

Elevated resting heart rate is associated with mortality in patients with chronic kidney disease

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Abstract

Background

A higher heart rate is recognized as an independent risk factor for all-cause mortality and cardiovascular events in the general population. However, the association between elevated heart rate and clinical adverse outcomes in patients with non-dialysis-dependent chronic kidney disease (CKD) has not been sufficiently investigated.

Methods

A total of 1,353 participants enrolled in the Fukushima CKD Cohort Study were examined to investigate associations between resting heart rate and clinical adverse outcomes using Cox proportional hazards analysis. The primary outcome of the present study was all-cause mortality, with cardiovascular events as the secondary outcome. Participants were stratified into four groups based on resting heart rate levels at baseline (heart rate < 70/min, ≥ 70 and < 80/min, ≥ 80 and < 90/min, and ≥ 90 /min).

Results

During the median observation period of 4.9 years, 123 participants died, and 163 cardiovascular events occurred. Compared with the reference level heart rate < 70/min group, the adjusted hazard ratios (HRs) for all-cause mortality were 1.74 (1.05–2.89) and 2.61 (1.59–4.29) for the heart rate ≥ 80 and < 90/min group and heart rate ≥ 90 /min group, respectively. A significantly higher risk of cardiovascular events was observed in the heart rate ≥ 80 /min and < 90/min group (adjusted HR 1.70, 1.10–2.62), but not in the heart rate ≥ 90 /min group (adjusted HR 1.45, 0.90–2.34).

Conclusion

In patients with non-dialysis-dependent CKD, a higher resting heart rate was associated with increased all-cause mortality.

INTRODUCTION

An elevated resting heart rate has been identified as an independent risk factor for cardiovascular events and mortality. Notable studies, such as the Framingham Heart Study¹, demonstrated that an increased resting heart rate is associated with an elevated risk of cardiovascular events and all-cause mortality across diverse populations.

Several prospective studies have examined the association between resting heart rate and all-cause mortality^{1–5}. This association is not limited to cardiovascular mortality, but extends to deaths from

various causes⁶.

However, specifically in patients with chronic kidney disease (CKD), there has been insufficient exploration of the correlation between heart rate and mortality. Beddhu et al. reported that a higher resting heart rate is associated with increased mortality in CKD⁷ in a study with a limited number of participants, but more investigation to elucidate the association of heart rate with adverse outcomes in patients with CKD is needed. Therefore, in the present study, the association of resting heart rate with adverse outcomes, such as all-cause mortality and cardiovascular events, was investigated in patients with non-dialysis-dependent CKD using longitudinal data from the Fukushima CKD Cohort Study.

MATERIALS AND METHODS

Study Population

The Fukushima CKD Cohort study, a sub-cohort of the Fukushima Cohort study⁸⁻¹³, is a prospective survey of patient characteristics and outcomes for participants with non-dialysis-dependent CKD being followed at the Fukushima Medical University Hospital (Fukushima Prefecture, northeastern area of Japan). A total of 2,724 patients were enrolled in the Fukushima Cohort study, of whom patients with CKD were included for the Fukushima CKD Cohort study. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) UMIN000040848. Patient enrollment was conducted between June 2012 and July 2014. The inclusion criteria were as follows: (1) Japanese patient living in Japan; (2) aged 18 years or older; and (3) CKD according to the definition of an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² or proteinuria (positive dipstick results ≥ 1+), with stable renal function for at least three months before entry into the study. The exclusion criteria were as follows: (1) undergoing renal replacement therapy in the last three months; (2) active malignancy; (3) infectious disease; (4) pregnancy; and (5) history of organ transplantation. Patients who had missing data for serum creatinine and heart rate were also excluded. All patients were under the care of nephrology or diabetology specialists. The protocol was approved by the Ethics Committee of Fukushima Medical University (approval no. 2001), and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent.

Data Collection

Information regarding demographics, comorbidities, and medications at baseline was obtained from the patients' medical records or blood examination results at registration. The body mass index was calculated as weight (kg) divided by height squared (m²). Clinic blood pressures and resting heart rates were measured by trained staff using a standard sphygmomanometer or an automated device with the patient in a sitting position after 5 min of rest. Hypertension was defined as follows: (1) systolic blood pressure ≥ 140 mmHg; or (2) diastolic blood pressure ≥ 90 mmHg; or (3) the use of antihypertensive medication. Diabetes mellitus was identified as follows: (1) fasting plasma glucose concentration ≥ 126 mg/dL; (2) hemoglobin A1c value (National Glycohemoglobin Standardization Program) ≥ 6.5%; or (3)

use of insulin or oral antihyperglycemic drugs. Dyslipidemia was defined as follows: (1) triglycerides \geq 150 mg/dL; (2) low-density lipoprotein cholesterol concentration \geq 140 mg/dL; (3) high-density lipoprotein cholesterol concentration $<$ 40 mg/dL; or (4) use of antihyperlipidemic medications.

Exposure and Outcomes

The primary exposure of interest for this study was resting heart rate. The study cohort was stratified into four groups by heart rate levels (heart rate $<$ 70/min, \geq 70 and $<$ 80/min, \geq 80 and $<$ 90/min, and \geq 90/min). Patients were followed until study withdrawal, loss to follow-up (i.e., transferred to other medical institutions, started maintenance renal replacement therapy, or death), or the end-of-study date (June 30, 2019). The primary outcome was all-cause mortality, and cardiovascular events were also measured as secondary outcomes. The cardiovascular events included fatal or nonfatal myocardial infarction, angina pectoris, sudden death, congestive or acute heart failure, arrhythmias, cerebrovascular disorder, chronic arteriosclerosis obliterans, and aortic disease. Information on cardiovascular events was captured from the medical records by attending physicians.

Statistical Analyses

Categorical variables are expressed as percentages, and continuous variables are presented as median and interquartile range values. Values were compared using the Kruskal-Wallis test, nonparametric trend tests (Cuzick's test), one-way analysis of variance (ANOVA), or Fisher's exact test, as appropriate. Multiple imputation using chained equations with 20 datasets was used to complement the missing data after logarithmic transformation if the continuous variables did not follow the normal distribution. A Cox proportional hazards model analysis was used to examine the associations between heart rate and incidences of all-cause mortality and cardiovascular events. An unadjusted model and three adjusted models were created to adjust for covariates. Model 1 was the unadjusted model, Model 2 included age and sex, Model 3 included Model 2 plus body mass index, smoking history, and comorbidities (diabetes mellitus, history of cardiovascular disease), and eGFR, and Model 4 included Model 3 plus systolic blood pressure, serum albumin, hemoglobin, proteinuria (dipstick), use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs), and use of β -blockers. To evaluate non-linear associations between heart rate and each clinical outcome, restricted cubic splines (Model 4-adjusted) with four knots were used. Subgroup analyses were also performed as sensitivity analyses of the primary and secondary outcomes. All analyses were conducted using STATA MP, version 16.1 (Stata Corp., College Station, TX).

RESULTS

Patients' Characteristics

In the primary analysis, there were missing data for 3.3%, 5.5%, 3.1%, 2.7%, 1.7%, 35.1%, 10.4%, and 2.0% of patients for body mass index, smoking history, history of dyslipidemia, hyperuricemia, proteinuria (dipstick), proteinuria (g/gCr), serum albumin, and hemoglobin, respectively. According to the inclusion

and exclusion criteria, a total of 1,353 subjects were enrolled in the present analyses of the 2,724 subjects of the Fukushima Cohort study (Fig. 1). Baseline characteristics stratified by the resting heart rate level are shown in Table 1. The median age was 65 years, 56.7% were male, and the median eGFR was 52.2 mL/min/1.73 m². The median heart rate was 76/min, and female and diabetes mellitus were more frequent in subjects with higher heart rates. β -blockers were used in many subjects with heart rate < 70/min and the \geq 90/min group.

Table 1
Patients' baseline characteristics stratified by resting heart rate levels.

Variables (Missing data)	All patients	Heart rate (/min)				P value
		< 70	70 ≤ and < 80	80 ≤ and < 90	90 ≤	
N	1353	442	380	301	230	
Age (years) (0)	65 [56–75]	66 [59–74]	64 [56–75]	66 [55–76]	65 [52–74]	0.31
Male sex (%) (0)	56.7	66.5	52.9	50.8	51.7	< 0.001
Body mass index (kg/m ²) (45)	24.2 [21.8–27.1]	24.3 [21.8–26.6]	24.0 [21.7–27.1]	24.5 [21.7–27.5]	24.6 [22.0–28.0]	0.19
Smoking history (%) (79)	49.7	54.5	45.3	47.2	50.9	0.02
History of cardiovascular disease (%) (0)	12.1	12.2	11.8	11.3	13.0	0.94
Diabetes (%) (0)	48.1	38.9	45.0	56.5	60.0	< 0.001
Hypertension (%) (0)	84.9	87.6	85.5	79.1	86.1	0.02
Dyslipidemia (%) (42)	66.2	62.7	66.6	67.4	70.4	0.05
Hyperuricemia (%) (36)	46.3	51.8	42.6	43.5	45.2	0.11
Systolic blood pressure (mmHg) (0)	130 [119–143]	130 [119–143]	130 [119–143]	132 [120–144]	133 [120–144]	0.52
Diastolic blood pressure (mmHg) (0)	76 [68–83]	74 [67–81]	77 [69–84]	76 [67–84]	77 [69–87]	< 0.001
Heart rate (/min) (0)	76 [67–85]	63 [59–67]	75 [72–77]	84 [81–86]	96 [92–102]	< 0.001
Estimated GFR (mL/min/1.73m ²) (0)	52.2 [38.0–63.8]	51.3 [36.3–62.3]	52.0 [40.2–63.7]	53.0 [36.7–68.5]	51.4 [39.4–66.7]	0.43
Proteinuria (dipstick) (%) (23)						0.23
(-)	32.8	36.4	36.3	27.2	27.4	
(1+)	27.6	25.6	26.1	29.6	31.7	

Values are expressed as medians [interquartile range] or percentages, as appropriate. GFR, glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Variables (Missing data)	All patients	Heart rate (/min)				P value
		< 70	70 ≤ and < 80	80 ≤ and < 90	90 ≤	
(2+)	20.6	21.2	19.5	20.6	20.9	
(3+)	11.7	11.1	11.1	13.0	12.2	
(4+)	5.6	4.5	5.0	7.0	7.0	
Proteinuria (g/gCr) (475)	0.19 [0.03–0.74]	0.16 [0–0.63]	0.19 [0–0.61]	0.25 [0.05–0.84]	0.19 [0.07–0.83]	0.07
Serum albumin (g/dL) (141)	4.0 [3.7–4.2]	4.0 [3.7–4.2]	4.0 [3.7–4.2]	3.9 [3.6–4.2]	4.0 [3.7–4.2]	0.47
Hemoglobin (g/dL) (27)	12.9 [11.7–14.1]	13.1 [11.8–14.2]	13.0 [11.8–14.0]	12.7 [11.3–14.1]	13.0 [11.8–14.2]	0.55
ACEi or ARB use (%) (0)	67.7	71.3	66.1	65.1	67.0	0.26
Calcium channel blocker (0)	51.5	49.1	50.3	51.2	58.7	0.11
β-blocker (0)	15.3	19.2	12.9	11.0	17.4	0.007
Statin (0)	45.8	42.3	45.0	47.8	50.9	0.16
Xanthin oxidase inhibitor (0)	30.6	35.5	28.4	26.9	29.6	0.05
Aspirin (0)	16.0	17.2	14.5	17.6	13.9	0.48
Warfarin (0)	8.1	7.9	7.6	8.0	9.1	0.93

Values are expressed as medians [interquartile range] or percentages, as appropriate. GFR, glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Association between resting heart rate and all-cause mortality

During the median observation period of 4.9 years, 123 of the 1,353 subjects died. The causes of death were: malignancy (n = 42), cardiovascular disease (n = 22), sepsis (n = 18), unknown (n = 15), and others (n = 26). Cox regression analyses showed that the heart rate ≥ 90/min group was at significantly higher risk for all-cause mortality, and this was significant after adjustment for covariates (Table 2). In model 4, the heart rate ≥ 80/min and < 90/min group was also at significantly higher risk for all-cause mortality, and the adjusted hazard ratios (HRs) were 1.74 (95% confidence interval, 1.05 to 2.89) and 2.61 (1.59 to 4.29) for the heart rate ≥ 80/min and < 90/min group and the heart rate ≥ 90/min group, respectively,

compared with the reference heart rate < 70/min group. Using restricted cubic spline functions, there was a U-curve relationship between resting heart rate and the risk of all-cause mortality (Fig. 2A).

Table 2
Association between resting heart rate and all-cause mortality, and cardiovascular events.

Outcomes	Heart rate (/min)	Incident rate (/1000 person-years)	Hazard ratios (95% Confidence interval)			
			Model 1	Model 2	Model 3	Model 4
All-cause mortality	< 70	14.9	<i>Reference</i>			
	70 ≤ and < 80	14.1	0.94 (0.57–1.56)	1.08 (0.65–1.79)	1.06 (0.64–1.78)	1.07 (0.64–1.80)
	80 ≤ and < 90	20.9	1.40 (0.86–2.29)	1.62 (0.99–2.66)	1.60 (0.97–2.64)	1.74 (1.05–2.89)
	90 ≤	30.6	2.05 (1.26–3.32)	2.46 (1.51–4.01)	2.40 (1.47–3.93)	2.61 (1.59–4.29)
Cardiovascular events	< 70	22.7	<i>Reference</i>			
	70 ≤ and < 80	25.8	1.13 (0.76–1.69)	1.30 (0.87–1.94)	1.33 (0.89–2.00)	1.47 (0.98–2.20)
	80 ≤ and < 90	28.5	1.26 (0.82–1.91)	1.49 (0.98–2.28)	1.45 (0.94–2.22)	1.70 (1.10–2.62)
	90 ≤	26.9	1.19 (0.74–1.90)	1.44 (0.89–2.31)	1.43 (0.89–2.31)	1.45 (0.90–2.34)
Model 1 unadjusted; Model 2 adjusted for age and sex; Model 3 Model 2 plus body mass index, smoking history, diabetes, history of cardiovascular disease, and eGFR; Model 4 Model 3 plus systolic blood pressure, serum albumin, hemoglobin, proteinuria, use of ACEis or ARBs and use of β-blockers. eGFR, estimated glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.						

Association between resting heart rate and cardiovascular events

During the follow-up period, 163 of the 1,353 subjects developed cardiovascular events. Details of these events were: heart failure (n = 64), cerebral infarction (n = 18), angina pectoris (n = 16), arrhythmia (n = 16), myocardial infarction (n = 15), cerebral hemorrhage (n = 15), aortic disease (n = 6), arteriosclerosis

obliterans (n = 3), sudden death (n = 2), and others (n = 8). Cox regression analyses showed that patients with a higher heart rate were at higher risk for cardiovascular events, but only those with heart rate \geq 80/min and $<$ 90/min showed a significantly higher risk for cardiovascular events in Model 4, compared with the reference $<$ 70/min group (Table 2). The adjusted HR was 1.70 (95% CI, 1.10 to 2.62). A significantly higher risk of cardiovascular events was not observed in the heart rate \geq 90/min group (adjusted HR 1.45, 0.90–2.34). Using restricted cubic spline functions, there was a non-linear relationship between resting heart rate and the risk of cardiovascular events (Fig. 2).

Sensitivity analyses

Subgroup analyses were performed for sensitivity analysis of the primary outcome (Fig. 3), and they showed that there were no interactions in subgroups by age, sex, eGFR, diabetes mellitus, proteinuria, and use of β -blockers (*P* values for interaction were 0.45, 0.49, 0.20, 0.87, 0.30, and 0.23, respectively). In analyses for the secondary outcome (Fig. 4), there were no interactions in subgroups by age, sex, eGFR, diabetes mellitus, proteinuria, and use of β -blockers (*P* values for interaction were 0.66, 0.92, 0.40, 0.64, 0.55, and 0.73, respectively).

DISCUSSION

In this study of the association between resting heart rate and adverse outcomes in patients with non-dialysis-dependent CKD, elevated heart rate was associated with a higher risk of all-cause mortality and cardiovascular events. Typically, the resting heart rate for adults falls between 60 and 100/min. The present results showed that a higher heart rate, even within the normal range, was associated with an increased risk of mortality and cardiovascular events.

Previous studies have consistently identified a higher heart rate (also even within the normal range) as an independent risk factor for all-cause mortality or cardiovascular events, not only in the general population, but also in patients with hypertension or coronary artery diseases^{1,2,14,15}. However, whether this association holds true for the CKD population has not been examined sufficiently. Beddhu et al. investigated 460 CKD patients and found that a higher resting heart rate, even within the normal range ($<$ 100/min), was associated with increased mortality and cardiovascular events⁷. In comparison with this previous study, the present sample size was larger, and there were adequate numbers of clinical outcomes, allowing for the sufficient and adequate adjustment of clinical parameters in the statistical analyses. From the present study, it can be concluded that a higher resting heart rate is an independent risk factor for all-cause mortality in patients with non-dialysis-dependent CKD.

A previous interventional study suggested that reducing heart rate could improve clinical outcomes¹⁶. Ivabradine, a selective inhibitor of the I_f current in the sinoatrial node of the heart, has shown a protective effect in patients with chronic heart failure by reducing the heart rate. The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) demonstrated a reduced risk of a composite endpoint of cardiovascular death or heart failure hospitalization by adding ivabradine to standard therapy for

patients with chronic heart failure and a left ventricular ejection fraction of $\leq 35\%$ ¹⁷. The patients in SHIFT had a baseline heart rate of ≥ 70 /min. The present study supported the idea that reducing heart rate might be effective for CKD patients with a heart rate ≥ 70 /min, since the lowest risk of mortality was seen in patients with heart rate < 70 /min. This prompts the need for further interventional studies focusing on CKD patients.

The mechanism linking higher resting heart rate to worse clinical outcomes is complex and multifactorial. Several hypotheses, such as reduced coronary artery perfusion¹⁸, progression of coronary atherosclerosis^{19,20}, dysregulation of the autonomic nervous system²¹, increased levels of inflammation²², oxidative stress²³, and endothelial dysfunction²³⁻²⁵ have been proposed to increase the risk of mortality or cardiovascular events.

The present study had several limitations. First, most previous studies used heart rate measured by electrocardiography as a parameter, whereas pulse rate measured by a standard sphygmomanometer or an automated device was used for the heart rate in the present study. Heart rate refers specifically to the number of heart beats per minute. Pulse rate also refers to the number of heart beats per minute, but it specifically refers to the pulsation of arteries that occurs as a result of the heart's contractions. These terms are closely related and are indicative of the same physiological phenomenon, but they can have slightly different meanings, which is a limitation of this study. Second, cause-and-effect relationships between heart rate and clinical outcomes cannot be inferred due to the observational nature of this study. Furthermore, unmeasured variables, such as lifestyle factors (including alcohol consumption, sleeping, or physical activity), underlying health conditions (such as respiratory disorders), socioeconomic factors (including education, income, or access to healthcare), laboratory data (such as C-reactive protein), or other heart rate-modifying medications may act as confounding factors.

In summary, the results of the present study demonstrated that a higher resting heart rate was associated with all-cause mortality and cardiovascular events in patients with non-dialysis-dependent CKD. Interventional studies targeting CKD patients are needed to investigate whether a higher heart rate should be treated to improve clinical outcomes in this population. It is important to note that, though associations between higher heart rate and clinical adverse outcomes have been observed in various studies, the relationship between heart rate and mortality is complex, and other factors such as age, comorbidities, and overall cardiovascular health contribute to the overall risk profile of an individual; therefore, the management of heart rate should be individualized, and decisions regarding treatment strategies should be made based on an assessment of the patient's overall health.

Declarations

Disclosures

K. Asahi reports receiving research funding from Chugai Pharmaceutical, Kowa Pharmaceutical, and Ono Pharmaceutical. J. J. Kazama reports receiving research funding from Chugai, Kissei, Kyowa-Kirin, Ono,

and Tanabe-Mitsubishi. All remaining authors have nothing to disclose.

Author Contribution

HS and KT wrote the paper with input from all authors. All authors have reviewed and approved the manuscript. Research idea and study design: KT; data acquisition: KT, HK; data analysis/interpretation: HS, KT, MS, KA, TW; statistical analysis: HS; supervision or mentorship: TW, JK.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figures

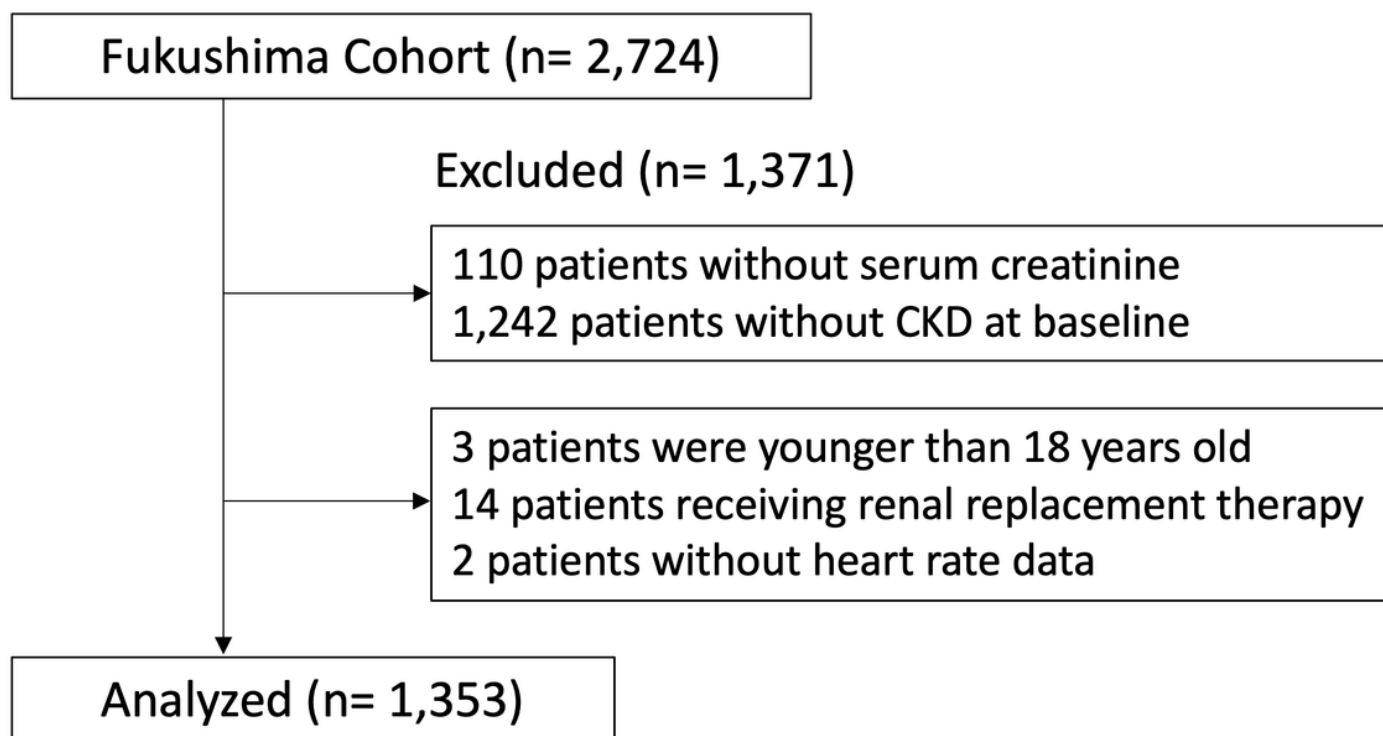


Figure 1

Flow of participants in the present study.

CKD, chronic kidney disease.

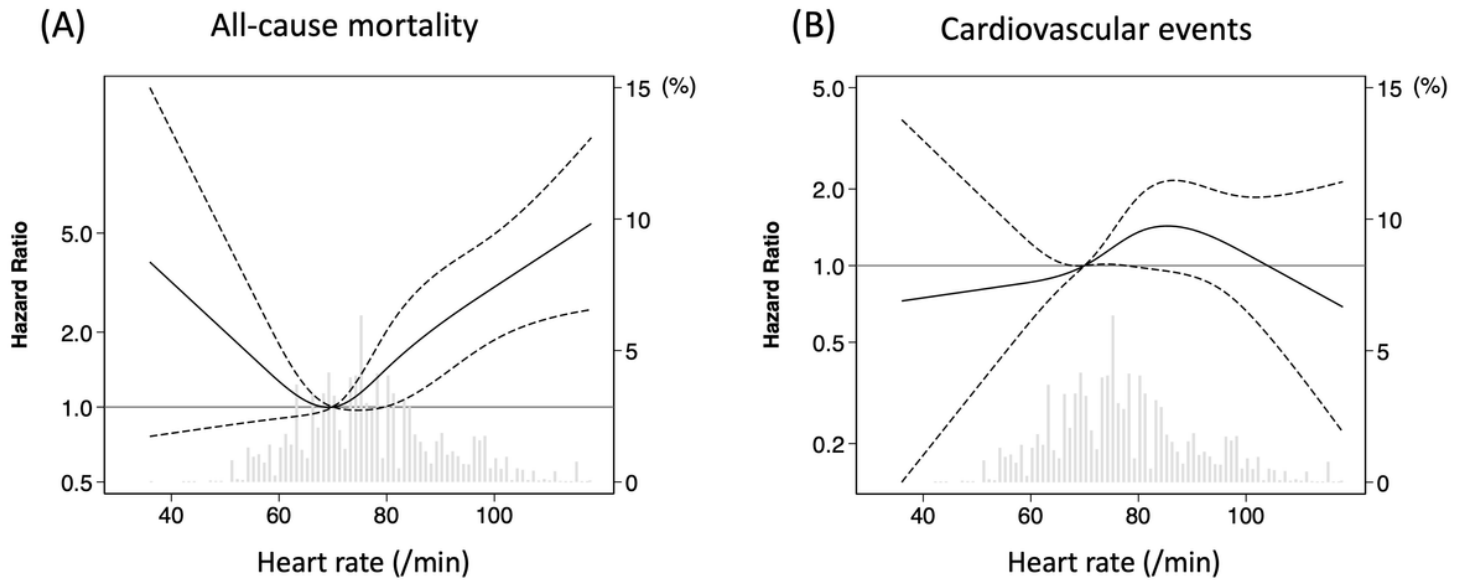


Figure 2

Distributions and Model 4-adjusted restricted cubic splines comparing the relationship of resting heart rate with clinical outcomes in 1,353 participants with non-dialysis-dependent CKD. Solid lines represent adjusted hazard ratio estimates, and dashed lines represent 95% confidence intervals. (A) All-cause mortality, (B) cardiovascular events. Model 4: adjusted for age, sex, body mass index, smoking history, diabetes mellitus, history of cardiovascular disease, eGFR, systolic blood pressure, serum albumin, hemoglobin, proteinuria, use of ACEis or ARBs, and use of β -blockers. eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

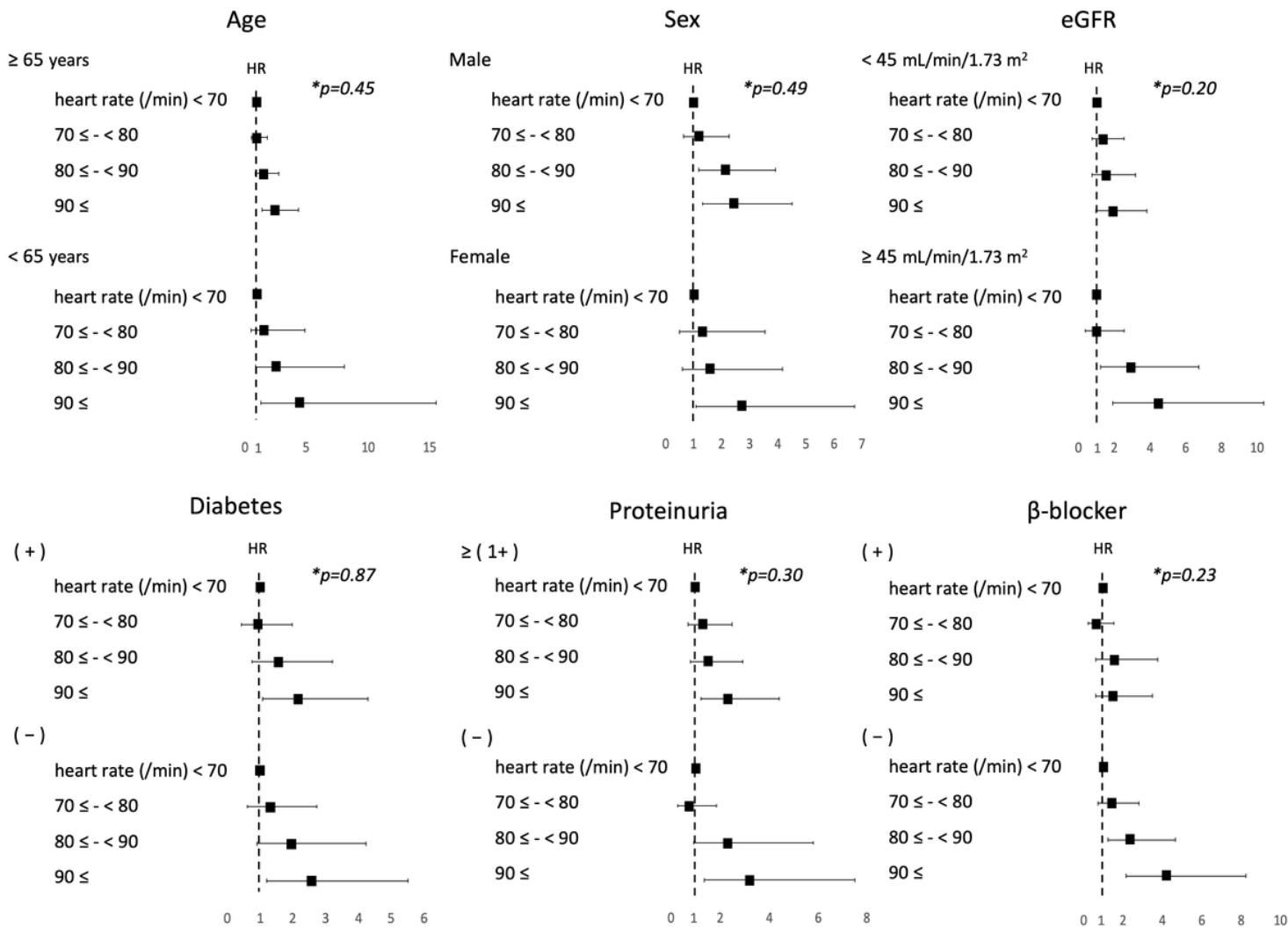


Figure 3

Subgroup analyses for the primary outcome (all-cause mortality). *p-value for interaction. eGFR, estimated glomerular filtration rate; HR, hazard ratio.

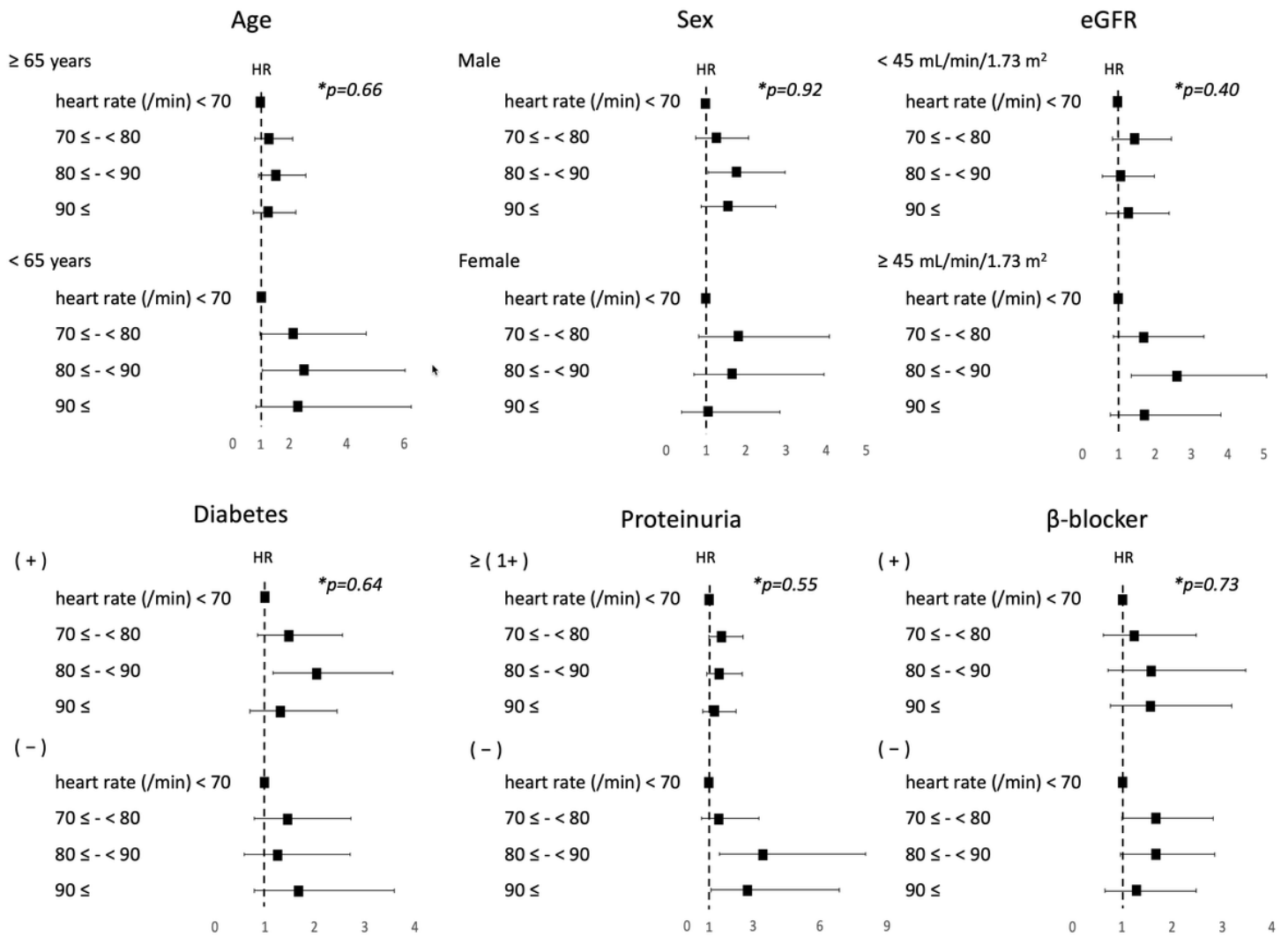


Figure 4

Subgroup analyses for the secondary outcome (cardiovascular events). $*p$ -value for interaction. eGFR, estimated glomerular filtration rate; HR, hazard ratio.