Prognostic Impact of Subclinical Microalbuminuria in Patients With Chronic Heart Failure
– Report From the CHART-2 Study –

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Background: Microalbuminuria, traditionally defined as urinary albumin/creatinine ratio (UACR) ≥30 mg/g, is a risk factor for mortality even in patients with preserved glomerular filtration rate (GFR). The prognostic impact of subclinical microalbuminuria, however, remains unknown in patients with chronic heart failure (CHF).

Methods and Results: In the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 Study, we enrolled 2,039 consecutive symptomatic CHF patients (median age, 67.4 years; 68.9% male) after excluding those on hemodialysis. On classification and regression tree analysis, UACR=10.2 mg/g and 27.4 mg/g were identified as the first and second discriminating points to stratify the risk for composite of death, acute myocardial infarction, HF admission and stroke, therefore subclinical microalbuminuria was defined as UACR ≥10.2 and <27.4 mg/g. There were 506 composite endpoints (24.8%) during the median follow-up of 2.69 years. On Kaplan-Meier analysis and multivariate Cox modeling, subclinical microalbuminuria was significantly associated with increased composite endpoints with hazard ratios of 1.90 (P<0.001) and 2.29 (P<0.001) in patients with preserved (>60 ml·min^{-1}·1.73 m^{-2}, n=1,129) or mildly reduced eGFR (30–59.9 ml·min^{-1}·1.73 m^{-2}, n=789), respectively. In patients with severely reduced GFR (eGFR <30 ml·min^{-1}·1.73 m^{-2}, n=121), >80% had microalbuminuria or macroalbuminuria, and only 9.1% were free from any composite endpoints.

Conclusions: Subclinical microalbuminuria was associated with increased risk of cardiovascular events in CHF patients with mildly reduced or preserved renal function. (*Circ J* 2014; **78**: 2890–2898)

Key Words: Chronic heart failure; Chronic kidney disease; Prognosis; Subclinical microalbuminuria

icroalbuminuria, traditionally defined as between 30 and 300 mg/g urinary albumin/creatinine ratio (UACR),[1] is an independent risk for mortality in the general population and in patients with hypertension or diabetes mellitus.[2–4] The latest classification of chronic kidney disease (CKD) has defined microalbuminuria as a risk for adverse outcome even in patients with preserved glomerular filtration rate (GFR; ml·min^{-1}·1.73 m^{-2}).[1] Recently, however, several large population studies suggested that the normal albuminuria level is much lower than 30 mg/g.[5–7] For example, the Prevention of Renal and Vascular End/stage Disease (PREVEND) Trial in the Netherlands reported that the median UACR was 6.1 mg/g (95% confidence interval [95% CI]: 2.3–

28.7 mg/g),[5] and the most recent evaluation of the National Health and Nutrition Examination Survey (NHANES) Data noted a mean UACR of 12.3 mg/g in young healthy participants.[6] Moreover, subclinical microalbuminuria was significantly associated with the development of heart failure (HF) in the general population.[8,9] Thus, it is now considered that even subclinical microalbuminuria, usually <30 mg/g UACR, is likely to have a prognostic impact.[8–14]

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In patients with chronic heart failure (CHF), it has been reported that microalbuminuria is also associated with poorer

Table 1. Baseline Patient Characteristics

UACR (mg/g)	All patients (n=2,039)	Normoalbuminuria <10.2 (n=614)	Subclinical microalbuminuria 10.2–27.3 (n=534)	Microalbuminuria 27.4–300 (n=684)	Macroalbuminuria >300 (n=207)	P-value
Age (years)	67.5±12.4	64.5±12.5	67.7±12.1	69.7±11.8	68.5±12.5	<0.001
Male (%)	68.9	74.3	65.9	65.6	71.0	0.003
History of admission for HF (%)	53.6	52.4	50.4	55.3	59.4	0.21
Ischemic heart disease (%)	46.2	44.3	49.1	42.5	56.5	0.002
Comorbidity (%)						
Hypertension	82.5	76.1	82.0	86.4	89.9	<0.001
Diabetes	40.3	31.3	34.6	45.2	66.0	<0.001
Hyperlipidemia	76.0	76.9	76.4	73.4	81.2	0.12
Hyperuricemia	46.8	44.8	42.7	46.6	63.8	<0.001
Atrial fibrillation	32.2	28.3	31.4	37.6	28.4	<0.001
Cerebrovascular disease	16.7	12.1	16.7	19.9	19.8	0.001
Clinical status						
NYHA class 3 and 4 (%)	11.2	9.0	10.8	12.4	15.0	0.03
BMI (kg/m^2)	23.7±4.6	23.8±4.2	23.6±4.4	23.7±4.8	23.5±5.2	0.81
SBP (mmHg)	127.0±18.7	123.2±16.7	126.0±17.4	128.8±19.5	134.3±21.7	<0.001
DBP (mmHg)	72.7±12.0	72.1±11.5	72.8±11.2	73.3±12.6	73.8±15.0	0.40
Heart rate (beats/min)	72.3±14.9	70.6±14.2	72.3±14.7	73.5±15.5	73.8±15.0	0.002
Laboratory data						
LVEF (%)	55.3±15.7	54.1±16.2	55.8±15.7	55.7±15.6	55.7±14.8	0.20
LVEF ≥50% (%)	64.6	62.8	63.3	66.7	66.5	0.41
LVDd (mm)	52.5±9.4	53.4±9.9	52.4±9.3	52.1±9.4	52.0±8.6	0.08
Hemoglobin (g/dl)	13.3±2.2	13.7±2.1	13.4±2.2	13.2±2.1	12.3±2.6	<0.001
BUN (mg/dl)	19.3±10.4	17.0±6.2	17.7±6.5	20.2±11.8	26.7±17.4	<0.001
Serum sodium (mEq/L)	141.0±2.8	141.2±2.5	140.8±2.7	140.8±3.0	141.1±3.2	0.02
Serum potassium (mEq/L)	4.4±0.4	4.4±0.4	4.3±0.4	4.3±0.4	4.4±0.5	0.02
GFR (ml·min^{-1}·1.73m^{-2})	62.8±20.9	66.9±18.4	66.1±19.1	60.8±21.5	48.7±23.0	<0.001
UACR (mg/g)	21.5 (8.3–74.4)	5.8 (3.9–7.5)	16.5 (13.0–21.4)	64.0 (39.6–121)	679.0 (407–1,283)	<0.001
BNP (pg/ml)	99.3 (39.0–229)	67.8 (27.2–148)	96.0 (37.9–213)	130.5 (54.2–264)	180.1 (64.4–373)	<0.001
Medication (%)						
RAS inhibitor	73.2	70.4	71.3	74.9	80.7	0.02
β-blocker	52.2	52.5	51.5	52.7	53.6	0.90
CCB	37.3	27.5	33.9	43.6	54.6	<0.001
Loop diuretic	44.6	43.3	42.9	44.4	53.6	0.049
Aldosterone antagonists	25.9	29.2	24.7	26.6	17.4	0.008
Statins	40.5	39.1	41.6	37.9	50.7	0.008
Outcome						
Composite endpoints	24.8	13.4	23.4	31.6	40.1	<0.001

Data given as mean±SD, %, or median (IQR). BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HF, heart failure; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.
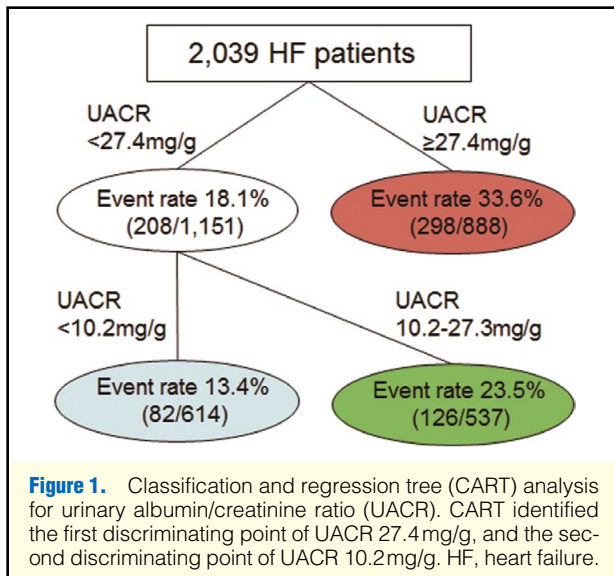
prognosis regardless of the presence of diabetes, hypertension or renal dysfunction.[15–17] Indeed, we recently found that urinary albumin excretion has a significant prognostic impact in CHF patients with preserved ejection fraction.[17] In contrast, only a few studies previously examined the clinical impact of subclinical microalbuminuria in CHF patients, and furthermore they did not examine that of subclinical albuminuria in detail.[18,19] Thus, it remains to be clarified whether subclinical microalbuminuria also has a significant prognostic impact in CHF patients, particularly with a reference to renal function. Thus, in the present study, we examined microalbuminuria level to determine mortality or cardiovascular events in CHF patients according to renal function status, in the Chronic Heart failure Analysis

and Registry in the Tohoku district 2 (CHART-2) Study.[17,20–23]

Methods

Subjects and Inclusion Criteria
Details of the design, purpose and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[17,21–23] Briefly, the CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients in stages B/C/D HF according to the ACCF/AHA guideline.[24] The study protocol was approved by the local ethics committee in the 24 participating hospitals and written informed consent was obtained from all

Figure 1. Classification and regression tree (CART) analysis for urinary albumin/creatinine ratio (UACR). CART identified the first discriminating point of UACR 27.4 mg/g, and the second discriminating point of UACR 10.2 mg/g. HF, heart failure.

Figure 2. Distribution of urinary albumin/creatinine ratio (UACR) according to estimated glomerular filtration rate (eGFR). More than 80% of the patients with eGFR <30 ml·min⁻¹·1.73 m⁻² had clinical albuminuria.

patients. Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[25] All data and events will be surveyed at least once a year until March 2018.[17,21–23]

Among the 10,219 patients, we enrolled 4,735 consecutive patients with stage C/D CHF in the present study. We excluded 63 patients on hemodialysis, 2,591 without UACR measurement, and 42 without appropriate follow-up. Finally, 2,039 patients with stage C/D CHF were included in the present study.
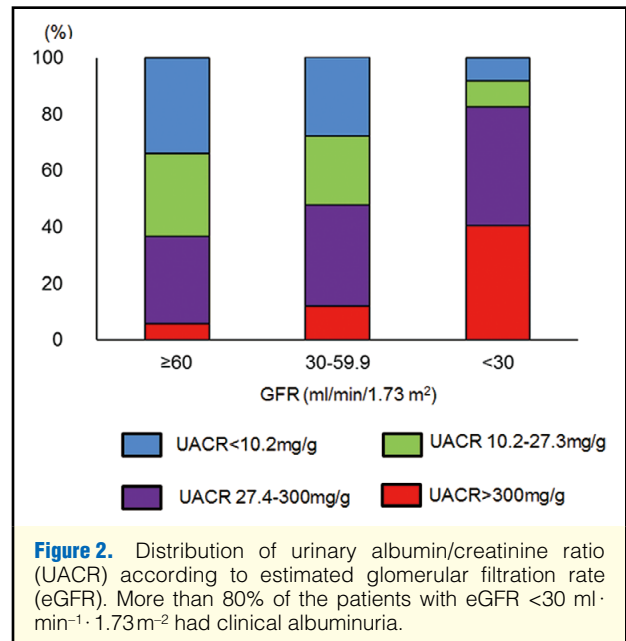
UACR and GFR Measurement

Albuminuria was quantitatively evaluated using UACR. Urine samples were collected in outpatient clinics or before discharge, and urine albumin was measured in a central laboratory (SRL, Tokyo, Japan) to calculate UACR. Estimated GFR (eGFR; ml·min⁻¹·1.73 m⁻²) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[26] at the time of enrollment. We defined preserved eGFR as ≥60 ml·min⁻¹·1.73 m⁻², mildly reduced eGFR as 30–59.9 ml·min⁻¹·1.73 m⁻², and severely reduced eGFR as <30 ml·min⁻¹·1.73 m⁻² according to the guidelines.[1]

Study Outcomes

The outcomes of the present study included composite of death, acute myocardial infarction, HF admission and stroke. Mode of death was determined by the attending physician and was confirmed by 1 independent physician who was a member of the Tohoku Heart Failure Association.[20]

Statistical Analysis

Classification and regression tree (CART) analysis[27] was done in order to identify the cut-off points of UACR to classify CHF patients for the composite endpoints. CART analysis is an empirical and statistical technique based on recursive partitioning of the data space to predict response.[28] The models are obtained by binary discrimination of the data by predictors, and the discrimination variable and discriminating point are automatically selected from possible predictor values to achieve the best fit. Then, one or both "child nodes" are discriminated into 2 or more regions recursively, and the process continues until some stopping rule is applied.[28] Finally, the result of this process is represented as a binary decision tree. We divided the patients into 4 groups according to UACR cut-offs obtained 1 CART analysis as follows: normoalbuminuria, subclinical microalbuminuria, microalbuminuria, and macroalbuminuria.

Kaplan-Meier curves and Cox proportional hazard models were used to compare the risk for composite endpoints among the 4 groups. Cox proportional hazard models were adjusted for the following covariates that could potentially influence outcome: age, sex, New York Heart Association (NYHA) class, history of HF admission and malignant tumor, ischemic etiology of HF, systolic blood pressure, heart rate, left ventricular ejection fraction (LVEF), body mass index, hemoglobin, serum sodium, serum potassium, blood urea nitrogen (BUN), brain natriuretic peptide (BNP), eGFR, comorbidities (atrial fibrillation, diabetes mellitus, hyperlipidemia, hyperuricemia and cerebrovascular disease), and medications (β-blockers, renin-angiotensin system [RAS] inhibitors, loop diuretics, aldosterone antagonists, calcium channel blockers and statins). We also performed subgroup analyses based on sex, age (<median or ≥median), LVEF (<50% or ≥50%), history of hypertension and diabetes mellitus, and medications (β-blockers, RAS inhibitors and statins). In addition, CART analysis was done using both UACR and eGFR to evaluate the importance of subclinical microalbuminuria on renal function. Comparisons among the 4 groups were done using chi-squared test. Continuous data are described as mean±SD and discrete data as %. UACR and BNP are described as median.

SPSS Statistics 21.0 (SPSS, Chicago, IL, USA) and R 2.15.2 were used for statistical analysis.[27] The statistical significance was defined as 2-sided P<0.05. Comparison of the baseline characteristics among the 4 groups was performed using ANOVA for continuous variables and chi-squared test for categorical variables. Comparison of BNP and UACR among the 4 groups was done using Kruskal-Wallis test.

Results

Baseline Characteristics

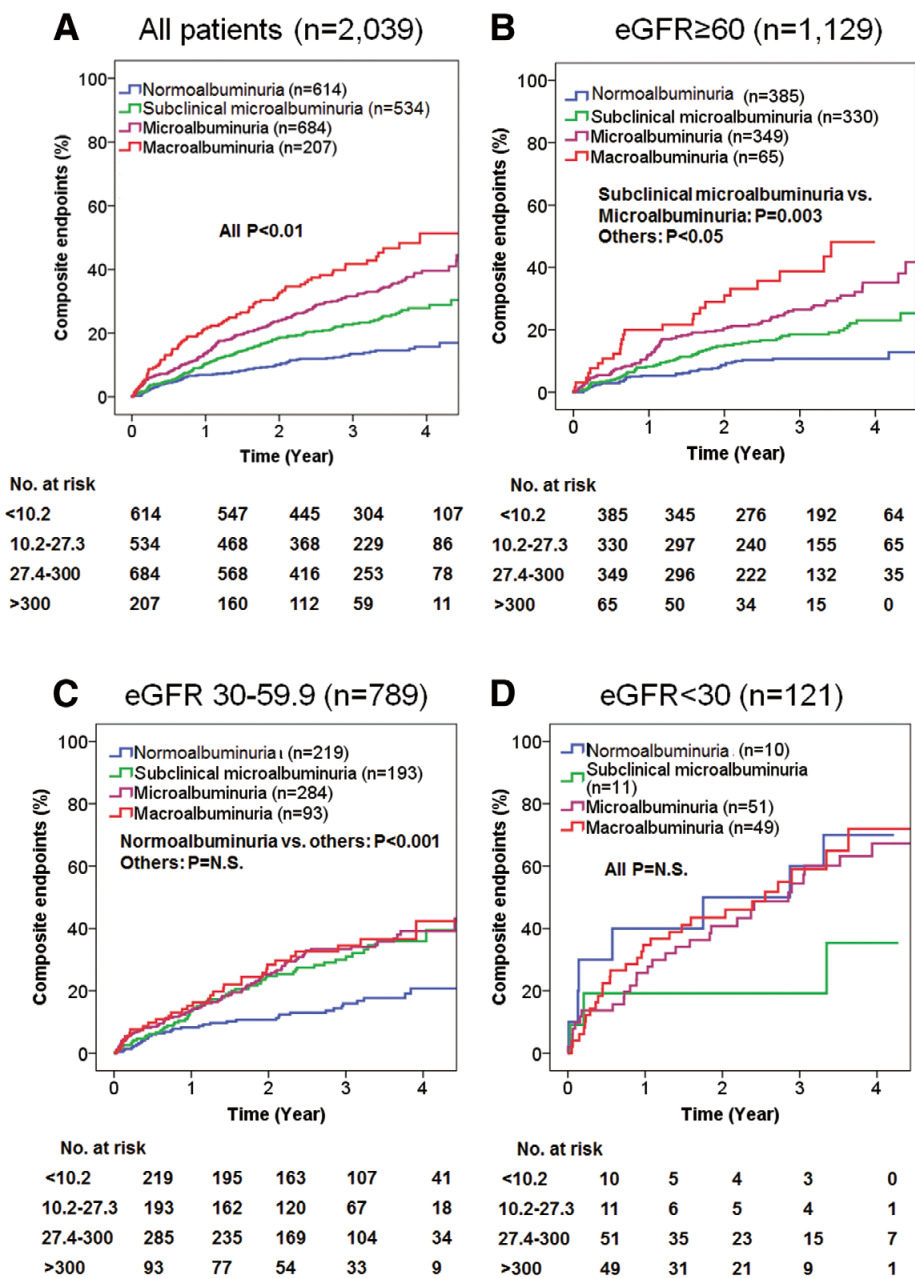**Table 1** lists patient baseline characteristics. Median age was

Figure 3. Kaplan-Meier curves for composite endpoints. (**A**) All patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73 m^{-2}; (**C**) eGFR 30–59.9 ml·min^{-1}·1.73 m^{-2}; (**D**) eGFR <30 ml·min^{-1}·1.73 m^{-2}.

67.4 years and male patients accounted for 68.9%. History of ischemic heart disease was noted in 46.2% and mean LVEF and eGFR were 55.3±15.7% and 62.8±20.9 ml·min^{-1}·1.73 m^{-2}, respectively. The prevalence of eGFR <60 ml·min^{-1}·1.73 m^{-2} was 44.6% (n=910), and median UACR was 21.5 mg/g. On CART analysis UACR=27.4 mg/g and 10.2 mg/g were identified as the first and the second discriminating points to stratify risk for composite endpoints, respectively (**Figure 1**). Thus, normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria were defined as UACR (mg/g) <10.2, 10.2–27.3, 27.4–300, and >300, respectively. The prev-

alence of normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria was 30.1%, 26.2%, 33.5%, and 10.2%, respectively. As shown in **Figure 2**, the prevalence of normoalbuminuria was decreased along with a decrease in eGFR categories. It was noted that, even in patients with preserved eGFR and mildly reduced eGFR, the prevalence of subclinical microalbuminuria was 29.2% and 24.5%, respectively. The characteristics of the patients with subclinical microalbuminuria or microalbuminuria were generally intermediate between those with normoalbuminuria and those with macroalbuminuria, in terms of age, comorbidity, NYHA class,
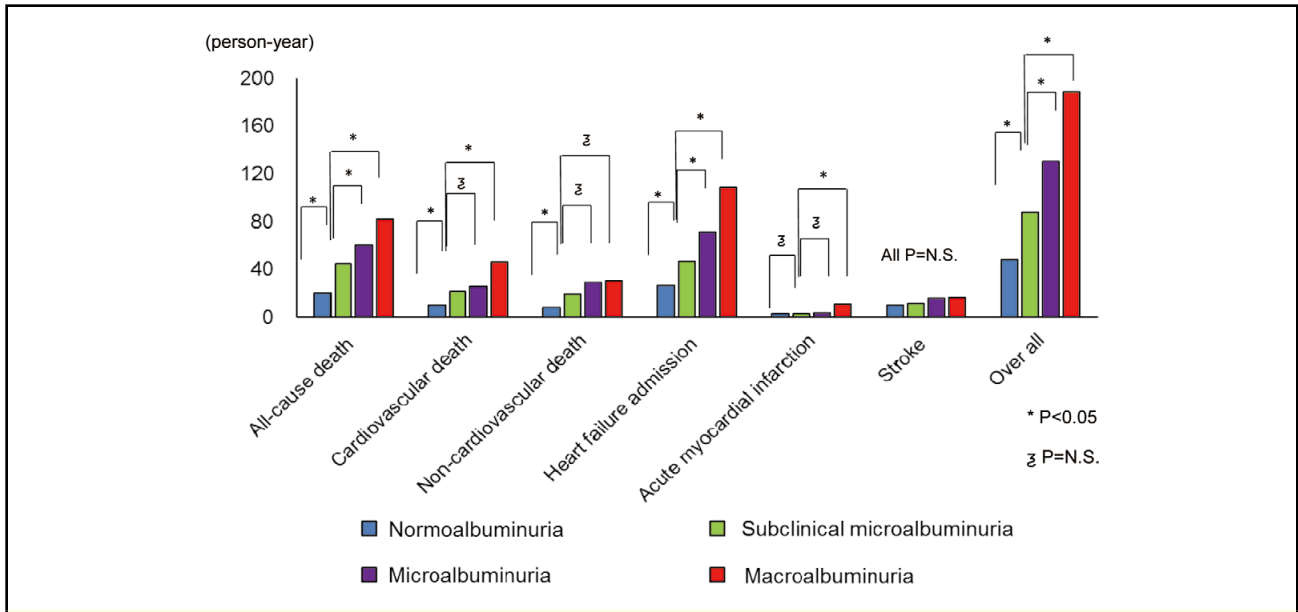
Figure 4. Incidence of composite endpoints. The patients with subclinical microalbuminuria had significantly higher event rates of death, heart failure admission.
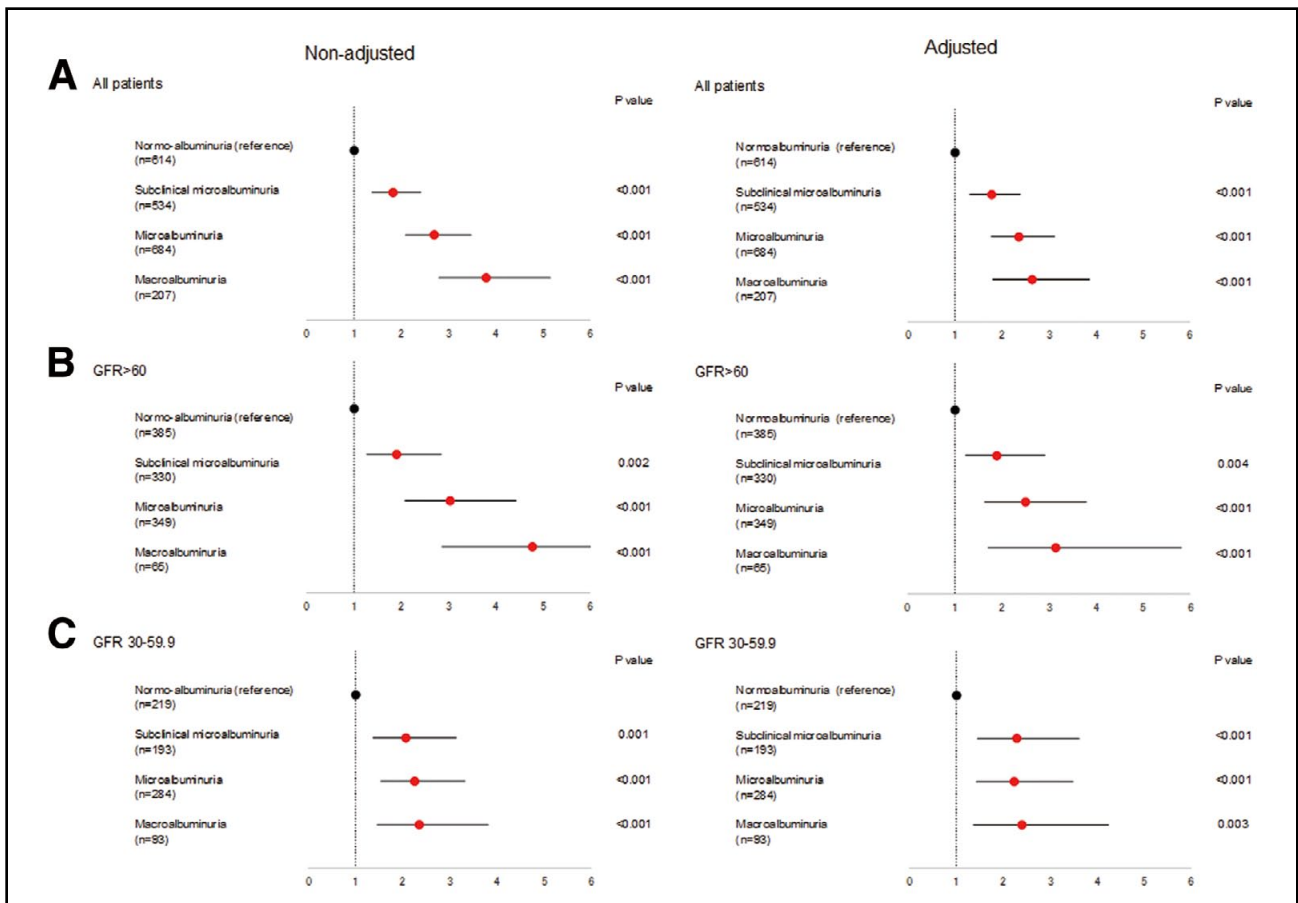

Figure 5. Non-adjusted and adjusted Cox hazard model adjusted for covariates that could potentially influence outcome: (**A**) all patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min⁻¹·1.73m⁻²; and (**C**) eGFR 30–59.9 ml·min⁻¹·1.73m⁻².

Table 2. Subgroup Analysis for Composite Endpoints

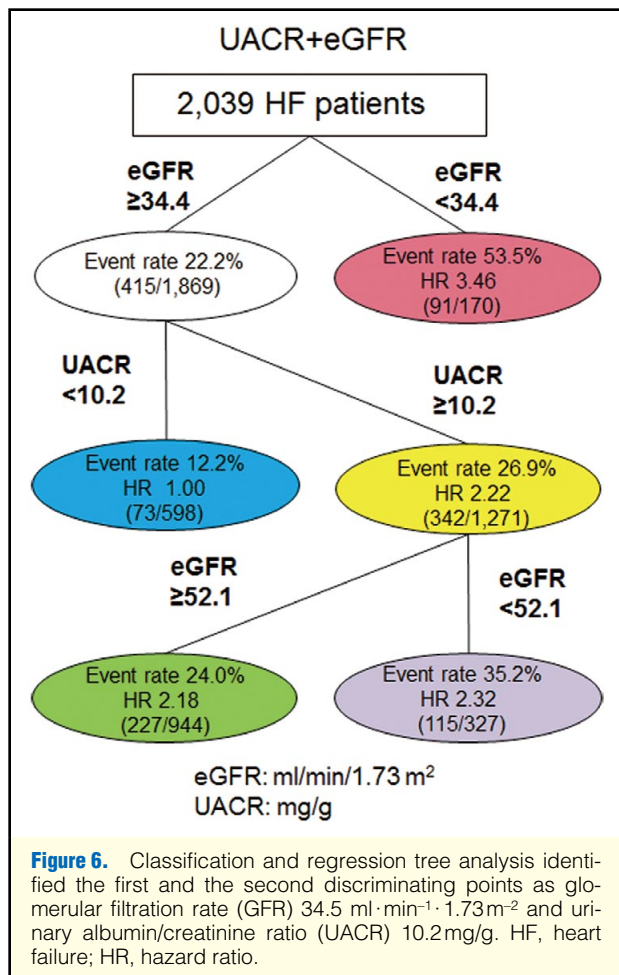|	HR	95% CI	P-value	HR	95% CI	P-value	P for interaction
		Male			**Female**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.96	1.37–2.79	<0.001	1.35	0.75–2.43	0.320	0.40
Microalbuminuria	2.27	1.61–3.19	<0.001	2.25	1.32–3.85	0.003	0.45
Macroalbuminuria	2.71	1.73–4.23	<0.001	3.10	1.50–6.41	0.002	0.33
		Age ≥69 years			**Age <69 years**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	2.04	1.37–3.05	<0.001	1.66	1.02–2.68	0.040	0.35
Microalbuminuria	2.56	1.76–3.73	<0.001	1.95	1.24–3.08	0.004	0.70
Macroalbuminuria	2.75	1.65–4.57	<0.001	3.31	1.83–6.00	<0.001	0.26
		LVEF ≥50%			**LVEF <50%**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.87	1.19–2.94	0.007	1.71	1.13–2.58	0.010	0.14
Microalbuminuria	2.31	1.51–3.55	<0.001	2.31	1.57–3.41	<0.001	0.33
Macroalbuminuria	2.57	1.48–4.47	0.001	2.66	1.55–4.56	<0.001	0.04
		(+) Hypertension			**(–) Hypertension**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.69	1.20–2.38	0.003	1.97	1.01–3.85	0.040	0.66
Microalbuminuria	2.37	1.72–3.26	<0.001	1.70	0.86–3.36	0.140	0.47
Macroalbuminuria	2.52	1.65–3.86	<0.001	5.41	2.30–12.69	<0.001	0.22
		(+) Diabetes			**(–) Diabetes**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.81	1.07–3.07	0.030	1.70	1.17–2.47	0.005	0.78
Microalbuminuria	2.30	1.42–3.73	0.001	2.13	1.48–3.07	<0.001	0.78
Macroalbuminuria	2.26	1.26–4.06	0.006	3.09	1.82–5.23	<0.001	0.17
		(+) β-blocker			**(–) β-blocker**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.98	1.31–2.97	0.001	1.57	0.98–2.50	0.120	0.61
Microalbuminuria	2.39	1.63–3.49	<0.001	1.98	1.28–3.07	0.002	0.87
Macroalbuminuria	2.78	1.66–4.64	<0.001	2.50	1.41–4.43	0.002	0.93
		(+) RAS inhibitor			**(–) RAS inhibitor**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.90	1.32–2.71	0.006	1.49	0.83–2.69	0.180	0.45
Microalbuminuria	2.57	1.83–3.59	<0.001	1.40	0.78–2.54	0.260	0.32
Macroalbuminuria	2.96	1.90–4.62	<0.001	1.62	0.75–3.50	0.220	0.18
		(+) Statin			**(–) Statin**		
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.77	1.04–3.01	0.030	1.78	1.23–2.58	0.002	0.76
Microalbuminuria	2.25	1.37–3.70	0.001	2.29	1.61–3.25	<0.001	0.46
Macroalbuminuria	2.52	1.37–4.64	0.003	2.85	1.74–4.68	<0.001	0.56

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

hemodynamics, and hemoglobin, BUN, eGFR and BNP. The patients with subclinical microalbuminuria and microalbuminuria, however, were characterized by lower prevalence of male gender, whereas LV function was similar among the 4 groups (**Table 1**).

Prognostic Impact of Clinical and Subclinical Microalbuminuria

During the median follow-up period of 2.69 years (IQR, 1.63–3.63 years), composite endpoints occurred in 506 patients (24.8%). **Figure 3A** shows the estimated curves for composite endpoints. As compared with the patients with normoalbumin-uria, those with macroalbuminuria, microalbuminuria and subclinical microalbuminuria had poorer prognosis. As compared with the patients with normoalbuminuria, those with subclinical microalbuminuria had significantly increased incidence of cardiovascular death, non-cardiovascular death, and HF admission, but had similar incidence of acute myocardial infarction and stroke (**Figure 4**). Importantly, the patients with subclinical microalbuminuria and preserved eGFR or mildly reduced eGFR had significantly poorer prognosis compared with those with normoalbuminuria (**Figures 3B,C**). Furthermore, in patients with mildly reduced eGFR, there was no difference in the occurrence of the composite endpoints regard-

Figure 6. Classification and regression tree analysis identified the first and the second discriminating points as glomerular filtration rate (GFR) 34.5 ml·min⁻¹·1.73 m⁻² and urinary albumin/creatinine ratio (UACR) 10.2 mg/g. HF, heart failure; HR, hazard ratio.

less of microalbuminuria, microalbuminuria or macroalbuminuria (**Figure 3C**). There was no difference in composite endpoints in patients with severely reduced GFR among the 4 groups (**Figure 3D**).

Figure 5 shows the results of non-adjusted and adjusted Cox proportional hazard regression models for composite endpoints. As compared with patients with normoalbuminuria (reference), multivariate adjusted Cox models showed that the patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria had 1.70-, 2.39- and 2.49-fold higher risk for composite endpoints, respectively (all P<0.001). In the patients with preserved GFR, the adjusted hazard ratio (HR) and 95%CI for composite endpoints was 1.90 (1.23–2.92), 2.50 (1.64–3.80) and 3.15 (1.71–5.81) for subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. Similarly, in patients with mildly reduced GFR, the adjusted HR (95% CI) was 2.29 (1.45–3.62), 2.24 (1.43–3.49) and 2.40 (1.36–4.24) in patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. On subgroup analysis for composite endpoints, subclinical microalbuminuria was significantly associated with poor prognosis regardless of age, LVEF, hypertension or diabetes (**Table 2**). There was no significant interaction regarding sex and medications on subclinical microalbuminuria for mortality (**Table 2**). In a model using both eGFR and UACR, CART analysis showed that the first discriminating points for composite endpoints was eGFR=34.5 ml·min⁻¹·1.73 m⁻² and the next split point was

UACR=10.2 mg/g (**Figure 6**).

Discussion

The novel findings of the present study are the follows. First, among the patients with stage C/D CHF, CART analysis showed that UACR=27.4 mg/g and 10.2 mg/g were the first and the second discriminating points to stratify risk for composite endpoints, respectively, suggesting the clinical importance of subclinical microalbuminuria in addition to microalbuminuria and macroalbuminuria. Second, approximately one-quarter of the CHF patients had subclinical microalbuminuria, which was associated with poor prognosis regardless of renal function. Importantly, subclinical microalbuminuria had a similar prognostic impact to microalbuminuria and macroalbuminuria in CHF patients with mildly impaired renal function. To the best of our knowledge, the present study is the first to demonstrate the clinical importance of subclinical microalbuminuria in the management of CHF patients in real-world practice.

UACR for Risk Stratification in CHF

Microalbuminuria has been traditionally defined as 30–300 mg/g UACR in the previous studies and the current guidelines,[1] but this definition was originally derived from previous studies with small sample size that focused on determining the level of albuminuria to predict progression to overt proteinuria.[29,30] In the present study, we thus investigated UACR level to discriminate prognostic levels in the general practice of CHF patients. As a result, on CART analysis 27.4 mg/g and 10.2 mg/g were identified as the first and the second cut-off points of UACR, respectively, to discriminate cardiovascular risk of CHF patients. Especially, it is clinically important that we were able to identify UACR=27.4 mg/g as the primary cut-off point to determine prognosis in CHF patients, given that the primary cut-off point for the definition of microalbuminuria is around 30 mg/g in general practice. Furthermore, it is also important that we were able to identify UACR=10.2 mg/g as the secondary discriminating point, suggesting the prognostic impact of subclinical microalbuminuria in CHF patients in general practice.

Subclinical Microalbuminuria and Microalbuminuria in CHF

The present study is the first to demonstrate the prevalence of subclinical microalbuminuria in association with renal function. In the present study, the prevalence of normoalbuminuria (UACR ≤10.2 md/g) was decreased as eGFR increased. Of note, more than half of the patients with preserved or mildly reduced GFR had subclinical microalbuminuria or microalbuminuria associated with worse prognosis. It has been reported that the prevalence of microalbuminuria (UACR >30 mg/g) was 5% in apparently healthy individuals, 16% in patients with hypertension, and almost 30% in those with diabetes mellitus or CHF.[5,6] In the present study, the prevalence of microalbuminuria was approximately 30% overall in the CHF patients regardless of renal function, while that of subclinical microalbuminuria was approximately 20% in CHF patients with preserved or mildly reduced GFR, but <10% in those with reduced GFR (**Figure 2**).

UACR and CHF

The present study primarily showed that CHF patients with microalbuminuria had worse prognosis than those without it, a consistent finding of the previous studies that reported that subjects with microalbuminuria, traditionally defined as UACR 30–300 mg/g, had poorer prognosis regardless of diabetes, hypertension or renal function.[15–17] As reported in patients with

hypertension or diabetes,[2–4] microalbuminuria is also important in CHF patients[6,31] because the disorder is likely to be associated with increased intravascular volume with resultant edema,[7] RAS activation and/or inflammation.[16] In addition, several studies reported that subclinical microalbuminuria (UACR <30 mg/g) was associated with cardiovascular events and HF in the general population and in patients with hypertension, diabetes and CVD.[5,8–14,32] For example, it was reported that the risk of cardiovascular death in patients with diabetes increased almost 10-fold when albuminuria rose from 10 to 30 mg/g,[32] and that this is also the case in the general population.[5] Although the underlying pathophysiology remains to be fully elucidated, subclinical microalbuminuria is considered to be associated with inflammation and hypertriglyceridemia,[5] LV hypertrophy,[7] and progression of atherosclerosis.[33] It was also reported that the mean or median UACR in the general population was around 10 mg/g.[5–7] Thus, it is reasonable to consider that subclinical microalbuminuria above the normal range is associated with poor prognosis.

In the present study, subclinical microalbuminuria was also associated with non-cardiovascular death. Although the underlying mechanisms remain to be elucidated, there are 2 possible explanations. First, it was reported that patients with advanced malignant tumor have a significantly higher urinary albumin excretion rate than those with localized disease.[34] Second, reduced eGFR and albuminuria are associated with increased risk for infection-related mortality.[35] Thus, it is conceivable that subclinical microalbuminuria was associated with non-cardiovascular death, at least in part, as a reflection of severer general condition in CHF patients in the present study.

To our knowledge, only 2 studies previously examined the association between CVD and increasing microalbuminuria in CHF patients.[18,19] Although these studies examined the impact of microalbuminuria, they did not specifically examine that of subclinical albuminuria in detail. The present study is the first to show that UACR=10.2 mg/g and 27.4 mg/g is useful for risk stratification of cardiovascular events in a large-scale observational cohort of CHF patients. In the present study, subclinical microalbuminuria was noted in approximately one-quarter of CHF patients with preserved or mildly reduced GFR (**Figure 2**), and the prognostic impact of subclinical microalbuminuria was similar to that of microalbuminuria and macroalbuminuria. Thus, the clinical importance of subclinical microalbuminuria should be further emphasized in real-world CHF management.

Microalbuminuria and CKD

According to the current classification of CKD, microalbuminuria is defined as a risk factor even though GFR was preserved.[12] In the present study, we were able to show for the first time that not only microalbuminuria (UACR ≥27.4 mg/g) but also subclinical microalbuminuria (UACR 10.2–27.3 mg/g) are significantly associated with poorer prognosis as compared with normoalbuminuria (UACR <10.2 mg/g), particularly in those with preserved or mildly reduced GFR. In the present study, on CART analysis both eGFR (34.5 ml·min^{-1}·1.73 m^{-2}) and UACR were useful as the first discriminating point for the composite endpoints, indicating that the prognostic impact of eGFR <34.5 ml·min^{-1}·1.73 m^{-2} outweighed any classification with UACR (**Figure 6**). Interestingly, however, CART analysis also showed that UACR=10.2 mg/g was the next discriminating point to stratify risk for composite endpoints (**Figure 6**), suggesting the superiority of UACR ≥10.2 mg/g to stratify risk in those without severe renal dysfunction (eGFR ≥34.5 ml·min^{-1}·1.73 m^{-2}). Among the patients with eGFR ≥34.5 ml·min^{-1}·1.73 m^{-2}, those with UACR ≥10.2 mg/g had

increased incidence of cardiovascular events as compared with those without it (HR, 2.22; P<0.001; **Figure 6**). These results indicate that subclinical microalbuminuria is a therapeutic target in patients with preserved or mildly reduced GFR. Thus, we should pay more attention to subclinical microalbuminuria especially in patients with preserved or mildly reduced GFR, including those who are not classified as having CKD according to the current guidelines.

Study Limitations

Several limitations should be mentioned for the present study. First, in the present study, the patients with UACR data accounted for only approximately 50% of the total cohort. Patient background was considerably different between the patients with UACR measurement and those without it (**Table S1**). To minimize the influence of this selection bias, we performed a consistency analysis. Based on the propensity scores derived from 24 clinical variables, we randomly selected 1,440 individuals from the final subject group whose characteristics were similar to those of 2,591 patients excluded from the present study because of lack of UACR measurement. There were no difference in patient background or prognosis between the selected 1,440 patients with UACR measurement and excluded 2,591 patents without it (**Figure S1**; **Table S1**). Thus, we consider that no significant selection bias of patients was involved in the present study. Second, the present results were analyzed using data collected at study entry and we did not take into consideration the possible changes in UACR during the follow-up period. Third, all subjects in the CHART-2 Study were Japanese, which may limit extrapolation of the present results to patients in Western countries. Finally, given that the CHART-2 Study is an observational study, there might be unmeasured confounding factors influencing the present results. Thus, interpretation of the present results should be done carefully when generalizing it to other cohorts.

Conclusions

UACR=27.4 mg/g and 10.2 mg/g are the first and the second discriminating points to stratify risk in CHF patients regardless of renal function. Thus, the clinical importance of subclinical microalbuminuria should be underlined in the management of CHF patients in real-world practice, although studies are needed to further confirm the present results.

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Supplementary Files

Supplementary File 1

Table S1. Baseline patient characteristics vs. presence of UACR measurement

Figure S1. Prognostic impact of subclinical microalbuminuria in the matched patients with urinary albumin/creatinine ratio measurement.

Appendix S1. Organization of the CHART-2 Study