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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Verification of the Impact of Changes in the Severity Classification of Proteinuria on the Prognosis of Hypertensive Patients Following the Initiation of Esaxerenone

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Background: The urinary albumin-to-creatinine ratio (UACR) or urinary protein-to-creatinine ratio (UPCR) has been reported as predictors of cardiovascular and renal events. We aimed to evaluate the impact of changes in proteinuria severity on the prognosis of hypertensive patients post-esaxerenone initiation.

Methods and Results: Hypertensive patients who commenced esaxerenone (n=164) were classified into 3 groups according to baseline UACR or UPCR, based on the modified proteinuria severity classification: A1 (normal; n=35); A2 (microalbuminuria/mild proteinuria; n=49); and A3 (macroalbuminuria/severe proteinuria; n=80). At 6 months post-esaxerenone initiation, these patients were then reclassified into 3 groups: Á1 (n=48); Á2 (n=66); and Á3 (n=50). Á2 was further subdivided into 2 groups: Á2a (n=34); and Á2b (n=32), the latter representing patients who improved from A3. The primary endpoint was defined as the composite of cardiovascular and renal death, heart failure hospitalization, non-fatal myocardial infarction, initiation of dialysis, and estimated glomerular filtration rate decline exceeding 40%. Severity of proteinuria improved significantly after 6 months (P=0.003). The incidence of the primary endpoint was significantly higher in Á3 compared with Á1 (log-rank P<0.001); however, no significant difference was observed between Á1 and Á2b (log-rank P=0.12).

Conclusions: Esaxerenone may ameliorate proteinuria severity and improve the prognosis of patients with macroalbuminuria or severe proteinuria.

Key Words: Albuminuria; Esaxerenone; Hypertension; Prognosis; Proteinuria

Microalbuminuria manifests at an early stage in the progression of cardiovascular and renal diseases,[1] making it highly valuable for identifying high-risk patients. The risk of cardiovascular events escalates with rising urinary albumin-to-creatinine ratio (UACR), regardless of diabetes status, and begins well below the threshold for microalbuminuria.[2] This indicates that albuminuria screening can effectively identify individuals at elevated risk for cardiovascular events. Likewise, elevated urinary protein-to-creatinine ratio (UPCR) is an independent predictor of cardiovascular events and all-cause mortality in patients with stage G2–G5 chronic kidney disease (CKD).[3] A meta-analysis revealed that in diabetic patients, albuminuria serves as a more accurate predictor of cardiovascular mortality and nephropathy progression compared with a decline in estimated glomerular filtration rate (eGFR).[4] Microalbuminuria is strongly linked to the prognosis of heart failure patients. It is associated with an almost 5-fold increase in the incidence of heart failure with reduced ejection fraction (HFrEF) and more than a 2-fold increase in heart failure with preserved ejection fraction (HFpEF).[5] Variations in UACR among patients with type 2 diabetes (T2D) are positively correlated with changes in the risk of macrovascular and renal events.[6] Fluctuations in proteinuria are similarly correlated with shifts in the incidence of myocardial infarction among patients with diabetes or prediabetes.[7] These findings underscore the importance of monitoring longitudinal changes in albuminuria or proteinuria and implementing interventions to mitigate these conditions, thereby improving the prognosis of diabetic patients. Spironolactone has been shown to reduce proteinuria and decelerate the progression of kidney disease in CKD patients.[8] Additionally, spironolactone reduced albuminuria in HFpEF patients, leading to lower all-cause mortality and reduced hospitalization rates due to heart failure.[9] Finerenone, a non-steroidal mineralocorticoid receptor antagonist (ns-MRA), significantly reduced albuminuria in CKD patients with T2D, while also slowing CKD progression and decreasing the risk of cardiovascular events.[10] Furthermore, finerenone

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A

	A1 Normal	A2 Microalbuminuria or mild proteinuria	A3 Macroalbuminuria or severe proteinuria
UACR (mg/gCr)	< 30	30 ~ 299	≥ 300
UPCR (g/gCr)	< 0.15	0.15 ~ 0.49	≥ 0.50

B

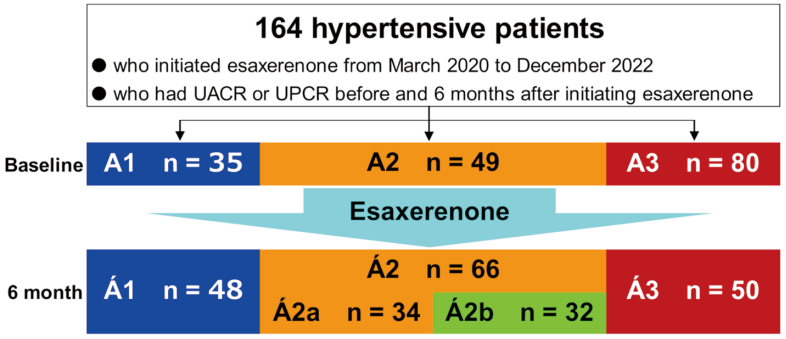

Figure 1. (**A**) Proteinuria severity classification in the modified Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Chronic Kidney Disease (CKD) Guideline for the Japanese population. (**B**) Study flowchart. UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

improved cardiovascular outcomes in T2D patients with stage 2–4 CKD and moderately elevated albuminuria, as well as in those with stage 1 or 2 CKD and severely elevated albuminuria.[11] In Japan, ns-MRA esaxerenone is used as an antihypertensive agent and has been shown to significantly reduce UACR in T2D patients with either microalbuminuria[12] or macroalbuminuria.[13] However, the impact of esaxerenone on cardiovascular and renal outcomes in relation to changes in severity classification of proteinuria remains unclear.

Methods

Study Design

This single-center, retrospective, observational study utilized a prospectively maintained database. The study adhered to the ethical principles of the Helsinki Declaration, and the protocol was approved by the Minoh City Hospital Ethics Committee (No. R0508B41). Informed consent was obtained via an opt-out procedure.

Patients

This study included 164 consecutive hypertensive patients who commenced esaxerenone between March 2020 and December 2022. We excluded patients who were aged <20 years, had a baseline serum potassium ≥5.0 mEq/L, eGFR <30 mL/min/1.73 m^2 at baseline, had a history of prior MRA use, or were missing UACR or UPCR data 6 months after the initiation of esaxerenone. Additionally, patients with severe valvular disease, amyloidosis, recent acute coronary syndrome (within 6 months prior to the initiation of esaxerenone), non-cardiac disease with a life expectancy <6 months, and those deemed unsuitable for the study by the attending physician were also excluded.

Blood Pressure Measurement and Esaxerenone Dosage

Blood pressure was routinely measured during outpatient visits after a minimum of 5 min of rest. Esaxerenone was initiated at a dose of 2.5 mg/day for patients with an eGFR of 60 mL/min/1.73 m^2 or higher, and at 1.25 mg/day for those with an eGFR between 30 and 60 mL/min/1.73 m^2. A dose reduction or discontinuation of esaxerenone was considered if serum potassium levels exceeded 5.0 mEq/L, at the discretion of the attending physician.

Data Collection

We extracted demographic information, including age, sex, body mass index, as well as clinical data such as medical history, comorbidities, medications, and laboratory and echocardiography findings from medical records. Baseline laboratory and echocardiography data were evaluated either at the initiation of esaxerenone or within the preceding 3 months. Patients were monitored every 1–2 months, as determined by the attending physician, with blood pressure and serum potassium levels being recorded during each visit. UACR or UPCR at baseline and 6 months following the initiation of esaxerenone were analyzed. Echocardiography assessments included left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and the ratio of E-wave velocity to the average early diastolic velocity of the lateral and septal segments at the mitral annulus (E/e′) as measured using tissue Doppler imaging.

Definitions of Hypertension and the Severity Classification of Albuminuria or Proteinuria

According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension,[14] hypertension is defined as blood pressure of 140/90 mmHg or higher, with specific exceptions. The severity classification

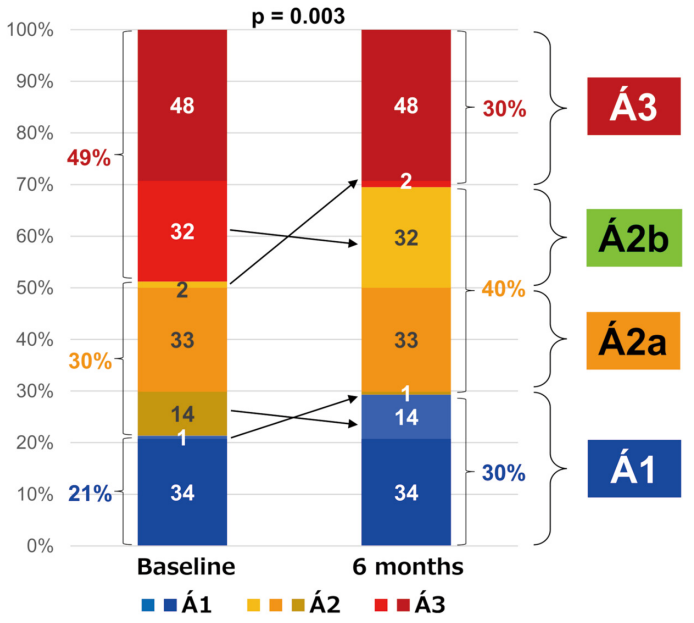

Figure 2. Changes in proteinuria severity classification from baseline to 6 months following esaxerenone initiation.

for the UACR or UPCR was determined in accordance with the proteinuria severity classification outlined in the modified Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Chronic Kidney Disease (CKD) guideline for the Japanese population[15] (**Figure 1A**).

Classification of Patients Into Subgroups

Initially, 164 patients were classified into 3 subgroups based on their UACR or UPCR at baseline, in accordance with the proteinuria severity classification outlined in the modified KDIGO 2012 CKD guideline for the Japanese population[15] (**Figure 1A**): A1 (normal; n=35); A2 (microalbuminuria or mild proteinuria; n=49); and A3 (macroalbuminuria or severe proteinuria; n=80; **Figure 1B**). Subsequently, the same 164 patients were reclassified into 3 subgroups based on their UACR or UPCR 6 months after the initiation of esaxerenone: Á1 (n=48); Á2 (n=66); and Á3 (n=50). Furthermore, Á2 was subdivided into Á2a (n=34) and Á2b (n=32), with the latter representing patients who had improved from A3 at baseline following 6 months of esaxerenone therapy (**Figure 1B**).

Clinical Outcomes

The primary endpoint was defined as a composite measure of cardiovascular or renal events. The secondary endpoint was defined as cardiovascular or renal events. Cardiovascular events were defined as a composite outcome of cardiovascular death, heart failure hospitalization, and non-fatal myocardial infarction. Cardiovascular death was defined as death resulting from heart failure, myocardial infarction, arrhythmia, sudden death, or other cardiovascular-related causes during follow up. Renal events were defined as a composite outcome of renal death, initiation of maintenance dialysis lasting at least 4 weeks, and an eGFR decline exceeding 40% from baseline in patients with an eGFR <60 mL/min/1.73 m^2, sustained for a minimum of 4 weeks during follow up. The follow-up period extended from the initiation of esaxerenone to the final outpatient visit. We examined the incidence rates of primary and secondary endpoints among the 4 subgroups and assessed factors associated with improvement in the severity classification of proteinuria from Group A3 to Group A2 6 months following the initiation of esaxerenone. Additionally, we identified predictors of hyperkalemia during the follow-up period.

Statistical Analysis

Continuous variables are presented as medians [interquartile range], while categorical data are expressed as percentages. Statistical significance was assessed using the Kruskal-Wallis test or Wilcoxon signed-rank test for continuous variables, and Fisher's exact test for categorical variables. The incidence rate of each endpoint was calculated per 100 person-years, and significance testing was performed using Fisher's exact test. Primary and secondary endpoints were estimated using Kaplan-Meier curves, and statistical differences were assessed through the log-rank test. Univariate and multivariate analyses were performed using a logistic regression model to assess factors associated with improvement in the severity classification of proteinuria from Group A3 to Group A2 6 months following the initiation of esaxerenone. Odds ratios (OR) and 95% confidence intervals (CI) were subsequently calculated. The multivariate analysis of factors associated with improvement in the severity classification of proteinuria was adjusted for age, sex, body mass index (BMI), systolic blood pressure 6 months after the initiation of esaxerenone, esaxerenone dosage at 6 months, current smoking status, presence of chronic heart failure, coronary artery disease, eGFR, serum albumin, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and the use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and statins. All analyses were conducted using Bell Curve for Excel statistical

Table 1. Baseline Characteristics of Patients at the Initiation of Esaxerenone in the 4 Subgroups Reclassified and Subdivided According to Proteinuria Severity at 6-Months

Clinical data	Overall (n=164)	Á1 (n=48)	Á2a (n=34)	Á2b (n=32)	Á3 (n=50)	P value
UACR (mg/gCr)	232 [37–767] (n=98)	23 [11–38] (n=30)	147 [62–221] (n=27)	749 [449–1,254] (n=16)	1,225 [698–1622] (n=25)	<0.001
UPCR (g/gCr)	0.70 [0.18–1.55] (n=66)	0.07 [0.06–0.14] (n=18)	0.29 [0.26–0.30] (n=7)	0.88 [0.66–1.57] (n=16)	1.56 [0.97–2.52] (n=25)	<0.001
Age (years)	71 [60–78]	71 [58–78]	73 [64–78]	72 [63–81]	69 [59–75]	0.20
Male	118 (72)	34 (71)	22 (65)	22 (69)	40 (80)	0.42
Body mass index (kg/m^2)	25.4 [22.9–27.7]	25.4 [22.8–28.1]	24.8 [23.0–26.7]	25.5 [23.4–27.5]	25.6 [22.2–27.9]	0.92
Systolic BP (mmHg)	139 [126–151]	141 [135–153]	133 [123–150]	139 [126–146]	137 [124–152]	0.30
Diastolic BP (mmHg)	77 [67–86]	79 [70–86]	79 [69–89]	68 [60–84]	75 [69–83]	0.18
Heart rate (beats/min)	79 [70–88]	75 [67–87]	81 [73–88]	81 [72–89]	79 [70–88]	0.46
Initial dose of esaxerenone	1.25 [1.25–2.50]	1.25 [1.25–2.50]	1.25 [1.25–1.25]	1.25 [1.25–1.25]	1.25 [1.25–1.25]	0.003
Dyslipidemia	136 (83)	36 (75)	29 (85)	29 (91)	42 (84)	0.34
Diabetes	129 (79)	25 (52)	31 (91)	28 (88)	45 (90)	<0.001
CKD (eGFR <60 mL/min/1.73 m^2)	80 (49)	18 (38)	17 (50)	17 (53)	28 (56)	0.29
Coronary artery disease	35 (21)	13 (27)	7 (21)	6 (19)	9 (18)	0.72
Chronic heart failure	30 (18)	6 (13)	5 (15)	7 (22)	12 (24)	0.45
Atrial fibrillation	27 (16)	16 (33)	3 (9)	2 (6)	6 (12)	0.97
Current smoker	24 (15)	9 (19)	6 (18)	1 (3)	8 (16)	0.18
Echocardiography data						
LVEF (%)	67 [62–72]	65 [61–72]	67 [65–69]	68 [63–73]	67 [61–72]	0.95
LVMI	87 [71–108]	92 [70–109]	81 [69–94]	95 [74–114]	90 [74–109]	0.43
LAVI	30 [20–39]	30 [22–39]	24 [18–33]	29 [16–39]	31 [22–37]	0.45
Average E/e′	10.5 [8.2–12.8]	10.7 [8.2–13.0]	10.3 [8.3–11.3]	13.0 [10.1–15.9]	9.8 [8.0–11.8]	0.06
Laboratory data						
Hemoglobin (g/dL)	13.6 [12.5–15.1]	14.0 [12.8–15.1]	14.2 [13.0–15.5]	13.3 [12.7–15.3]	13.0 [11.7–14.9]	0.06
eGFR (mL/min/1.73 m^2)	58 [44–76]	66 [53–77]	58 [44–75]	59 [46–76]	52 [38–75]	0.16
HbA1c (%)	7.2 [6.3–8.1]	6.5 [5.9–7.4]	7.6 [6.5–8.4]	7.7 [6.7–8.6]	7.3 [6.3–8.0]	0.011
Serum albumin (g/dL)	4.1 [3.8–4.3]	4.1 [3.9–4.3]	4.2 [4.1–4.4]	4.2 [3.8–4.3]	3.9 [3.7–4.2]	0.002
Serum potassium (mEq/L)	4.3 [4.1–4.6]	4.2 [3.9–4.3]	4.4 [4.2–4.8]	4.3 [4.2–4.5]	4.5 [4.2–4.8]	0.001
LDL-C (mg/dL)	92 [74–116]	93 [73–128]	93 [78–117]	90 [72–114]	93 [73–111]	0.74
Non-HDL-C (mg/dL)	117 [95–145]	116 [93–162]	121 [103–136]	119 [94–145]	115 [95–140]	0.86
CRP (mg/dL)	0.11 [0.05–0.23]	0.11 [0.05–0.20]	0.15 [0.06–0.24]	0.09 [0.05–0.26]	0.10 [0.06–0.23]	0.87
NT-proBNP (pg/mL)	183 [70–405]	201 [64–407]	130 [37–344]	183 [75–458]	227 [95–468]	0.35
Medication						
ACEi/ARB	132 (80)	37 (77)	28 (82)	30 (94)	37 (74)	0.13
β-blocker	46 (28)	18 (38)	6 (18)	8 (25)	14 (28)	0.26
SGLT2i	89 (54)	16 (33)	17 (50)	22 (69)	34 (68)	0.002
GLP1Ra	17 (10)	2 (4)	4 (12)	4 (13)	7 (14)	0.35
Statin	121 (74)	34 (71)	23 (68)	26 (81)	38 (76)	0.59

Continuous variables are presented as median [interquartile range]. Categorical data are presented as n (%). Tests for significance were conducted using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical data. ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GLP1Ra, glucagon-like peptide-1 receptor antagonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium/glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

software (version 4.01; Social Survey Research Information Co., Ltd, Tokyo, Japan).

Results

Change in Proteinuria Severity Classification Following Initiation of Esaxerenone

The proportion of A1 and A2 increased from 21% and 30% at baseline to 30% and 40%, respectively, 6 months following the initiation of esaxerenone, while the proportion of A3 decreased from 49% to 30%. A statistically significant improvement in the severity classification of proteinuria was observed from baseline to 6 months (P=0.003; **Figure 2**).

Patient Characteristics at the Initiation of Esaxerenone Among the 4 Subgroups

Table 1 presents the patient characteristics at the initiation

Table 2. Incident Rates of Each Endpoint in the 4 Subgroups

	Overall (n=164)	Á1 (n=48)	Á2a (n=34)	Á2b (n=32)	Á3 (n=50)	P value
Primary endpoint	5.0 (19)	0.8 (1)	2.4 (2)	4.1 (3)	12.4 (13)	<0.001
Secondary endpoint (cardiovascular events)	3.1 (12)	0.8 (1)	2.4 (2)	2.7 (2)	6.1 (7)	0.006
Secondary endpoint (renal events)	1.8 (7)	0.0 (0)	0.0 (0)	1.4 (1)	5.8 (6)	<0.001
Cardiovascular or renal death	1.5 (6)	0.0 (0)	1.2 (1)	2.7 (2)	2.5 (3)	0.030
Cardiovascular death	1.3 (5)	0.0 (0)	1.2 (1)	2.7 (2)	1.7 (2)	0.10
Renal death	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.8 (1)	0.09
Heart failure hospitalization	1.3 (5)	0.8 (1)	0.0 (0)	0.0 (0)	3.5 (4)	0.015
Non-fatal myocardial infarction	0.5 (2)	0.0 (0)	1.2 (1)	0.0 (0)	0.8 (1)	0.16
Initiation of maintenance dialysis	0.5 (2)	0.0 (0)	0.0 (0)	0.0 (0)	1.7 (2)	0.06
eGFR decline exceeding 40%	1.5 (6)	0.0 (0)	0.0 (0)	1.3 (1)	4.4 (5)	0.002

Incident rate of each endpoint is expressed as 100 person-years. Values in parentheses indicate the number of patients. Tests for significance were conducted using the Fisher's exact test. eGFR, estimated glomerular filtration rate.

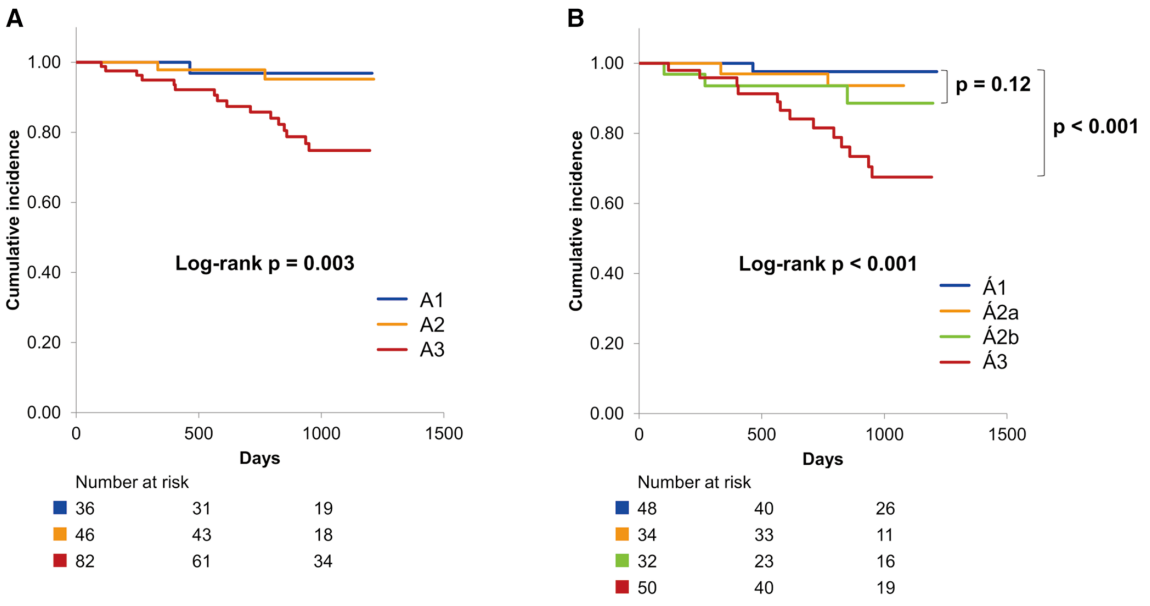

Figure 3. Kaplan-Meier curves and log-rank test for the primary endpoint in subgroups. (**A**) Subgroups classified according to proteinuria severity classification at baseline. (**B**) Subgroups reclassified and subdivided according to proteinuria severity classification 6 months following esaxerenone initiation. P value is the result of the log-rank test.

of esaxerenone among the 4 subgroups, reclassified and subdivided based on UACR or UPCR 6 months after the initiation of esaxerenone, in accordance with the proteinuria severity classification outlined in the modified KDIGO 2012 CKD guidelines for the Japanese population (**Figure 1A**). The median of all patients was 71 [60–78] years, with 72% male. The median UACR and UPCR levels were 232 [37–767] mg/gCr and 0.70 [0.18–1.55] g/gCr, respectively. The median systolic and diastolic blood pressures were 139 [126–151] and 77 [67–86] mmHg, respectively. The median eGFR and serum potassium levels were 58 [44–76] mL/min/1.73 m^2 and 4.3 [4.1–4.6] mEq/L, respectively. The prevalence of diabetes and CKD with an eGFR <60 mL/min/1.73 m^2 was 79% and 49%, respectively. The median initial dose of esaxerenone was 1.25 [1.25–2.50] mg. The administration rates of ACEi/ARB and SGLT2i were 80% and 54%, respectively. Significant differences among the subgroups were observed in the initial dose of esaxerenone, the prevalence of diabetes, serum albumin and potassium levels, HbA1c, and the administration rate of SGLT2i.

Outcomes

Incidence Rates of Each Endpoint Across the 4 Subgroups

Table 2 presents the incidence rates of each endpoint across the 4 subgroups. No cardiovascular or renal events were observed during the 6 months following the initiation of esaxerenone. Over a mean follow up of 894±264 days, 5 cardiovascular deaths and 1 renal death were recorded. The cardiovascular deaths included 4 sudden deaths and 1 resulting from acute aortic dissection. Among the 5 cases of heart failure hospitalization, Group Á1 included 1 case

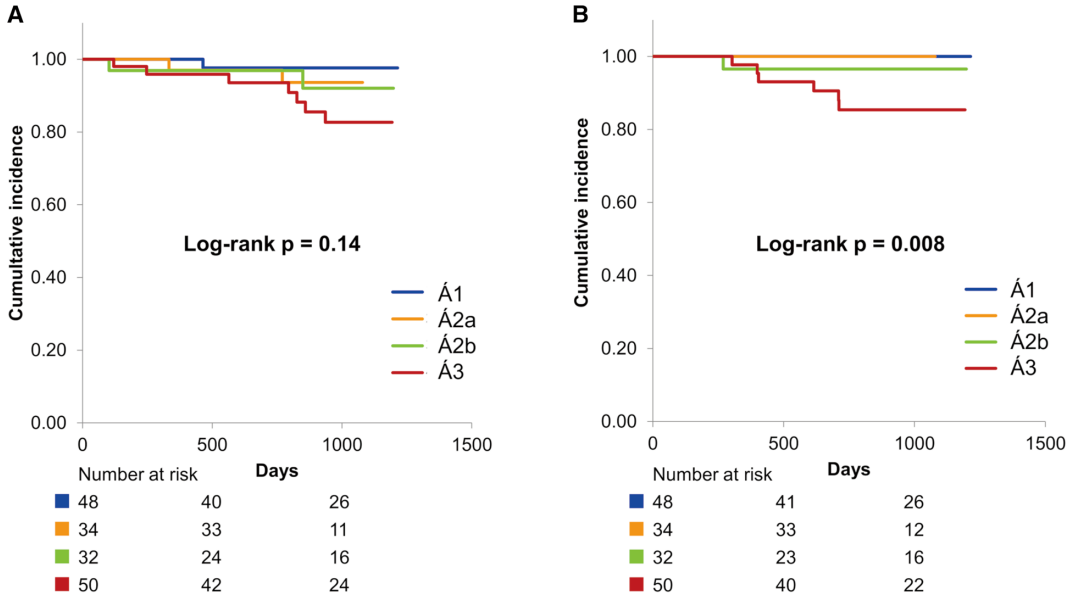

Figure 4. Kaplan-Meier curves and log-rank test for cardiovascular or renal events in subgroups reclassified and subdivided according to proteinuria severity classification 6 months following esaxerenone initiation. (**A**) Cardiovascular events. (**B**) Renal events. P value is the result of the log-rank test.

Table 3. Changes and Comparison in Clinical Data Within the 2 Subgroups of the Baseline Group A3 From Baseline to 6 Months Later

Clinical data	Improved from A3 to A2 (n=32; 16 UACR, 16 UPCR)		P value	Unimproved in A3 (n=48; 23 UACR, 25 UPCR)		P value	P value†	P value‡
	Baseline	At 6 months		Baseline	At 6 months			
UACR (mg/gCr)	749 [449–1,288]	184 [127–237]	<0.001	925 [708–1,492]	899 [490–1,312]	0.25	0.28	<0.001
UPCR (g/gCr)	0.88 [0.66–1.57]	0.27 [0.20–0.36]	<0.001	1.70 [1.20–2.52]	1.79 [0.86–3.85]	0.53	0.009	<0.001
Dose of esaxerenone	1.25 [1.25–1.25]	1.25 [1.25–2.50]	0.023	1.25 [1.25–1.56]	1.25 [1.25–2.50]	0.001	0.46	0.98
Systolic BP (mmHg)	139 [126–146]	128 [120–138]	0.18	137 [124–152]	130 [124–141]	0.12	0.81	0.37
Diastolic BP (mmHg)	68 [60–84]	70 [59–80]	0.63	75 [69–83]	77 [68–86]	0.91	0.43	0.20
Laboratory data								
Hemoglobin (g/dL)	13.3 [12.7–15.3]	13.6 [12.7–15.1]	0.57	13.1 [12.0–14.9]	13.5 [11.8–14.8]	0.46	0.24	0.52
eGFR (mL/min/1.73 m²)	59 [46–76]	46 [39–64]	<0.001	52 [38–74]	48 [33–62]	<0.001	0.33	0.78
HbA1c (%)	7.7 [6.7–8.6]	7.5 [6.8–8.9]	0.88	7.3 [6.4–8.0]	7.2 [6.7–8.4]	0.58	0.24	0.41
Serum albumin (g/dL)	4.2 [3.8–4.3]	4.3 [3.9–4.5]	0.33	3.9 [3.7–4.2]	4.0 [3.7–4.2]	0.07	0.017	0.023
Serum potassium (mEq/L)	4.3 [4.2–4.5]	4.5 [4.3–4.7]	0.001	4.5 [4.2–4.8]	4.5 [4.2–4.8]	0.62	0.039	0.62
LDL-C (mg/dL)	90 [72–114]	78 [70–90]	0.050	93 [73–111]	82 [62–107]	0.40	0.87	0.56
CRP (mg/dL)	0.09 [0.05–0.26]	0.11 [0.07–0.33]	0.14	0.10 [0.06–0.21]	0.09 [0.05–0.22]	0.89	0.70	0.33
NT-proBNP (pg/mL)	183 [75–458]	111 [72–353]	0.040	227 [92–502]	165 [94–514]	0.96	0.55	0.37

†Improved from A3 to A2 vs. unimproved in A3 at baseline. ‡Improved from A3 to A2 vs. unimproved in A3 at 6 months. Tests for significance were conducted using the Mann-Whitney U test or Wilcoxon signed-rank test. Abbreviations as in Table 1.

Table 4. Factors Associated With Improvement in Proteinuria Severity Classification Within Baseline Group A3

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.04	1.00–1.08	0.068	1.09	0.99–1.20	0.08
Sex, male	0.63	0.23–1.74	0.37	0.48	0.06–4.02	0.50
Body mass index	1.03	0.92–1.14	0.64	1.09	0.89–1.33	0.39
Systolic BP at 6 months	0.98	0.95–1.01	0.19	0.95	0.91–1.00	0.044
Esaxerenone dosage at 6 months	0.88	0.51–1.51	0.63	0.56	0.16–1.93	0.36
Chronic heart failure	1.03	0.37–2.93	0.95	0.28	0.03–2.67	0.27
Coronary artery disease	1.30	0.42–4.00	0.65	0.86	0.13–5.68	0.88
Current smoker	0.31	0.06–1.58	0.16	0.08	0.00–2.86	0.17
eGFR	1.01	0.99–1.03	0.34	1.01	0.97–1.05	0.69
HbA1c	1.14	0.87–1.5	0.34	1.51	0.89–2.53	0.12
Serum albumin	5.45	1.55–19.2	0.008	27.6	2.23–341.5	0.010
LDL-C	1.00	0.98–1.01	0.97	0.99	0.96–1.02	0.42
NT-proBNP	1.00	1.00–1.00	0.72	1.00	1.00–1.00	0.34
ACEi/ARB	5.33	1.11–25.7	0.037	3.57	0.37–34.1	0.27
SGLT2i	0.99	0.41–2.39	0.97	0.63	0.13–3.07	0.56
Statin	1.39	0.46–4.21	0.56	1.43	0.13–15.8	0.77

Tests for significance were conducted using a logistic regression model. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

of worsening chronic heart failure, and Group Á3 included 2 cases of worsening chronic heart failure and 2 cases of newly diagnosed heart failure. The 2 non-fatal myocardial infarction, both of which were ST-segment elevation myocardial infarction without a history of PCI, were included in groups Á2a and Á3, respectively. The overall incidence rate of the primary endpoint was observed to be 5.0 events per 100 person-years. The incidence rates for the secondary endpoints – cardiovascular events and renal events – were 3.1 and 1.8 events per 100 person-years, respectively. Significant variations in incidence rates across subgroups were observed for the primary endpoint (P<0.001), both cardiovascular events (P=0.006) and renal events (P<0.001), cardiovascular or renal death (P=0.030), heart failure hospitalization (P=0.015), and an eGFR decline exceeding 40% (P=0.002).

Incidence Rates of Both the Primary and Secondary Endpoints Across the 4 Subgroups **Figure 3A** illustrates that the incidence rates of the primary endpoint across the 3 subgroups, classified based on baseline UACR or UPCR at the initiation of esaxerenone, were significantly different (overall log-rank P=0.003). **Figure 3B** illustrates that the incidence rates of the primary endpoint across the 4 subgroups, reclassified and subdivided based on UACR or UPCR 6 months after the initiation of esaxerenone, were significantly higher in Group Á3 than in Group Á1 (log-rank P<0.001). Conversely, no statistically significant difference was observed between Group Á1 and the improved Group Á2b (originating from Group A3) following the initiation of esaxerenone (log-rank P=0.12). **Figure 4A** illustrates that the incidence rates of the secondary endpoint for cardiovascular events across the 4 subgroups showed no significant difference (log-rank P=0.14). Conversely, **Figure 4B** indicates that the incidence rates of the secondary endpoint for renal events across the 4 subgroups differed significantly (log-rank P=0.008).

Changes and Comparison in Clinical Data Within the 2 Subgroups of the Baseline Group A3 From Baseline to 6 Months Later

Table 3 presents the changes and comparison in clinical data from baseline to 6 months after the initiation of esaxerenone in Group Á2b, which showed improvement in proteinuria severity classificaiton, and in the subgroup without improvement within baseline Group A3. Both UACR and UPCR exhibited significant reductions in the improved group; conversely, no decrease was observed in the unimproved group. At baseline, only UPCR exhibited a significant difference between the 2 subgroups. However, after 6 months, UACR also demonstrated a significant difference between them. The dosage of esaxerenone increased significantly in both groups after 6 months; nonetheless, no significant differences were observed between the groups at either baseline or the 6-month follow up. No significant changes were noted in either systolic or diastolic blood pressure in either group, and no significant differences were observed between them at either baseline or the 6-month follow up. Serum potassium levels increased significantly only in the improved group, resulting in a notable difference between the groups at baseline; however, after 6 months, no significant differences were observed.

Factors Associated With Improvement in the Severity Classification of Proteinuria Within Baseline Group A3

Table 4 presents the results of univariate and multivariate logistic regression analyses to identify factors associated with improvement in the severity classification of proteinuria from baseline Group A3 to Group A2, observed 6 months following the initiation of esaxerenone. The multivariate analysis revealed that an elevated baseline serum albumin level (adjusted OR 27.6; 95% CI 2.23–341.5; P=0.010) and reduced systolic blood pressure at 6 months (adjusted OR 0.95; 95% CI 0.91–1.00; P=0.044) constituted independent factors of improvement in proteinuria severity classification at 6 months following the initiation of esaxerenone.

Incidence of Hyperkalemia and Discontinuation of Esaxerenone During the Follow up Period

Mild hyperkalemia (serum potassium [K] levels >5.0 and <5.5 mEq/L) was observed in 34 (21%) patients, while moderate hyperkalemia (K levels ≥5.5 and <6.0 mEq/L) was noted in 4 (2%) patients (**Supplementary Table 1**). No cases of severe hyperkalemia (K levels ≥6.0 mEq/L) were observed. The incidence of mild hyperkalemia differed significantly across the 4 subgroups (P=0.014), whereas the incidence of moderate hyperkalemia did not show a significant difference across the subgroups (P=0.30). Among the 38 patients with hyperkalemia, 5 in Group Á3 experienced renal events, while no cardiovascular events were observed. The esaxerenone discontinuation was observed in 15 patients with mild hyperkalemia (10% of the total patient cohort, 44% of those with mild hyperkalemia) and in 1 patient with moderate hyperkalemia (1% of the total cohort, 25% of those with moderate hyperkalemia; **Supplementary Table 1**). The discontinuation of esaxerenone within 6 months was observed in 2 patients. The discontinuation rate among patients with mild hyperkalemia differed significantly across the subgroups (P=0.032). All discontinuations occurred in patients managed by non-cardiologists, with 94% (15/16) of these occurring in those with mild hyperkalemia. Among the 16 patients who discontinued esaxerenone, 2 experienced renal events, both requiring initiation of maintenance dialysis; however, no cardiovascular events were observed. The incidence of the primary endpoint among patients with esaxerenone discontinuation did not differ across subgroups (P=0.60). All episodes of hyperkalemia were transient, with no adverse events related to hyperkalemia observed after dose reduction or discontinuation of esaxerenone. Multivariate analysis using a logistic regression model identified that baseline eGFR (adjusted OR 0.97; 95% CI 0.94–0.99; P=0.018), baseline serum potassium level (adjusted OR 4.75; 95% CI 1.61–14.0; P=0.005) and proteinuria severity at 6 months (adjusted OR 1.65; 95% CI 1.10–2.48; P=0.016) as independent predictors of hyperkalemia during the follow-up period (**Supplementary Table 2**).

Discussion

Impact of Esaxerenone on Enhancing the Proteinuria Severity Classification

The present study demonstrated that esaxerenone significantly enhanced the modified classification of proteinuria severity in hypertensive patients 6 months following the initiation of esaxerenone (**Figure 2**). Previous studies have indicated that 51.8% of T2D patients with macroalbuminuria receiving treatment with renin-angiotensin system inhibitors (RASi) achieved regression to microalbuminuria with the addition of esaxerenone,[13] whereas 22% of patients with microalbuminuria achieved remission to normal albuminuria.[12] In the present study, 40% (32/80) of hypertensive patients with macroalbuminuria or severe proteinuria achieved regression to microalbuminuria or mild proteinuria, whereas 29% (14/49) of patients with microalbuminuria or mild proteinuria achieved remission to normal albuminuria or proteinuria. The observed rates of regression and remission closely corresponded with those reported in previous studies.[12,13] The present findings are consistent with these observations. Slight variations between our results and previous studies may be attributable to factors such as the prevalence of diabetes, the rate of RAS inhibitor administration, the dosage of esaxerenone, and the severity of albuminuria or proteinuria.

Impact of Change in Proteinuria Severity Classification on Cardiovascular and Renal Events

Our study further demonstrated that improvement in proteinuria severity following the initiation of esaxerenone was associated with a more favorable prognosis for composite cardiovascular and renal events in hypertensive patients with macroalbuminuria or severe proteinuria (**Figure 3B**). Previous reports indicate that a reduction of 30% or more in UACR after 1 year among T2D patients with microalbuminuria or macroalbuminuria is associated with improved cardiovascular and renal outcomes, regardless of treatment.[16] In the present study, in Group Á2b, the median UACR significantly decreased from 749 mg/gCr to 184 mg/gCr, with a median reduction rate of 75%. Similarly, the median UPCR significantly decreased from 0.88 g/gCr to 0.27 g/gCr, representing a median reduction rate of 56% (**Table 3**). As noted above, improvement in proteinuria severity was accompanied by a significant decrease in UACR and UPCR, potentially contributing to a relatively low incidence of cardiovascular and renal events. Regarding the association between heart failure and changes in proteinuria, it has been reported that among health checkup participants without a prior history of heart failure, those with resolved proteinuria demonstrated a relatively lower risk of heart failure compared with those with persistent proteinuria.[17] Studies have reported that, in patients with HFpEF, elevated UACR is associated with reduced coronary flow reserve,[18] whereas in diabetic patients, the degree of albuminuria is strongly linked to impaired myocardial flow reserve.[19] These findings suggest that coronary microvascular dysfunction may be one of the mechanisms through which albuminuria contributes to heart failure. Persistent microalbuminuria is associated with increased myocardial extracellular volume, heightened myocardial damage, and impaired left ventricular diastolic function in patients with T2D.[20] Furthermore, albuminuria is independently associated with right ventricular remodeling and dysfunction, as well as impaired left ventricular systolic and diastolic function.[21] These findings suggest that albuminuria may contribute to heart failure through mechanisms involving myocardial fibrosis and remodeling, ultimately leading to biventricular dysfunction. Regarding the association between myocardial infarction and changes in albuminuria, a meta-regression analysis of randomized trials involving diabetic or hypertensive patients has reported that a 10% reduction in albuminuria correlates with a 13% decrease in the risk of myocardial infarction.[22] It has been reported that microalbuminuria is associated with impaired coronary endothelium-dependent vasodilation in patients with T2D,[23] suggesting that damage to the vascular endothelium of both coronary arteries and renal glomeruli occurs as part of a common pathophysiological process. In patients with T2D, albuminuria is associated with endothelial dysfunction and chronic inflammation, both of which occur concurrently and are strongly correlated with mortality risk.[24] This report may suggest a relationship between albuminuria and the formation and rupture of coronary plaques. Furthermore, patients with T2D and microalbuminuria demonstrate a higher frequency of activated platelet aggregations[25] and severe fibrinolytic abnormalities,[26] which may contribute to coronary artery occlusion following

plaque rupture.

Factors Associated With Improvement in Proteinuria Severity Within the Baseline Group A3

The present study demonstrated that higher baseline serum albumin levels and lower systolic blood pressure during follow up were associated with improvements in proteinuria severity among hypertensive patients with macroalbuminuria or severe proteinuria following the initiation of esaxerenone (**Table 4**). Lower urinary albumin excretion at baseline has been identified as a factor associated with the remission of microalbuminuria in patients with T2D.[27] It is hypothesized that elevated levels of albuminuria or proteinuria are associated with reduced serum albumin levels. Consequently, we contend that the aforementioned report and our findings convey a similar conclusion. Furthermore, it has been reported that lower systolic blood pressure is associated with the remission or regression of microalbuminuria in patients with T2D.[28] This finding aligns with the results of the present study.

Discontinuation of Renin-Angiotensin System Inhibitors or Mineralocorticoid Receptor Antagonist

The present study demonstrated that the likelihood of hyperkalemia and discontinuation of esaxerenone increased with advancing proteinuria severity (**Supplementary Table 1**). Although patients with macroalbuminuria or severe proteinuria should ideally require treatment with RASi and MRA, hyperkalemia may impede the continuation of optimal therapy. Discontinuation of RASi or MRA has been associated with increased risks of cardiovascular events, all-cause mortality, and progression to end-stage renal disease.[29,30] Nevertheless, in our study, 94% (15/16) of esaxerenone discontinuations were observed among patients with mild hyperkalemia, and these discontinuations were attributable to patients under the care of non-cardiologists. Particularly in the context of mild hyperkalemia among high-risk populations, including individuals with macroalbuminuria or severe proteinuria, it is preferable to maintain treatment with RASi or MRA through dose reduction or the administration of a potassium binder to mitigate the deterioration of the clinical prognosis. Equally, it is crucial to disseminate this policy among non-cardiologists. Additionally, the present study identified that the predictors of hyperkalemia during the follow-up period included decreased baseline eGFR, elevated baseline serum potassium levels, and a greater severity of proteinuria at 6 months (**Supplementary Table 2**). A previous study has identified that predictors of hyperkalemia following spironolactone administration in HFpEF patients include a reduced eGFR and elevated baseline potassium levels.[31] Additionally, predictors of mild hyperkalemia following finerenone administration in diabetic patients with CKD include elevated serum potassium, reduced eGFR, and increased UACR.[32] These findings align with our results.

Study Limitations

This present study is subject to several limitations. First, it is a single-center retrospective analysis. Second, the sample size is limited. Third, it is a single-arm study lacking a control group. Fourth, the data are derived exclusively from cases that exhibited UACR or UPCR 6 months following the initiation of esaxerenone. Fifth, certain cases did not receive RASi prior to the initiation of esaxerenone. Sixth, certain cases, even those with mild hyperkalemia, had esaxerenone discontinued. Seventh, the effects of medications, aside from cardio–renal protective agents, that were modified during the study period could not be evaluated. Last, there may have existed confounding factors that were not investigated. To validate the findings of this study and mitigate these limitations, a larger sample size utilizing a multicenter prospective control group is warranted.

Conclusions

Esaxerenone significantly enhanced the proteinuria severity classification in hypertensive patients, with the improvement correlating with a favorable prognosis for certain individuals. Nevertheless, cases of treatment-resistant albuminuria or proteinuria continue to persist even after the initiation of esaxerenone, potentially presenting an increased risk of cardiovascular or renal events. Furthermore, the risk of hyperkalemia may escalate as the severity of albuminuria or proteinuria intensifies. To maintain optimal treatment, early detection of albuminuria or proteinuria, along with prompt therapeutic intervention to prevent their progression, will be essential for improving prognosis.

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IRB Information

The present study was approved by Minoh City Hospital Ethics Committee (Reference no. R0508B41).

References

1. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: A workshop consensus statement. *Am Heart J* 1991; **121:** 1244–1263.
2. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286:** 421–426.
3. Song H, Liao Y, Hu H, Wan Q. Nonlinear association between proteinuria levels and the risk of cardiovascular disease events and all-cause mortality among chronic kidney disease patients. *Ren Fail* 2024; **46:** 2310727.
4. Toyama T, Furuichi K, Ninomiya T, Shimizu M, Hara A, Iwata Y, et al. The impacts of albuminuria and low eGFR on the risk of cardiovascular death, all-cause mortality, and renal events in diabetic patients: Meta-analysis. *PLoS One* 2013; **8:** e71810.
5. Nayor M, Larson MG, Wang N, Santhanakrishnan R, Lee DS, Tsao CW, et al. The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2017; **19:** 615–623.
6. Jun M, Ohkuma T, Zoungas S, Colagiuri S, Mancia G, Marre M, et al. Changes in albuminuria and the risk of major clinical outcomes in diabetes: Results from ADVANCE-ON. *Diabetes Care* 2018; **41:** 163–170.
7. Wang A, Sun Y, Liu X, Su Z, Li J, Luo Y, et al. Changes in proteinuria and the risk of myocardial infarction in people with diabetes or pre-diabetes: A prospective cohort study. *Cardiovasc Diabetol* 2017; **16:** 104.
8. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with

chronic kidney disease. *Kidney Int* 2006; **70:** 2116–2123.
9. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006; **1:** 940–951.
10. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; **383:** 2219–2229.
11. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021; **385:** 2252–2263.
12. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, et al. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN): Phase 3 randomized controlled clinical trial. *Clin J Am Soc Nephrol* 2020; **15:** 1715–1727.
13. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, et al. Efficacy and safety of esaxerenone (CS-3150) in Japanese patients with type 2 diabetes and macroalbuminuria: A multicenter, single-arm, open-label phase III study. *Clin Exp Nephrol* 2021; **25:** 1070–1078.
14. 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:** 1235–1481.
15. Japan Nephrology Society. [Special issue: Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012]. *Nihon Jinzo Gakkai Shi* 2012; **54:** 1034–1191.
16. Persson F, Bain SC, Mosenzon O, Heerspink HJL, Mann JFE, Pratley R, et al. Changes in albuminuria predict cardiovascular and renal outcomes in type 2 diabetes: A post hoc analysis of the LEADER trial. *Diabetes Care* 2021; **44:** 1020–1026.
17. Chang Y, Kang MK, Park MS, Leem GH, Song TJ. Resolved Proteinuria may attenuate the risk of heart failure: A nationwide population-based cohort study. *J Pers Med* 2023; **13:** 1662.
18. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018; **39:** 3439–3450.
19. Potier L, Chequer R, Roussel R, Mohammedi K, Sismail S, Hartemann A, et al. Relationship between cardiac microvascular dysfunction measured with 82Rubidium-PET and albuminuria in patients with diabetes mellitus. *Cardiovasc Diabetol* 2018; **17:** 11.
20. Swoboda PP, McDiarmid AK, Erhayiem B, Ripley DP, Dobson LE, Garg P, et al. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: Identification and monitoring of individuals at risk of heart failure. *J Am Heart Assoc* 2017; **6:** e005539.
21. Katz DH, Burns JA, Aguilar FG, Beussink L, Shah SJ. Albuminuria is independently associated with cardiac remodeling, abnormal right and left ventricular function, and worse outcomes in heart failure with preserved ejection fraction. *JACC Heart Fail* 2014; **2:** 586–596.
22. Savarese G, Dei Cas A, Rosano G, D'Amore C, Musella F, Mosca S, et al. Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients: A meta-regression analysis of 32 randomized trials. *Int J Cardiol* 2014; **172:** 403–410.
23. Cosson E, Pham I, Valensi P, Pariès J, Attali JR, Nitenberg A. Impaired coronary endothelium-dependent vasodilation is associated with microalbuminuria in patients with type 2 diabetes and angiographically normal coronary arteries. *Diabetes Care* 2006; **29:** 107–112.
24. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: Progressive, interrelated, and independently associated with risk of death. *Diabetes* 2002; **51:** 1157–1165.
25. Araki S, Matsuno H, Haneda M, Koya D, Kanno Y, Itho J, et al. Correlation between albuminuria and spontaneous platelet microaggregate formation in type 2 diabetic patients. *Diabetes Care* 2009; **32:** 2062–2067.
26. Kamgar M, Nobakhthaghighi N, Shamshirsaz AA, Estacio RO, McFann KK, Schrier RW. Impaired fibrinolytic activity in type II diabetes: Correlation with urinary albumin excretion and progression of renal disease. *Kidney Int* 2006; **69:** 1899–1903.
27. Nakamura N, Narita I, Fujita T, Murakami R, Shimada M, Nakamura M, et al. Factors associated with microalbuminuria remission in patients with type 2 diabetes: Importance of early intervention for microalbuminuric patients (TSUGARU STUDY). *In Vivo* 2017; **31:** 285–290.
28. Araki S, Haneda M, Sugimoto T, Isono M, Isshiki K, Kashiwagi A, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. *Diabetes* 2005; **54:** 2983–2987.
29. 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:** 1525–1535.
30. Trevisan M, Fu EL, Xu Y, Savarese G, Dekker FW, Lund LH, et al. Stopping mineralocorticoid receptor antagonists after hyperkalaemia: Trial emulation in data from routine care. *Eur J Heart Fail* 2021; **23:** 1698–1707.
31. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF, et al. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: Analysis of the TOPCAT trial. *J Card Fail* 2018; **24:** 313–320.
32. Agarwal R, Joseph A, Anker SD, Filippatos G, Rossing P, Ruilope LM, et al. Hyperkalemia risk with finerenone: Results from the FIDELIO-DKD trial. *J Am Soc Nephrol* 2022; **33:** 225–237.

Appendix

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Supplementary Files

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