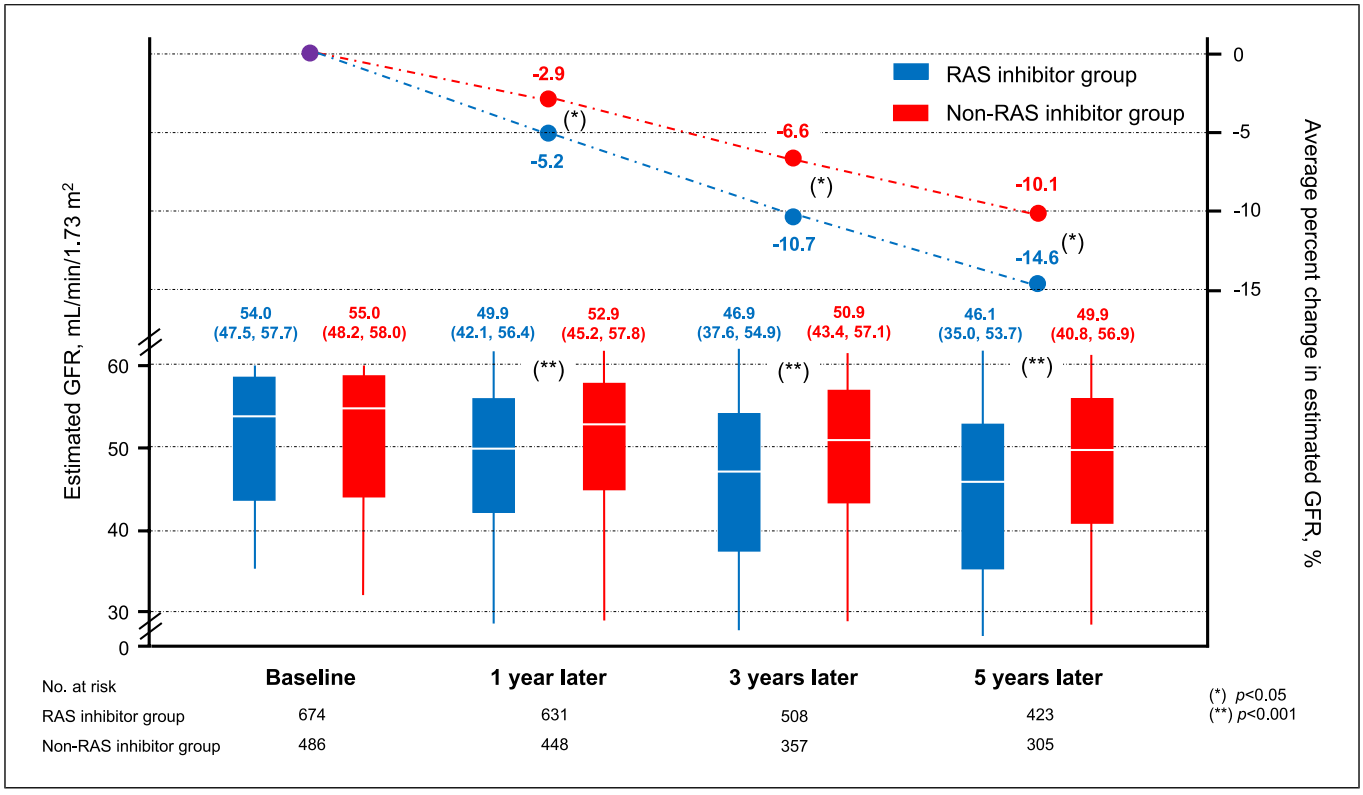


**Fig. 4.** Long-term trends in estimated GFR between the RAS inhibitor group and the non-RAS inhibitor group. There was no significant difference for estimated GFR between the RAS inhibitor group and the non-RAS inhibitor group at the baseline (54.0 [47.5–57.7] mL/min/1.73 $m^2$ vs. 55.0 [48.2–58.0] mL/min/1.73 $m^2$, $p = 0.128$). The slope of decreased estimated GFR in the RAS inhibitor group was greater than that in the non-RAS inhibitor group, and the average percent change in estimated GFR was −14.6% in the RAS inhibitor group and −10.1% in the non-RAS inhibitor group after 5 years, showing a significant difference. GFR, glomerular filtration rate; RAS, renin-angiotensin system.

of HF involved in renal dysfunction exacerbation, especially in patients with preserved EF and without acute MI and proteinuria.

This study had several limitations that require consideration. First, this was a single-center, retrospective, observational study, and unknown confounding factors might have affected the outcomes, regardless of the analytical adjustments. Also, the relatively small number of enrolled patients limited the statistical power of the study. Second, this study included only patients in their own country. Thus, the RAS inhibitor dose used in other countries may differ. Third, because of retrospective research, this study could not follow up on changes in estimated GFR over time for all enrolled patients. In addition, there was no agreement regarding the new addition of RAS inhibitor for hypertension due to retrospective research; thus, it was left to the discretion of each attending physician. Fourth, although proteinuria was consistently tested in this study, albuminuria could not be evaluated in CKD with diabetes mellitus.

In conclusion, the long-term RAS inhibitor use was significantly associated with a reduced risk of adverse cardiovascular events but an increased risk of hospitalization for HF in patients with CKD after PCI. In addition, RAS inhibitors might be more harmful than beneficial for patients with preserved EF, and without acute MI and proteinuria. Thus, we should perform personalized evaluations to weigh the protective effect on the cardiovascular system versus the potential risk to the kidneys rather than uniformly starting or continuing RAS inhibitors for patients with CKD after PCI.

## Acknowledgments

The authors are grateful to the staff of the Department of Cardiovascular Medicine at Juntendo University. The authors also appreciate the secretarial assistance of Ms. Yumi Nozawa.

## Statement of Ethics

The Ethics Committee of Juntendo Clinical Research and Trial Center approved this study (reference number 17-0206), and this study was conducted in accordance with the Declaration of Helsinki. A written informed consent to participate was obtained from all patients.

## Conflict of Interest Statement

The authors declare no conflicts of interest.


## Funding Sources

The authors declare no funding sources.


## Author Contributions

Analysis: T. Fukase; concept and design: T. Fukase and T. Dohi; interpretation of the data: T. Fukase, T. Dohi, R. Nishio, M. Takeuchi, N. Takahashi, Y. Chikata, H. Endo, S. Doi, H Nishiyama, I. Okai, H. Iwata, S. Okazaki, K. Miyauchi, H. Daida, and T. Minamino; drafting of the manuscript: T. Fukase; clinical data acquisition: T. Fukase, R. Nishio, M. Takeuchi, N. Takahashi, Y. Chikata, H. Endo, and S. Doi; writing – editing: T. Fukase and T. Dohi; writing – review and editing: T. Minamino; and supervision: T. Dohi and T. Minamino.

## Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

## References


1 Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens. 2007;21(1):20–7.
2 Robles NR, Cerezo I, Hernandez-Gallego R. Renin-angiotensin system blocking drugs. J Cardiovasc Pharmacol Ther. 2014;19(1):14–33.
3 Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669–77.
4 SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293–302.
5 Japanese Society of Nephrology. Essential points from evidence-based clinical practice guidelines for chronic kidney disease 2018. Clin Exp Nephrol. 2019;23:1–15.
6 Ahuja TS, Freeman D Jr, Mahnken JD, Agraharkar M, Siddiqui M, Memon A. Predictors of the development of hyperkalemia in patients using angiotensin-converting enzyme inhibitors. Am J Nephrol. 2000;20(4):268–72.
7 Schmidt M, Mansfield KE, Bhaskaran K, Nitsch D, Sørensen HT, Smeeth L, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. BMJ. 2017;356:j791.
8 Naveed H, Tirumandyam G, Krishna Mohan GV, Gul S, Ali S, Siddiqui A, et al. Effect of discontinuation of renin angiotensin-system inhibitors in patients with advanced chronic kidney disease: a meta-analysis. Cureus. 2023;15(4):e37813.
9 Nakayama T, Mitsuno R, Azegami T, Sato Y, Hayashi K, Itoh H. A systematic review and meta-analysis of the clinical impact of stopping renin-angiotensin system inhibitor in patients with chronic kidney disease. Hypertens Res. 2023;46(6):1525–35.
10 Yang A, Shi M, Lau ESH, Wu H, Zhang X, Fan B, et al. Clinical outcomes following discontinuation of renin-angiotensin-system inhibitors in patients with type 2 diabetes and advanced chronic kidney disease: a prospective cohort study. EClinicalMedicine. 2023;55:101751.
11 Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. N Engl J Med. 2022;387(22):2021–32.
12 Fu EL, Evans M, Clase CM, Tomlinson LA, van Diepen M, Dekker FW, et al. Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study. J Am Soc Nephrol. 2021;32(2):424–35.
13 Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.
14 Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology foundation/American heart association task force on practice guidelines, and the American College of physicians, American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. J Am Coll Cardiol. 2012;60(24):e44–164.
15 Rickham PP. Human experimentation. Code of ethics of the world medical association. Declaration of helsinki. Br Med J. 1964;2(5402):177.
16 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982–92.
17 Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res. 2019;42(9):1235–481.
18 Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan atherosclerosis society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb. 2018;25(9):846–984.
19 International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32(7):1327–34.
20 Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968;405:5–37.
21 Scheuner MT, Whitworth WC, McGruder H, Yoon PW, Khoury MJ. Familial risk assessment for early-onset coronary heart disease. Genet Med. 2006;8:525–31.
22 Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB 3rd, Loop FD, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American heart association task force on assessment of diagnostic and therapeutic cardiovascular procedures (subcommittee on percutaneous transluminal coronary angioplasty). Circulation. 1988;78(2):486–502.

23 Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Eur Heart J. 2018;39(23):2192–207.
24 Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137(9):961–72.
25 Lansky AJ, Messé SR, Brickman AM, Dwyer M, Bart van der Worp H, Lazar RM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an academic research Consortium initiative. Eur Heart J. 2018;39(19):1687–97.
26 Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. PLoS Med. 2007;4(9):e270.
27 Perkovic V, Verdon C, Ninomiya T, Barzi F, Cass A, Patel A, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Med. 2008;5(10):e207.
28 Cabrera CS, Lee AS, Olsson M, Schnecke V, Westman K, Lind M, et al. Impact of CKD progression on cardiovascular disease risk in a contemporary UK cohort of individuals with diabetes. Kidney Int Rep. 2020;5(10):1651–60.
29 Qiao Y, Shin JI, Chen TK, Inker LA, Coresh J, Alexander GC, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med. 2020;180(5):718–26.
30 Husain K, Hernandez W, Ansari RA, Ferder L. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. World J Biol Chem. 2015;6(3):209–17.
31 Hirohata A, Yamamoto K, Miyoshi T, Hatanaka K, Hirohata S, Yamawaki H, et al. Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. J Am Coll Cardiol. 2010;55(10):976–82.
32 Smith RD, Yokoyama H, Averill DB, Schiffrin EL, Ferrario CM. Reversal of vascular hypertrophy in hypertensive patients through blockade of angiotensin II receptors. J Am Soc Hypertens. 2008;2(3):165–72.
33 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
34 Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in progressive renal insufficiency study group. N Engl J Med. 1996;334(15):939–45.
35 Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870–8.
36 Bakris GL. Slowing nephropathy progression: focus on proteinuria reduction. Clin J Am Soc Nephrol. 2008;3(Suppl 1):S3–10.
37 Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362(9386):772–6.
38 Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893–906.