

# Urinary albumin excretion in heart failure with preserved ejection fraction: an interim analysis of the CHART 2 study

Masanobu Miura<sup>1</sup>, Nobuyuki Shiba<sup>2</sup>, Kotaro Nochioka<sup>1</sup>, Tsuyoshi Takada<sup>1</sup>, Jun Takahashi<sup>1</sup>, Haruka Kohno<sup>1</sup>, and Hiroaki Shimokawa<sup>1\*</sup>, on behalf of the CHART-2 Investigators

<sup>1</sup>Department of Cardiovascular Medicine and Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; and  
<sup>2</sup>Department of Cardiovascular Medicine, International University of Health and Welfare, Nasushiobara, Japan

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## Aims

Heart failure with preserved ejection fraction (HFpEF) is characterized by multiple co-morbidities, including chronic kidney disease that is one of the prognostic risks for these patients. This study was performed to evaluate the value of determination of albuminuria using a urine dipstick test (UDT), combined with estimated glomerular filtration rate (eGFR), for prediction of mortality in HFpEF.

## Methods and results

We enrolled 2465 consecutive patients with overt HF with EF  $\geq 50\%$  in our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) study (NCT00418041). We defined trace or more UDT as positive. We divided the patients into the following four groups based on eGFR and UDT; group 1 (G1) (eGFR  $\geq 60$ , negative UDT), G2 (eGFR  $\geq 60$ , positive UDT), G3 (eGFR  $< 60$ , negative UDT), and G4 (eGFR  $< 60$ , positive UDT). In total, 29.5% of the HFpEF patients had a positive UDT. HFpEF patients with a positive UDT were characterized by higher brain natriuretic peptide levels and frequent histories of hypertension or diabetes. During a mean follow-up of 2.5 years, HFpEF patients with a positive UDT showed higher mortality in each stratum of eGFR levels. A multivariable adjusted Cox model showed that when compared with G1 (reference), the hazard ratio of all-cause death for G2, G3, and G4 was 2.44 (95% confidence interval 1.47–4.05,  $P=0.001$ ), 1.43 (0.92–2.23,  $P=0.12$ ), and 2.71 (1.72–4.27,  $P<0.001$ ), respectively. Furthermore, the prognostic value of a positive UDT was robust for both cardiovascular and non-cardiovascular deaths.

## Conclusions

These results indicate that measurement of albuminuria in addition to eGFR is useful for appropriate risk stratification in HFpEF patients.

## Keywords

Heart failure with preserved ejection fraction • Albuminuria • Urine dipstick test • Estimated glomerular filtration rate

## Introduction

A meta-analysis reported that patients with heart failure with preserved ejection fraction (HFpEF) might have a lower risk of death compared with those with heart failure with reduced ejection fraction (HFrEF); however, the mortality in HFpEF is still high.<sup>1</sup> Furthermore, there are no authorized treatment guidelines for HFpEF due to its pathophysiological heterogeneity.<sup>2,3</sup> Recent

guidelines recommend the inclusion of objective evidence of diastolic dysfunction in diagnosing HFpEF;<sup>4</sup> however, diagnostic methods for diastolic dysfunction using echocardiography are clinically difficult. Therefore, simple diagnosing tools are needed for appropriate risk stratification in HFpEF patients.

HFpEF is typically characterized by multiple co-morbidities.<sup>5</sup> The co-existence of HF and chronic kidney disease (CKD) carries an extremely poor prognosis.<sup>6</sup> Furthermore, the prognosis of

\* Corresponding author. Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. Tel: +81 22 717 7151, Fax: +81 22 717 7156, Email: shimo@cardio.med.tohoku.ac.jp

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HFpEF patients may be more influenced by the existence of CKD compared with those with HFrEF.<sup>5,7</sup> Thus, the effective treatment of CKD may be more essential in HFpEF than in HFrEF.

Albuminuria is a well-known independent risk factor for mortality in the general population,<sup>8</sup> and in those with hypertension<sup>9</sup> and diabetes,<sup>10</sup> reflecting glomerular injury, systemic inflammation, and activation of the renin–angiotensin system (RAS). Therefore, the use of the urine albumin to creatinine ratio (UACR) is currently emphasized to evaluate the severity of CKD.<sup>11</sup> However, the severity of CKD is usually defined by a reduced estimated glomerular filtration rate (eGFR). In HF patients, it has been reported that the prevalence of patients with albuminuria ( $\geq 30$  mg/g) was  $\sim 30\%$ .<sup>12,13</sup> Furthermore, HF patients with albuminuria ( $\geq 30$  mg/g) had poorer prognosis.<sup>13–16</sup> However, most of the HF patients included in these studies had HFrEF.

The aim of this study was to evaluate the prognostic value of albuminuria using a urine dipstick test (UDT) combined with eGFR in HFpEF patients in our Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) study.

## Methods

### Population and inclusion criteria

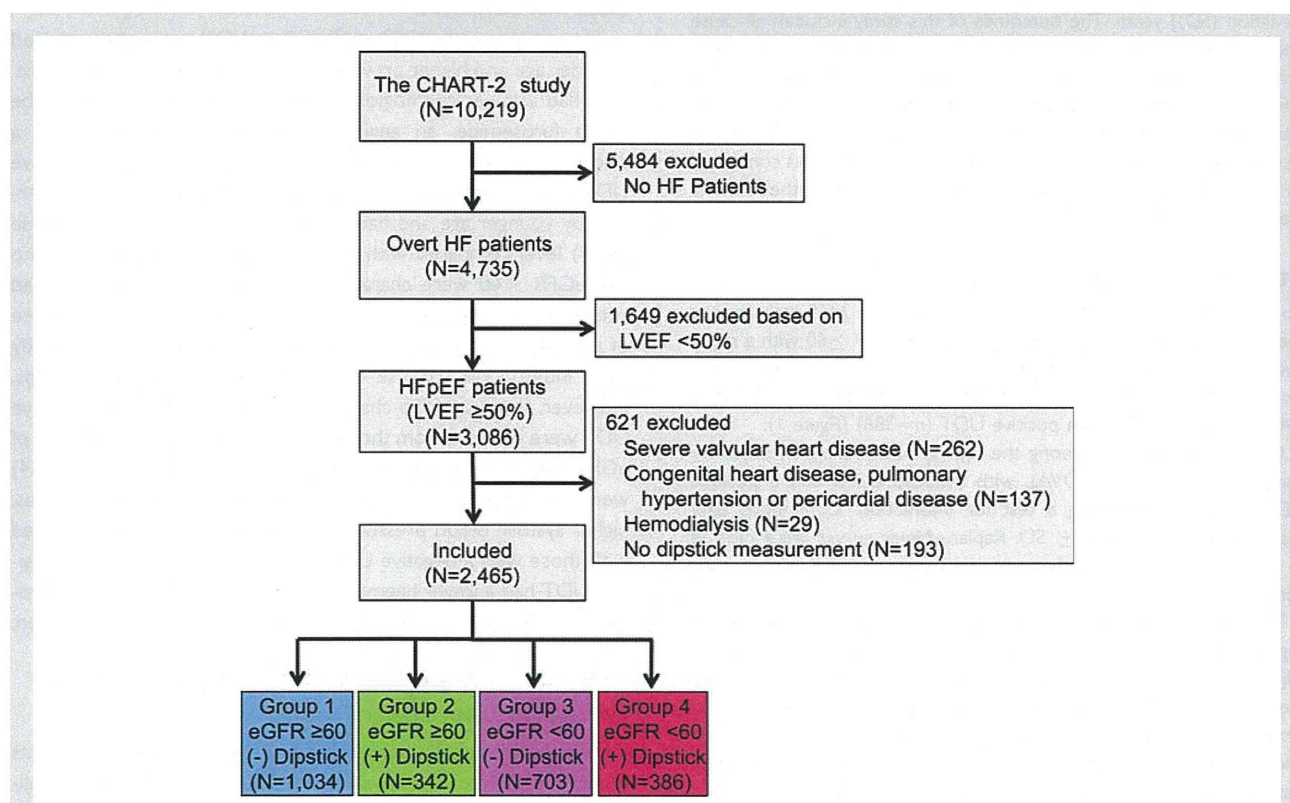
Details of the design, purpose, and basic characteristics of the CHART-2 study have been described previously (NCT00418041).<sup>17</sup> Briefly, eligible patients were aged  $\geq 20$  years with significant coronary

artery disease or in stage B, C, or D defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults.<sup>18</sup> Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.<sup>19</sup> We excluded patients consuming alcohol or drugs, using alternative therapies, and undergoing chemotherapy. The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively recruited after written informed consent was obtained. The CHART-2 study was started in October 2006 and the entry period was successfully closed in March 2010 with 10 219 patients registered from the 24 participating hospitals. All data and events will be surveyed at least once a year until March 2013.

In the CHART-2 study, left ventricular ejection fraction (LVEF) was measured by echocardiography at the time of enrolment. In the present study, patients with LVEF  $\geq 50\%$  were classified as having HFpEF, whereas those with LVEF  $< 50\%$  were classified as having HFrEF.<sup>1</sup> The study flow diagram is shown in Figure 1. In the present study, we excluded patients in stage B and those with severe valvular heart disease (VHD), congenital heart disease, pulmonary arterial hypertension, pericardial disease, or on haemodialysis (Figure 1). Severe VHD was defined by the Guidelines for the management of patients with VHD.<sup>20</sup> We also excluded patients who did not have UDT measurement. Therefore, 2465 HFpEF patients were finally included in the present study (Figure 1).

### Measurements of albuminuria

Albuminuria in the study population was qualitatively evaluated using UDT. UDT was performed at the outpatient department of each



**Figure 1** Study flow diagram. eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction.

institute but not in a central laboratory. In those patients who agreed to participate in this study during their admission for HF, UDT was performed at discharge. Eight kinds of UDTs marketed by five medical corporations were used in the participating hospitals. The names of the corporations and percentage of patients were as follows: ARKLEY, Inc., Kyoto, Japan (39.4%), Eiken Chemical Co. Ltd, Tokyo, Japan (26.2%), Siemens AG, Munich, Germany (21.9%), SYSMEX Corporation, Kobe, Japan (8.6%), Roche Diagnostics, Basel, Switzerland (3.6%), and unknown, 0.4%. All UDTs were calibrated to indicate 1+ qualitatively at a urine protein concentration of  $\geq 0.3$  g/L. The dipsticks of the four corporations (ARKELEY, Siemens AG, Eiken Chemical, and SYSMEX) were calibrated to indicate trace proteinuria at  $\geq 0.15$  g/L,  $\geq 0.1$  g/L,  $\geq 0.15$  g/L, and  $\geq 0.1$  g/L, respectively.

It has been reported that trace proteinuria evaluated by UDT could be a useful indicator of albuminuria ( $\geq 30$  mg/g) in subjects at high risk of cardiovascular disease.<sup>21</sup> Furthermore, a recent study reported that trace UDT could identify urine albuminuria ( $\geq 30$  mg/g) with high specificity and negative predictive value.<sup>22</sup> Thus, in the present study, we defined a positive UDT for proteinuria as trace or more and the remainder as a negative UDT.

### Renal function

Estimated GFR (mL/min/1.73 m<sup>2</sup>) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient<sup>23</sup> at the time of enrolment. We defined reduced eGFR as  $< 60$  mL/min/1.73 m<sup>2</sup> according to the guideline.<sup>11</sup>

### Follow-up survey and study outcomes

We conducted the first survey of survival in August 2010, and the mean follow-up period of the study population was  $2.5 \pm 1.0$  [standard deviation (SD)] years. The outcomes of this study included all-cause death, cardiovascular death (CVD), and non-cardiovascular death (NCVD). CVD was defined as deaths due to myocardial infarction, HF, cerebrovascular disease, aortic aneurysm rupture, and sudden death. Deaths other than CVD were classified as NCVD. The mode of death was determined by the attending physician and was confirmed by one independent physician who was a member of the Tohoku Heart Failure Association.<sup>17</sup>

### Statistical analysis

To evaluate the usefulness of UDT, we divided the 2465 patients into the following four groups: group 1 (G1) with eGFR  $\geq 60$  with a negative UDT ( $n=1043$ ), G2 with eGFR  $\geq 60$  with a positive UDT ( $n=342$ ), G3 with eGFR  $< 60$  with a negative UDT ( $n=703$ ), and G4 with eGFR  $< 60$  with a positive UDT ( $n=386$ ) (Figure 1).

Comparisons of data among the four groups were performed by analysis of variance (ANOVA), with reduced eGFR and a positive UDT as factors, including a test for interaction. Continuous data were described as mean  $\pm$  SD. Kaplan–Meier curves were plotted to evaluate the association between the results of UDT and all-cause death, CVD, and NCVD.

We also constructed the following four Cox proportional hazard regression models: (a) unadjusted; (b) age- and sex-adjusted; (c) adjusted by the clinical status and co-morbidities in addition to model (b); and (d) fully adjusted including medical treatments. In model (c), we included the following covariates that potentially influence the outcomes; age, sex, New York Heart Association class, history of admission for HF and malignant tumour, body mass index, systolic blood pressure,<sup>24</sup> heart rate,<sup>25</sup> serum sodium, serum potassium, co-morbidities<sup>24</sup> (anaemia defined as haemoglobin  $< 12$  g/dL in females and  $< 13$  g/dL in males, diabetes mellitus, hyperuricaemia,

atrial fibrillation, history of coronary artery disease, and cerebrovascular disease), and brands of UDT. In model (d), we included treatment (beta-blockers, RAS inhibitors, calcium channel blockers, loop diuretics, and aldosterone antagonists) in addition to model (c). Finally, to determine the prognostic value of UDT in addition to eGFR, we constructed Cox proportional hazard models in patients with eGFR  $\geq 60$  or  $< 60$  separately including all covariates in model (d) plus eGFR level.

All statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was defined as a two-sided *P*-value  $< 0.05$ .

## Results

### Baseline characteristics (Table 1)

Mean age was  $69.6 \pm 11.7$  years and male patients accounted for 68.2% of the study population. Coronary artery disease was observed in 52.1% and the mean LVEF and eGFR were  $65.3 \pm 9.0\%$  and  $62.4 \pm 24.3$  mL/min/1.73 m<sup>2</sup>, respectively. The prevalence of patients with eGFR  $< 60$  was 44.1% ( $n=1089$ ). The prevalence of patients with a positive UDT was 29.5% ( $n = 728$ ). Furthermore, the prevalence of patients with a positive UDT and with eGFR  $< 60$  was higher (35.4%,  $n = 386$ ) than that of patients with a positive UDT and with eGFR  $\geq 60$  (24.9%,  $n = 342$ ). Among the positive dipsticks, the prevalence of trace proteinuria was the highest. Male and older patients had higher prevalence of positive UDT. Furthermore, the patients with eGFR  $< 60$  had more severe positive dipsticks compared with those with eGFR  $\geq 60$ .

The patients with eGFR  $< 60$  (G3 and G4) were characterized by older age and higher prevalence of HF admission. Furthermore, they had a lower haemoglobin level and were more likely to be taking furosemide, an angiotensin II receptor blocker, and a calcium channel blocker. The G1 and G3 patients had a negative UDT. The patients in G1 who had an eGFR  $\geq 60$  were characterized by younger age and had the lowest brain natriuretic peptide (BNP) level compared with other groups. The G3 patients who had eGFR  $< 60$  were characterized by more females compared with other groups. There were no differences in the prevalence of past history of coronary artery disease, atrial fibrillation, body mass index, LVEF, or use of beta-blockers among the groups. However, some baseline characteristics of patients with a positive UDT were different from those with a negative UDT. Regardless of eGFR decline, HFpEF patients with a positive UDT (G2 and G4) were characterized by higher prevalence of diabetes mellitus, higher systolic blood pressure, and elevated heart rate compared with those with a negative UDT. Furthermore, those with a positive UDT had a lower haemoglobin level, higher blood urea nitrogen level, lower eGFR level, and higher BNP level with interaction.

### Impact of a positive urine dipstick test for all-cause death

During the mean follow-up period of  $2.5 \pm 1.0$  years, 213 patients (8.6%) died. Figure 2A shows Kaplan–Meier survival curves for all-cause death. Groups with a positive UDT (G2 and G4) had poorer prognosis than those with a negative UDT (G1 and G3) within each stratum of eGFR (both  $P < 0.001$ ). Importantly, patients with



**Table I** Baseline characteristics of the study patients

Reduced eGFR Urine dipstick test	Group 1 (n=1034)	Group 2 (n=342)	Group 3 (n=703)	Group 4 (n=386)	P-value among the four groups	ANOVA		
	- Negative	- Positive	+ Negative	+ Positive		Reduced eGFR	Positive UDT	Interaction
Age (years)	66.2 ± 11.8	67.3 ± 12.4	73.9 ± 9.5	73.1 ± 10.8	<0.001	<0.001	0.001	0.98
Male (%)	69.4	76.3	62.2	68.9	<0.001	<0.001	0.82	0.07
History of admission for HF (%)	38.8	48.4	53.1	56.1	<0.001	0.86	0.42	0.06
History of malignant tumour (%)	9.5	12.0	13.1	13.2	0.10			
Co-morbidities (%)								
Hypertension	70.8	75.6	76.4	85.1	<0.001	0.003	<0.001	0.62
Diabetes	22.0	29.2	21.6	33.2	<0.001	0.35	<0.001	0.62
Hyperuricaemia	26.0	26.6	55.0	60.1	<0.001	<0.001	0.17	0.28
Atrial fibrillation	27.8	33.0	35.2	31.7	0.05			
Coronary artery disease	52.2	48.5	51.1	56.7	0.15			
Cerebrovascular disease	12.2	16.7	19.8	21.5	<0.001	<0.001	0.06	0.40
Clinical status								
NYHA class III and IV (%)	6.3	5.6	12.1	11.5	<0.001	<0.001	0.06	0.40
Body mass index (kg/m <sup>2</sup> )	23.9 ± 4.5	23.9 ± 5.6	23.7 ± 4.7	23.7 ± 4.4	0.87			
Systolic blood pressure (mmHg)	127 ± 17.1	132 ± 18.9	128 ± 19.2	133 ± 20.1	<0.001	0.24	<0.001	0.38
Diastolic blood pressure (mmHg)	74.1 ± 11.1	75.1 ± 12.6	71.7 ± 12.3	72.5 ± 12.1	<0.001	<0.001	0.08	0.82
Heart rate (b.p.m.)	70.9 ± 13.9	73.6 ± 15.8	70.7 ± 13.8	72.5 ± 12.1	0.003	0.45	<0.001	0.63
Measurement								
LVEF (%)	65.2 ± 9.0	65.0 ± 9.4	65.7 ± 9.1	64.8 ± 8.5	0.40			
LVDd (mm)	48.8 ± 6.9	49.0 ± 7.3	48.7 ± 7.5	49.1 ± 7.4	0.74			
Haemoglobin (g/dL)	13.7 ± 1.7	13.8 ± 2.4	12.7 ± 2.0	12.2 ± 2.1	<0.001	<0.001	0.002	0.001
Blood urea nitrogen (mg/dL)	15.3 ± 4.2	15.5 ± 4.1	22.3 ± 8.8	26.2 ± 12.0	<0.001	<0.001	<0.001	<0.001
Serum sodium (mEq/L)	141 ± 2.6	141 ± 2.9	141 ± 2.8	141 ± 3.2	0.40			
Serum potassium (mEq/L)	4.3 ± 0.4	4.2 ± 0.4	4.5 ± 0.5	4.4 ± 0.5	<0.001	<0.001	0.005	0.38
GFR (mL/min/1.73 m <sup>2</sup> )	76.5 ± 29.6	77.3 ± 15.7	45.6 ± 11.0	40.5 ± 12.9	<0.001	<0.001	0.002	<0.001
Brain natriuretic peptide (pg/mL)	95 ± 118	135 ± 162	160 ± 177	242 ± 467	<0.001	<0.001	<0.001	0.047

Medications	40.9	50.3	43.5	39.4	0.01	0.06	0.23	0.002
ACE inhibitor (%)	40.9	50.3	43.5	39.4	0.01	0.06	0.23	0.002
ARB (%)	30.7	27.2	37.4	40.9	<0.001	<0.001	0.96	0.09
Beta-blocker (%)	43.0	49.7	44.4	44.8	0.20	<0.001	<0.001	0.28
Calcium channel blocker (%)	41.8	48.0	48.4	59.3	0.03	<0.001	<0.001	0.73
Loop diuretics (%)	32.8	34.8	52.3	52.8	<0.001	<0.001	0.56	0.51
Furosemide dose (mg)	6.8 ± 13.7	8.7 ± 17.0	12.6 ± 19.2	13.4 ± 19.1	<0.001	<0.001	0.08	0.01
Aldosterone inhibitor (%)	14.1	16.1	23.8	17.4	<0.001	0.001	0.19	
Statins (%)	40.1	35.7	41.8	43.3	0.17			

Analysis of variance (ANOVA) with reduced eGFR and positive urine dipstick test (UDT) as factors, including a test for interaction, was used to identify variables that were associated with reduced eGFR and/or positive urine dipstick test. Numerical data are shown as mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

a positive UDT and eGFR ≥ 60 (G2) showed significantly poorer prognosis compared with those with a negative UDT and eGFR ≥ 60 (G1).

Table 2 shows the results of multivariable Cox proportional hazard regression analysis for all-cause death (the upper portion). In the unadjusted model (a), as compared with G1 (reference), G2, G3, and G4 showed 202, 239, and 500% increases in the risk for all-cause death, respectively (all  $P < 0.001$ ). In model (c), as compared with G1, the hazard ratios (HRs) (95% confidence intervals) for all-cause death of G2, G3, and G4 were 2.60 (1.59–4.24), 1.47 (0.94–2.27), and 2.63 (1.67–4.13), respectively. Importantly, the significance of HRs for all-cause death in G2 and G4 remained robust after the adjustment by HF treatments in model (d).

### Impact of a positive urine dipstick test for cardiovascular and non-cardiovascular death

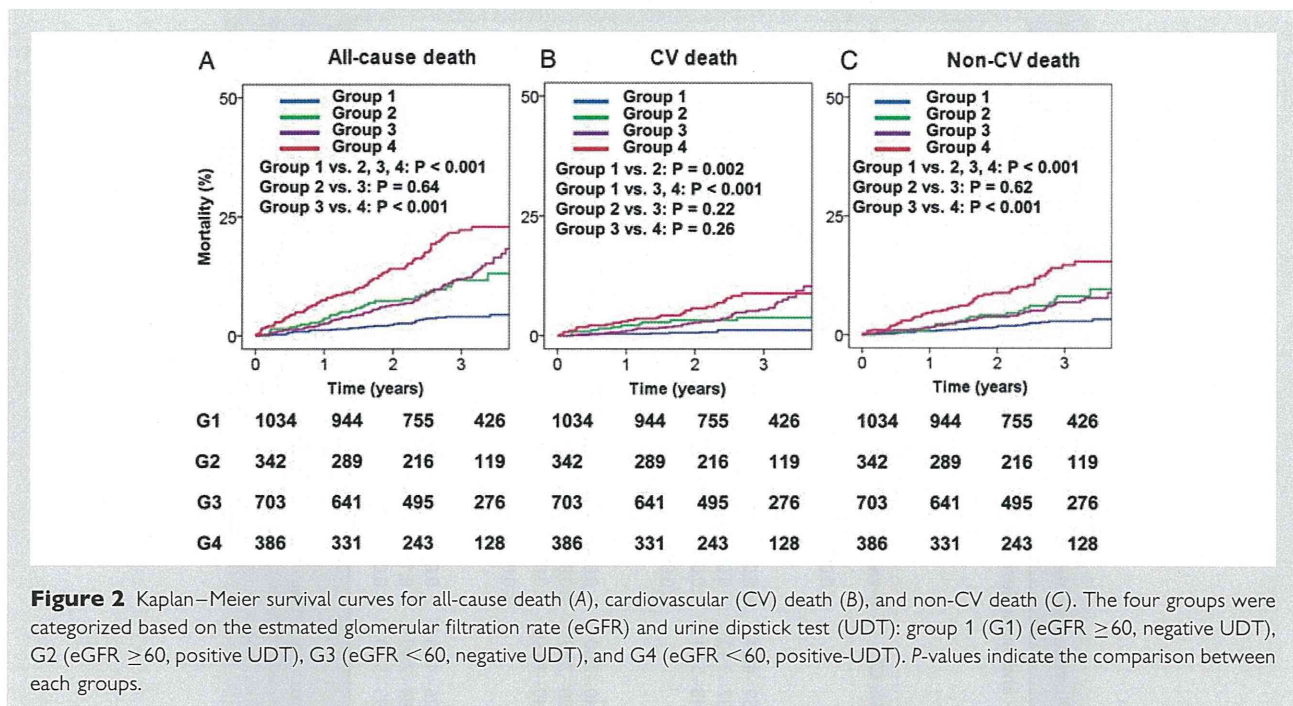
Of the 213 deaths noted, 86 (40.4%) were due to a cardiovascular cause. Figure 2B shows Kaplan–Meier survival curves for CVD. G2 showed significantly higher cardiovascular mortality compared with G1 ( $P < 0.001$ ). However, there was no significant difference in CVD between G3 and G4. Table 2 shows the results of multivariable Cox proportional hazard regression analysis for CVD (the middle portion). In the fully adjusted model (d), as compared with G1 (reference), the HRs (95% CI) for CVD of G2, G3, and G4 were 3.58 (1.50–8.58), 2.34 (1.10–4.98), and 3.29 (1.48–7.31), respectively. Importantly, the significance of HRs for CVD in G2 and G4 remained robust in models (b), (c), and (d).

Non-cardiovascular death was observed in 127 patients during the study period. Figure 2C shows Kaplan–Meier survival curves for NCVD. Groups with a positive UDT had significantly more NCVDs than those with a negative UDT within each stratum of GFR (both  $P < 0.001$ ). Table 2 shows the results of multivariable Cox proportional hazard regression analysis for NCVD (the lower portion). In model (a), as compared with G1 (reference), the HRs (95% CI) for NCVD of G2, G3, and G4 were 2.75 (1.52–4.98), 2.41 (1.45–4.01), and 5.37 (3.26–8.83), respectively. However, in models (b), (c), and (d), the HR for NCVD in G3 was not significantly higher compared with those in G1 (Table 2). Again, the significance of HRs for NCVD in G2 and G4 remained robust in models (b), (c), and (d).

### Prognostic importance of urine dipstick test in addition to estimated glomerular filtration rate

About one-third of HFpEF patients in the present study had a positive UDT. Figure 3 shows the results of Cox proportional hazard regression analysis for eGFR ≥ 60 or < 60 adjusted by the covariates including eGFR. In HFpEF patients with eGFR ≥ 60, as compared with G1, G2 showed a 227, 293, and 216% increase in the risk for all-cause death, CVD, and NCVD, respectively (all  $P < 0.001$ ). In HFpEF patients with eGFR < 60, as compared with G3, G4 showed a 174% and 212% increase in the risk for all-cause mortality and NCVD, respectively, whereas there was no significant difference for CVD.





## Discussion

The novel findings of the present study are as follows. First,  $\sim 30\%$  of the HFpEF patients had a positive UDT. Secondly, HFpEF patients with a positive UDT had significantly higher mortality as compared with those with a negative UDT in each stratum of eGFR levels. Thirdly, the prognostic impact of a positive UDT was significantly enhanced after adjustment by the covariates including eGFR. These findings indicate that we need to perform UDT in addition to eGFR in all HFpEF patients for appropriate risk stratification, especially in HFpEF patients with eGFR  $\geq 60$ .

### Albuminuria as a marker of cardiorenal syndrome in heart failure with preserved ejection fraction

Albuminuria is known to be an independent risk factor for mortality in the general population and in patients with hypertension or diabetes.<sup>8–10</sup> In HF patients, the prevalence of patients with albuminuria ( $\geq 30$  mg/g) is  $\sim 30\%$ .<sup>12,13</sup> Furthermore, HF patients with albuminuria ( $\geq 30$  mg/g) had a poorer prognosis independent of diabetes, hypertension, or renal function.<sup>13–16</sup> Anand et al. reported that proteinuria was associated with abnormal physical findings and clinical indicators of volume overload, which suggests a possible pathogenic role of increased intravascular volume.<sup>14</sup> Furthermore, RAS activation and inflammation have been suggested to play causal roles in increasing albuminuria.<sup>16</sup> Therefore, HF patients with albuminuria ( $\geq 30$  mg/g) may have higher RAS activity compared with those without albuminuria. However, most of the HF patients included in these studies had HFrEF.

To our knowledge, this is the first report of the relationship between HFpEF and albuminuria using UDT. In HFpEF patients,

the prevalence of albuminuria ( $\geq 30$  mg/g) was almost similar to that in those with HFrEF. Furthermore, HFpEF patients with a positive UDT had a significantly poorer prognosis. The mechanisms linking albuminuria and HFpEF remain unknown. However, there may not be a large difference between HFrEF and HFpEF in terms of the mechanism of elevated albuminuria.

Chronic kidney disease is a frequent complication of HF, and this close association has been called the cardiorenal syndrome (CRS).<sup>26</sup> Both CKD and HF are associated with an increased activity of the sympathetic nervous system, and RAS activation, oxidative stress, and inflammation.<sup>26</sup> Therefore, we usually pay attention to renal function in HF patients. Compared with HFrEF patients, HFpEF patients were considered to have lower RAS activity.<sup>27</sup> However, according to the pathophysiology of elevated albuminuria in HF patients, HFpEF patients with albuminuria ( $\geq 30$  mg/g) may have higher RAS activity than those with normal albuminuria. Therefore, the linkage between the heart and kidney in HFpEF patients with albuminuria ( $\geq 30$  mg/g) may be greater than in HFpEF patients with normal albuminuria. So, the measurement of albuminuria is essential to evaluate CRS in addition to eGFR in all HF patients.

### Benefit of the combination of estimated glomerular filtration rate and urine dipstick test in predicting the prognosis in heart failure with preserved ejection fraction

Patients with HFpEF usually tend to be older and female.<sup>1</sup> In most clinical settings, eGFR is calculated by age, sex, and serum creatinine.<sup>23</sup> Therefore, some HFpEF patients may have an eGFR  $< 60$  without significant renal damage. Indeed, in the present study,

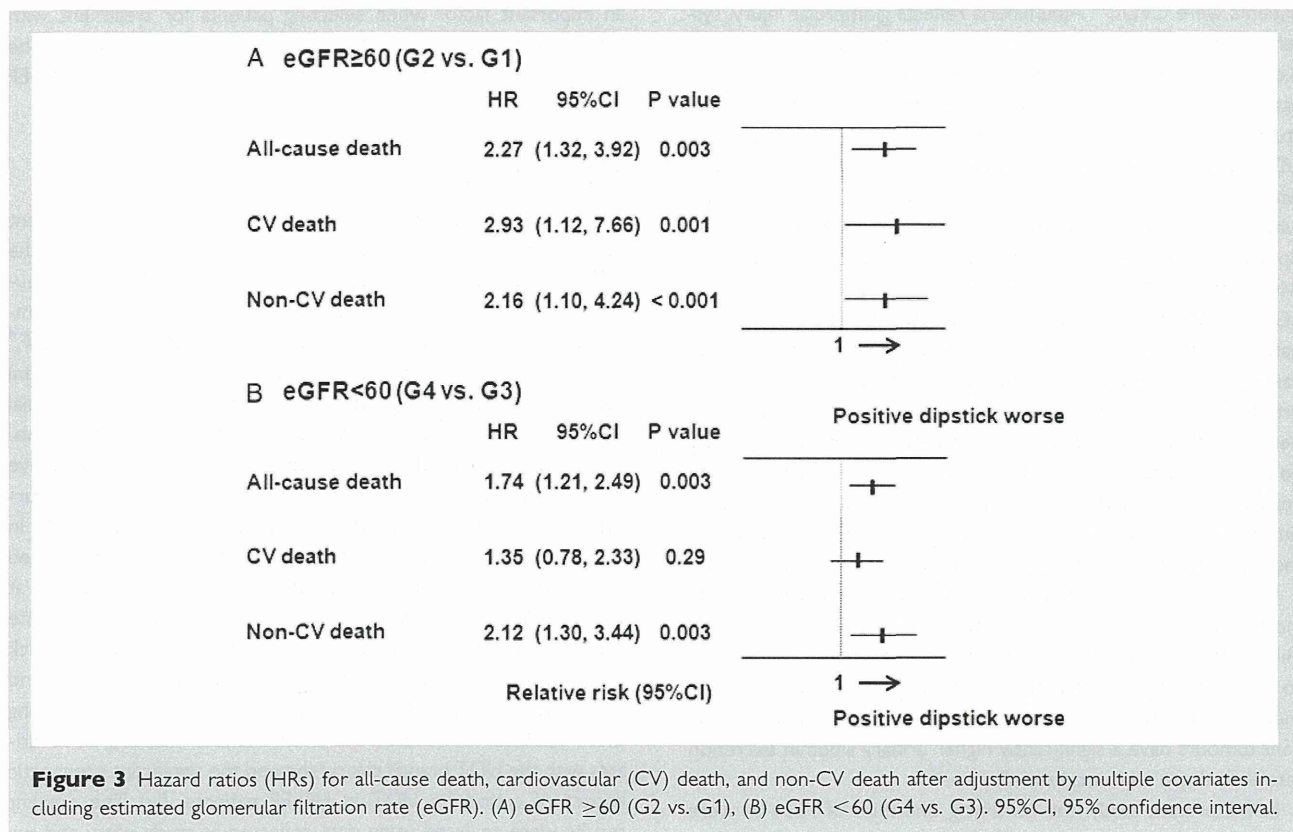
**Table 2** Cox proportional hazard model for all-cause death, cardiovascular death, and non-cardiovascular death

HR categories	eGFR <60	Dipstick	No. of events (%)	No. of events/100 person/year	(a) Unadjusted			(b) Age- and sex-adjusted			(c) All baseline adjusted			(d) Fully adjusted including treatment							
					HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value					
All-cause death																					
					Group 1 (reference)	-	-	34 (3.3)	1.5	1.00											
					Group 2	-	+	31 (9.0)	4.0	3.02	1.85-4.91	<0.001	2.60	1.59-4.24	<0.001	2.57	1.56-4.25	<0.001	2.44	1.47-4.05	0.001
					Group 3	+	-	78 (11.0)	4.4	3.39	2.26-5.07	<0.001	2.07	1.37-3.13	0.001	1.46	0.94-2.27	0.09	1.43	0.92-2.23	0.12
			Group 4	+	+	70 (18.1)	7.9	6.00	3.98-9.04	<0.001	3.78	2.48-5.74	<0.001	2.63	1.67-4.13	<0.001	2.71	1.72-4.27	<0.001		
Cardiovascular death																					
					Group 1 (reference)	-	-	10 (1.0)	0.4	1.00											
					Group 2	-	+	11 (3.2)	1.4	3.65	1.55-8.59	0.003	3.30	1.40-7.80	0.006	3.66	1.53-8.72	0.003	3.58	1.50-8.58	0.004
					Group 3	+	-	39 (5.5)	2.2	5.72	2.85-11.45	<0.001	3.68	1.80-7.49	<0.001	2.34	1.13-5.09	0.023	2.34	1.10-4.98	0.03
			Group 4	+	+	26 (6.7)	2.9	7.53	3.63-15.63	<0.001	5.06	2.40-10.60	<0.001	3.25	1.47-7.18	0.004	3.29	1.48-7.31	0.003		
Non-cardiovascular death																					
					Group 1 (reference)	-	-	24 (2.3)	1.1	1.00											
					Group 2	-	+	20 (5.8)	2.6	2.75	1.52-4.98	0.001	2.29	1.26-4.16	0.007	2.03	1.09-3.78	0.026	1.89	1.01-3.54	0.048
					Group 3	+	-	39 (5.5)	2.2	2.41	1.45-4.01	0.001	1.42	0.84-2.40	0.18	1.06	0.61-1.86	0.83	1.05	0.60-1.84	0.88
			Group 4	+	+	44 (11.4)	5.0	5.37	3.26-8.83	<0.001	3.24	1.95-5.40	<0.001	2.41	1.39-4.19	0.002	2.51	1.44-4.37	0.001		

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

In model (c), we adjusted the model by age, sex, and clinical status (New York Heart Association class, systolic blood pressure, heart rate, body mass index, left ventricular ejection fraction), serum sodium, serum potassium, history of malignant tumour, and admission for heart failure, and co-morbidities (diabetes, hyperuricaemia, anaemia, coronary artery disease, cerebrovascular disease, atrial fibrillation), and five urine dipstick test brands. In model (d), in addition to model (c), we adjusted the model by treatment (beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, loop diuretics, aldosterone antagonist).





**Figure 3** Hazard ratios (HRs) for all-cause death, cardiovascular (CV) death, and non-CV death after adjustment by multiple covariates including estimated glomerular filtration rate (eGFR). (A) eGFR  $\geq$ 60 (G2 vs. G1), (B) eGFR <60 (G4 vs. G3). 95%CI, 95% confidence interval.

HFpEF patients in G3 were older and there were more females as compared with other groups. The present result shows that HFpEF patients with a negative UDT tend to have a better prognosis than those with a positive UDT.

The UDT has been widely used as an initial screening method for evaluation of proteinuria on the basis of low cost and the ability to provide rapid point-of-care information to clinicians and patients.<sup>22</sup> Furthermore, UDT is very sensitive to albumin but is less sensitive to globulins and secreted proteins.<sup>22</sup> Konta *et al.* reported the significant usefulness of trace or more UDT to predict albuminuria ( $\geq$ 30 mg/g) in the general population.<sup>21</sup> Furthermore, the negative predictive value of UDT for identification of albuminuria ( $\geq$ 30 mg/g) was higher than the threshold of  $\geq$ 1+.<sup>21</sup> Thus, in the present study, we defined positive UDT for albuminuria ( $\geq$ 30 mg/g) when the analysis showed trace or more.

Anand *et al.* reported that the percentage of positive UDTs in HF patients was 8.9%.<sup>14</sup> However, they defined a positive UDT as 1+ or more. In the present study, the prevalence of patients with a positive UDT was 29.5%. Among the patients with a positive UDT, the percentage of trace proteinuria was the highest. Therefore, the difference in the definition of a positive UDT may influence the difference in the percentage. Albuminuria ( $\geq$ 30 mg/g) is observed in approximately one-third of HF patients.<sup>12,13</sup> Thus, our findings indicate that a positive UDT defined as trace or more is useful for detection of albuminuria ( $\geq$ 30 mg/g) and could be a reasonable surrogate of UACR measurement in HFpEF patients.

In HFpEF patients with eGFR  $\geq$ 60, those with a positive UDT showed about twice as high mortality as those with a negative UDT. Furthermore, in HFpEF patients with eGFR <60, those with a positive UDT also showed significantly higher mortality compared with those with a negative UDT. This result indicates that we should perform UDT in addition to eGFR evaluation in HFpEF patients regardless of the eGFR level.

### Implications of a positive urine dipstick test in heart failure with preserved ejection fraction

The reason for the poorer prognosis of HFpEF patients with a positive UDT remains to be fully clarified. In the present study, HFpEF patients with a positive UDT were characterized by a higher BNP level, suggesting that venous filling pressure is significantly increased. Venous congestion was shown to cause proteinuria in dogs,<sup>28</sup> suggesting that elevated venous pressure may be associated with the development of albuminuria. Furthermore, albuminuria may attenuate the effect of furosemide because filtered albumin may bind furosemide in the tubular fluid and impair the interaction with the luminal co-transporting proteins.<sup>29</sup> Resistance to diuretics may cause a deterioration of the venous congestion status with a resultant vicious cycle of albumin excretion into the urine. Thus, the therapeutic strategy for reducing albuminuria is important in HFpEF patients.

In the present study, 40% of deaths were caused by cardiovascular events. Zile *et al.* also reported that 60% of deaths in HFpEF



patients were CVDs.<sup>30</sup> Albuminuria reflects glomerular injury, systemic inflammation, and endothelial dysfunction that lead to cardiovascular events.<sup>13</sup> Furthermore, albuminuria has been associated with changes in coagulation factors.<sup>31</sup> In the present study, the rate of CVD was relatively low; however, a positive UDT could predict CVD in HFpEF patients, especially in those with an eGFR  $\geq 60$ . In HFpEF patients with eGFR  $< 60$ , those with a positive UDT showed no significant difference in the development of CVD after adjustment by eGFR compared with those with a negative UDT. This result indicated that the influence of eGFR decline on CVD may be larger than that of albuminuria in patients with eGFR  $< 60$ . However, Perkins *et al.* reported that cases of early eGFR decline occurred in 9% of the normal albuminuria group and 31% of the albuminuria ( $\geq 30$  mg/g) group in diabetes patients.<sup>32</sup> Therefore, in the follow-up period, there may be a considerable eGFR decline in patients with a positive UDT compared with those with a negative UDT that leads to poor outcome. Therefore, we need to perform UDT in addition to measurement of eGFR even in HFpEF patients with eGFR  $< 60$ .

In the present study, a positive UDT was also associated with increased NCVD, a finding consistent with a previous report by Hillege *et al.*<sup>31</sup> Approximately one-third of the NCVDs were due to malignant tumours in the present study. Although the underlying mechanisms remain to be elucidated, patients with advanced malignant tumours have a significantly higher urinary albumin excretion rate than those with localized disease.<sup>33</sup>

In the present study, the remaining one-third of NCVDs were due to infectious diseases. HFpEF patients with albuminuria ( $\geq 30$  mg/g) tended also to have cerebrovascular disease that leads to impaired activities of daily living (Table 1). Such patients are particularly at high risk of contracting infectious disease. The present results also indicate that the prevention of infectious diseases and cerebrovascular disease is important to reduce the mortality of HFpEF patients.

### Treatment strategy of patients with heart failure with preserved ejection fraction with a positive urine dipstick test

The underlying mechanisms of the close relationship between the heart and the kidney include inflammation and an activated RAS and/or sympathetic nervous system.<sup>7</sup> Importantly, these mechanisms are also involved in the pathogenesis of albuminuria.<sup>7</sup> It was reported that RAS inhibitors cause a significant decrease in albuminuria and a trend of a decrease in cardiovascular events in patients with hypertension, LV hypertrophy, and diabetes.<sup>34</sup> On the other hand, RAS inhibition in HFpEF is not associated with a consistent reduction in HF admission or mortality.<sup>27</sup> The overall failure of RAS inhibitors to improve morbidity and mortality of HFpEF patients suggests a relatively smaller contribution of neurohumoral activation on HF progression as compared with the case for HFrEF patients.<sup>27</sup> However, HFpEF patients with a positive UDT may have higher RAS activity than those with a negative UDT. It was reported that telmisartan treatment was associated with an increased risk of adverse renal events in patients without albuminuria, whereas it tended to improve outcomes of patients with albuminuria.<sup>35</sup> Thus, the baseline albuminuria level may be

an important factor when selecting patients for treatment with RAS inhibitors.<sup>36</sup> Again, the importance of UDT should be emphasized before we start to use RAS inhibitors for HFpEF patients.

### Study limitations

Several limitations should be mentioned regarding the present study. (i) We had no information on LV function other than the LVEF, and it therefore remains unknown whether the study population had objective evidence of diastolic dysfunction recommended by the recent guidelines in the diagnosis of HFpEF.<sup>4</sup> However, we excluded patients with severe VHD, congenital heart disease, pulmonary arterial hypertension, and pericardial disease. Therefore, our study subjects can be categorized as probable diastolic HF as defined by Vasan *et al.*<sup>2</sup> (ii) UDT is a qualitative measurement of proteinuria and, furthermore, UDT is a less accurate and less sensitive measure of urinary albumin excretion. (iii) In the present study, UDTs from five different companies were used in the participating hospitals. Moreover, UDT was not measured at a central laboratory. Four dipsticks were calibrated to indicate trace at  $\geq 0.1$  g/L or  $\geq 0.15$  g/L of proteinuria and one dipstick did not originally indicate trace. Furthermore, the sensitivity and specificity for detecting albuminuria may be different among these dipsticks. However, multivariate analyses including all covariates with the UDT brands clearly showed the significant prognostic impact of a positive UDT in HFpEF patients. (iv) The present results were analysed using data collected at study entry and we did not take into consideration the possible changes in UDT during the follow-up period. (v) The primary design of the present study did not cover chronic lung disease, which has been recognized as one of the important prognostic factors of HFpEF.<sup>5</sup> (vi) All subjects in the CHART-2 study were Japanese people, which may limit extrapolation of the present results to patients in Western countries. Finally, since the CHART-2 study is an observational study, the present results need to be carefully interpreted especially when the effects of treatment are evaluated.

### Conclusions

The present results demonstrate that albuminuria predicts the mortality of HFpEF patients in each stratum of eGFR levels, suggesting its usefulness for appropriate risk stratification in these patients.

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